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Rohini Manaktala, Jose D Tafur-Soto & Christopher J White

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Renal Artery Stenosis in the Patient with Hypertension: Prevalence, Impact and Management

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Rohini Manaktala

Jose D Tafur-Soto

Christopher J White 

Ochsner Clinic Foundation, Department
of Cardiovascular Medicine, New
Orleans, LA, USA

Abstract: Atherosclerosis is the primary cause of renal artery stenosis. Atherosclerotic renal artery stenosis (ARAS) is associated with three clinical problems: renovascular hypertension, ischemic nephropathy and cardiac destabilization syndrome which pose huge healthcare implications. There is a significant rate of natural disease progression with worsening severity of renal artery stenosis when renal revascularization is not pursued in a timely manner. Selective subgroups of individuals with ARAS have had good outcomes after percutaneous renal artery stenting (PTRAS). For example, individuals that underwent PTRAS and had improved renal function were reported to have a 45% survival advantage compared to those without improvement in their renal function. Advances in the imaging tools have allowed for better anatomic and physiologic measurements of ARAS. Measuring translesional hemodynamic gradients has allowed for accurate assessment of ARAS severity. Renal revascularization with PTRAS provides a survival advantage in individuals with significant hemodynamic renal artery stenosis lesions. It is important that we screen, diagnosis, intervene with invasive and medical treatments appropriately in these high-risk patients.

Keywords: atherosclerotic renal artery stenosis, ARAS, percutaneous renal artery stenting, PTRAS, renin-angiotensin-aldosterone system, RAAS, acute decompensated heart failure, ADHF, chronic kidney disease, CKD, optimal medical therapy, OMT

Introduction

Atherosclerosis is by far the most prevalent etiology of renal artery stenosis. Atherosclerotic renal artery stenosis (ARAS) contributes to the development and progression of systemic atherosclerotic disease. It stems from having a hemodynamically significant renal artery atherosclerotic lesion that causes upregulation of the renin-angiotensin-aldosterone system (RAAS) resulting in accelerated hypertension that then adversely impacts pre-existing cardiovascular disease. Additionally, ARAS can also cause three clinical problems: renovascular hypertension, ischemic nephropathy and cardiac destabilization syndrome that include, acute decompensated heart failure (ADHF), recurrent ADHF and acute coronary syndromes (ACS). The prevalence of ARAS identified by Doppler ultrasound (DUS) within a US Medicare population ranges from 0.5% to 7% of individuals.¹ ARAS accounts for 10–20% of individuals with end stage renal disease who are on dialysis.² Furthermore, concurrent diagnosis of coronary artery disease (CAD) among individuals with ARAS ranges from 11.3% to 39%.³ There is a significant

Correspondence: Rohini Manaktala
Ochsner Clinic Foundation, Department
of Cardiovascular Medicine, 3rd Floor
Atrium Tower, Room #3D718, 1514
Jefferson Highway, New Orleans, LA
70121, USA
Tel +1 504-842-0879
Fax +1 504-842-3278
Email Rohini.manaktala@ochsner.org

rate of natural disease progression with worsening severity of renal artery stenosis shown by previous studies reporting the progression of ARAS by 50% at 5 years.⁴

Randomized clinical trials have not shown a benefit for renal artery stenting in the management of ARAS when used as an adjunct treatment to optimal medical therapy (OMT).⁵⁻⁷ However, selective sub-groups of individuals with ARAS that include those with resistant hypertension, ischemic nephropathy and cardiac destabilization syndrome have had good outcomes after percutaneous renal artery stenting (PTRAS).⁸ Measuring translesional hemodynamic gradients allows for accurate assessment of ARAS severity and identifies patients likely to benefit from stenting.⁹⁻¹¹ Advances in the imaging tools used to make anatomic and physiologic measurements of ARAS can facilitate identifying the best candidates for PTRAS. These technologies include: blood oxygenation level-dependent magnetic resonance imaging (BOLD MRI), dynamic contrast-enhanced MRI, intravascular ultrasound (IVUS) and renal frame counts. Moreover, research efforts have identified biomarkers such as brain natriuretic peptide (BNP) that may aid in patient selection.¹² A small series of patients with BNP greater than 80 pg/mL obtained better blood pressure control after undergoing PTRAS.¹²

From experimental animal models, ARAS was found to cause inflammation resulting in microvascular damage via ischemia, fibrosis and apoptosis of cells.¹³ These findings led to the development of low-energy shock wave therapy that improved microcirculation.¹⁴ ARAS is known to be a progressive disease. However, studies have shown similar long-term clinical outcomes with no difference in mortality or event-free survival in ARAS individuals who initially develop impaired renal function with initiation of medications compared to those individuals without decline in renal function that are also on medical therapy.¹⁵ Regarding disease progression, the 2-year cumulative incidence is 6% of ARAS individuals with greater than 60% stenosis of the renal artery who develop reduction in renal length by greater than 1 cm.^{16,17} A natural history study of individuals with high-grade ARAS, who were medically managed without renal revascularization, was performed to determine the rate of progression to renal failure and development of accelerated hypertension. This study showed that over 3-year follow-up the number of antihypertensive medications to effectively control blood pressure in this patient population increased.¹⁸ Additionally, renal function declined and mortality risk rose specifically in those patients with bilateral ARAS or ARAS with a solitary functioning kidney.¹⁸

Observational studies have shown that PTRAS in individuals with ARAS who also have concomitant chronic kidney disease (CKD) can improve or stabilize renal function and preserve kidney size.¹⁹ Renal size assessed by pole-to-pole kidney length with ultrasound measurement is an important predictor of clinical response.²⁰ Overall, renal revascularization with PTRAS provides patient survival advantage in those with significant hemodynamic renal artery stenosis lesions and advanced CKD (stage 4 and stage 5).²¹ It is important that we screen, diagnosis, intervene with invasive and medical treatments appropriately in these high-risk patients.

Pathophysiology

Physician scientist, Goldblatt conducted foundational animal experiments investigating the effect of unilateral and bilateral renal artery stenosis on systemic blood pressure.^{21,22} Restricting blood flow to one kidney with a functioning contralateral kidney resulted in upregulation of the neurohormonal pathway of RAAS. The affected juxtaglomerular apparatus of the nephron senses the low flow state and releases renin. Renin then causes systemic vasoconstriction and affects the efferent arteriole of the unaffected kidney causing an increased glomerular filtration rate (GFR) and a pressure diuresis. Over time, the unaffected kidney develops hypertensive nephropathy, no longer able to maintain pressure diuresis, so systemic hypertension ensues. Aldosterone, which is also released from the RAAS, promotes sodium and water retention. In bilateral ARAS or a solitary kidney with significant ARAS, Goldblatt found a state of fluid retention due to decreased diuresis because of the absence of an unaffected kidney to balance the fluid retention, so volume-dependent hypertension develops.²³

Individuals with clinically significant ARAS also suffer from cardiovascular disease. These individuals experience proinflammatory effects on their cardiovascular system resulting in the development of: smooth muscle cell proliferation, endothelial cell dysfunction, arterial medial hypertrophy, myocardial fibrosis and plaque rupture.²⁴

Clinical Conditions

ARAS is associated with three main clinical disease processes that include: renovascular hypertension, cardiac destabilization syndromes and ischemic nephropathy. Renovascular hypertension is defined as an increase in arterial pressure caused by hemodynamically significant renal artery stenosis.²⁵ In this disease, resistant (refractory)

Table 1 Functional Classification of ARAS in Association with Hypertension²⁶

Grade	Description
I	Asymptomatic ARAS with normotensive blood pressure and normal renal function
II	ARAS with well controlled hypertension using medical therapy and normal renal function
III	ARAS with uncontrolled hypertension despite optimal medical therapy or clinical signs of volume overload and abnormal renal function

Note: Data from Rocha-Singh et al.²⁶

hypertension develops which is difficult to control blood pressure despite maximally tolerated doses of three antihypertensive agents including a diuretic. In these individuals, after they undergo PTRAS they experience a significant reduction and/or normalization in their blood pressure.²⁶ A functional classification system has been developed to categorize ARAS and associated hypertension (Table 1).²⁶ Cardiac destabilization syndromes include: “flash” pulmonary edema events, ADHF and ACS.^{27–30} Pickering syndrome describes a specific condition seen in individuals that have bilateral ARAS as they lack the compensatory mechanism of a functional kidney in regulating the body’s salt and fluid balance. These individuals also have hypertension and are prone to frequent “flash” pulmonary edema episodes. Ischemic nephropathy is a condition where local ischemia to the kidney causes tubulointerstitial injury and microvascular damage.³¹ This creates a state of oxidative injury that leads to the production of cytokines and inflammation resulting in interstitial fibrosis and renal atrophy.³¹

Diagnostic Modalities

The American College of Cardiology (ACC) and American Heart Association (AHA) clinical practice guidelines describe a variety of diagnostic imaging tools such as: DUS, computed tomography angiography (CTA) and magnetic resonance angiography (MRA) as screening tests to aid in the diagnosis of ARAS.²⁸ When non-invasive imaging tests are inconclusive and there is high degree of clinical suspicion for ARAS then catheter angiography is indicated.^{32–35} To eliminate the inter-observer variability in the visual estimation of renal artery stenosis, a translesional pressure gradient is measured (ratio of the distal pressure to proximal pressure across the stenosis) to determine if ARAS is hemodynamically significance.

A lesion is hemodynamically significant if on renal angiography the stenosis is 50–70% with a peak translesional gradient of at least 20 mmHg or a mean gradient of at least 10 mmHg.³⁴ However, angiographic ARAS lesions do not always indicate that there is renal ischemia. Newer technologies such as: BOLD MRI and dynamic contrast-enhanced MRI are used to quantify the degree of renal ischemia by measuring decreased renal tissue oxygenation with experimental-graded reduction in renal blood flow.³⁵ Although these imaging modalities are still being researched they have the potential to aid in distinguishing between viable and non-viable kidneys. Table 2 compares the various imaging modalities for the detection of ARAS.^{32–38} There are additional diagnostic tests that assess both the functional and physiological changes when evaluating ARAS and the interaction between the stenotic lesion and activation of RAAS. Table 3 compares three physiologic diagnostic tests for ARAS.^{39–41}

Optimal Medical Therapy

Lifestyle modifications with diet, physical activity and smoking cessation in addition to optimal medical therapy (OMT) are the initial steps for newly diagnosed ARAS. Furthermore, co-morbidities such as hypertension, hyperlipidemia and diabetes need to be well managed as they contribute to the deterioration in renal function and accelerate the disease progression in ARAS. The ACC and AHA recommend the use of an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB) and calcium channel blockers for medical therapy in treatment of hypertension in the setting of ARAS.^{42,43} There is also evidence to support the use of other antihypertensive agents such as: thiazides, hydralazine, alpha-blockers and beta-blockers in addition to diuretics to effectively control blood pressure. ACE-I and ARB are 86% to 92% effective in lowering blood pressure in individuals with ARAS and should be one of the agents in their antihypertensive medication regimen.⁴³ However, individuals with ARAS and solitary functioning kidney, severe bilateral renal artery stenosis or advanced chronic kidney disease should be cautiously monitored while on ACE-I or ARB therapy as there is a slight risk for acute renal failure.⁴³ There have been no randomized-controlled studies studying the effects of various medical regimens on the management of hypertension associated with ARAS. This is due to individuals with ARAS having refractory hypertension and requiring multiple antihypertensive medications. Statin and antiplatelet therapies are

Table 2 Imaging Modalities Utilized for Diagnosing ARAS^{32–38}

Imaging Test	Advantages	Disadvantages
Doppler Ultrasound (DUS) ³²	<ul style="list-style-type: none"> -able to pinpoint the exact location of ARAS -the degree of stenosis can be identified with direct visualization of renal arteries and doppler velocity measurements of blood flow -PSV > 200 cm/s has a 95% sensitivity and 90% specificity for renal artery stenosis >50% -utilized to follow up after PTRAS and monitor for restenosis 	<ul style="list-style-type: none"> - insufficient evaluation of accessory renal arteries in overweight individuals - presence of bowel gases impairs visualization of the renal artery - the quality of study is dependent on the operator
Computerized Tomographic Angiography (CTA) ³³	<ul style="list-style-type: none"> - there is high spatial resolution and increased speed of image acquisition -the sensitivity is 94% and specificity is 93% for a renal artery stenosis lesion greater than 50% 	<ul style="list-style-type: none"> - lack of information on renal flow or pressure distal to RAS -radiation exposure - risks associated with using iodinated contrast - there is increased risk of nephrotoxic effects of the contrast
Magnetic Resonance Angiography (MRA) ³³	<ul style="list-style-type: none"> - allow for visualization of the renal artery without the need for ionizing radiation -can obtain hemodynamic data such as, increased blood flow turbulence -can be used to evaluate in-stent restenosis -the sensitivity is 96% and specificity is 92% in detecting renal artery stenosis greater than or equal to 50% 	<ul style="list-style-type: none"> - there is a risk of causing nephrogenic systemic fibrosis with gadolinium contrast in patients with severe renal insufficiency or dialysis dependency
Arterial Angiography ³⁴	<ul style="list-style-type: none"> - usually follows a positive non-invasive screening test first and is the gold standard for diagnosing ARAS -there is better accuracy in identifying hemodynamically significant stenosis via measurement of the translesional pressure gradient 	<ul style="list-style-type: none"> - risks associated with the procedure include: vascular access related complications, embolization, radiation exposure, iodinated contrast related reaction and contrast induced nephropathy
BOLD MRI ³⁶	<ul style="list-style-type: none"> - an accurate way of monitoring renal tissue oxygenation and degree of renal hypoxia in ARAS by measuring levels of serum injury biomarkers in the draining renal vein -correlate with the severity of renal blood flow obstruction - can monitor therapeutic interventions or pretreatment with adjunct cellular based therapies for ARAS before renal revascularization is pursued 	<ul style="list-style-type: none"> - its use is restricted to research setting presently
Dynamic Contrast Enhanced MRI ³⁵	<ul style="list-style-type: none"> - can measure single kidney glomerular filtration rate, tissue perfusion and vascularity which can better characterize the overall functionality of the kidney and determine directly irreversible renal parenchymal damage -it can be used to assess functional outcomes after renal artery revascularization 	<ul style="list-style-type: none"> - affected by respiratory motion artifacts - the contrast agent has the potential of causing nephrotoxicity especially in patients with severe chronic kidney disease - there is a lack of standard imaging and analysis protocols
Intravascular Ultrasound (IVUS) ³⁷	<ul style="list-style-type: none"> - characterize renal artery plaque - well validated imaging modality to guide optimal stent implantation 	<ul style="list-style-type: none"> - it is of low quality and low resolution imaging compared to optical coherence tomography (OCT) intravascular imaging -it is difficult to decipher fine details such as stent strut versus thrombus
Renal Frame Count ³⁸	<ul style="list-style-type: none"> - an intraprocedural tool that can assess and quantify perfusion of kidneys in determining the severity of ARAS and predict a clinical response after PTRAS 	<ul style="list-style-type: none"> - there is risk of azotemia from the nephrotoxic effects of the contrast

Table 3 Physiologic Diagnostic Tests Used to Diagnose ARAS^{39–41}

Test	Advantages	Disadvantages
Plasma Renin Activity	-it can be used in procedural setting to predict which individuals with ARAS will have improvement in their resistant hypertension after PTRAS	- affected by physiological parameters (blood volume, sodium load, unilateral versus bilateral renal disease, age, race, sex and comorbidities) which can alter the circulating levels of renin -the test's sensitivity is 57% and specificity is 66%
Captopril Renography	- provides functional data with regards to GFR reduction with ARAS with angiotensin converting enzyme inhibitor (ACE-I) compared to the increase GFR in contralateral side -measures the plasma aldosterone concentration (PAC), plasma renin concentration (ARC) and plasma renin activity (PRA) -Diagnosis of renovascular hypertension made by PAC/ARC >40 or PAC/PRA >200 -sensitivity of the test is 74% while the specificity is 59%	-it cannot specify anatomical location of renal artery lesion -not a reliable test in those with poor renal function and bilateral renal disease
Bilateral Renal Vein Renin Assay	-the renal vein renin ratio is the renin level of the ischemic kidney compared to the contralateral kidney which allows selection of individuals with hypertension and ARAS who may benefit from interventions -in 90% of the situations these individuals will respond to treatment	-high false positives and negatives, both are 67% -difficult to differentiate hypertensive individuals with unilateral and bilateral ARAS and many of them will have essential hypertension rather than renin-mediated therefore necessitating the use of additional studies (doppler ultrasound and catheter based renal arteriography)

also indicated in medical treatment of ARAS given that ARAS is a peripheral vascular disease.^{44,45}

Clinical Trials

Three randomized-controlled trials have been conducted to compare PTRAS with OMT to OMT alone. The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL), Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) and Stent Placement in Patients with Atherosclerotic Renal Artery Stenosis and Impaired Renal Function (STAR) trials did not show PTRAS to be superior to OMT in the ARAS population with mild to moderate stenosis.^{5–7} The lack of benefit for PTRAS was attributed to 1) a selection of patients with mild to moderate ARAS and low-risk features and 2) the lack of hemodynamic confirmation of the severity of mild to moderate ARAS. These studies did not enroll high-risk participants who had resistant (refractory) hypertension, cardiac destabilization syndromes or ischemic nephropathy.

The CORAL trial compared OMT alone to PTRAS with OMT in individuals with ARAS. These low-risk patients had hypertension with a systolic blood pressure of 155 mm Hg or higher while receiving two or more antihypertensive medications or had CKD with GFR of less than 60 mL/min/m² calculated from the Modification

of Diet in Renal Disease (MDRD) formula and attributed their hypertension or CKD to ARAS. The mean ARAS stenosis for randomized patients was 67.3%, and hemodynamic translesional gradients were not measured in moderate ARAS (50–70% lesions).⁷ Primary endpoints included: mortality, renal function, and occurrence of adverse cardiovascular and renal events. They did not find any statistical difference after 43 months follow-up between the two groups.⁷ Specifically, stent treatment did not influence GFR over 3 years in participants receiving RAAS inhibitor medical therapy along with strict control of traditional risk factors for renal disease and atherosclerosis such as hypertension, hyperlipidemia and diabetes. However, there was a difference of 2.3 mmHg reduction in systolic blood pressure favoring PTRAS.⁷

The ASTRAL trial enrolled patients with an uncertain indication for PTRAS. These patients either had refractory hypertension or unexplained impaired renal function that was suggestive of ARAS. They underwent imaging either in the form of DUS, CTA, MRA or renal angiography. Physicians were unsure if these patients would benefit from renal revascularization. So they were randomized in the trial into an OMT group and OMT plus PTRAS group. They found that there were no benefits from PTRAS in terms of improving renal function or reducing

cardiovascular events and deaths.⁵ There was a small reduction in mean systolic blood pressure by 1.6 mmHg in the revascularization group compared to the control group.⁵ The experience and skill of the interventionalists performing PTRAS were questioned due to 9% complication rate reported in this trial.⁵

The STAR trial also compared renal artery stenting and OMT versus OMT alone for individuals with mild to moderate ARAS. Study participants had ARAS with greater than 50% stenotic lesion, estimated creatinine clearance (eCrCl) by Cockcroft-Gault equation with less than 80 mL/min/1.73 m² and stable blood pressure less than 140/90 mmHg⁸. The primary endpoint investigated was progression of renal disease defined as greater than 20% decrease in eCrCl from baseline within first two years of follow-up. There was no observed benefit with PTRAS over only medical treatment on the progression of CKD. However, it is important to take into consideration that 30% of the patients randomized to the renal revascularization group had ARAS with a lesion less than 50%.⁶

Observational cohort studies, in patients with high-risk ARAS have shown beneficial effects such as better hypertension management with renal stenting compared to OMT alone in treatment of patients with ARAS. The Herculink Elite Renal Stent to Treat Renal Artery Stenosis (HERCULES) trial studied individuals with ARAS that had greater than or equal to 60% stenosis detected by angiogram along with uncontrolled hypertension (on average taking 3.4 antihypertensive medications) and randomized them to OMT therapy alone or with PTRAS. The study's endpoints included: change in blood pressure, antihypertensive medication regimen and renal function comparing baseline with 9 months follow-up. Renal revascularization via PTRAS was shown to have a statistically significant reduction in systolic blood pressure and stable kidney function.⁴⁶

Furthermore, studies were performed investigating the treatment options for ARAS and their effect on the progression of left ventricular hypertrophy in patients with CAD and ARAS. The renal artery stenosis in coronary artery disease trial showed neither PTRAS with medical therapy or medical therapy alone led to significant change in renal function at 1-year follow-up.⁴⁷ However, both groups had a statistically significant reduction in left ventricular mass index.⁴⁷ Moreover, the Cardiac Benefits of Renal Artery Stenting (CARMEL) study showed marked improvement in left ventricular filling pressures in individuals with ARAS and heart failure after undergoing PTRAS.⁴⁸

There are two randomized trials that have yet to publish their results. The Nephropathy Ischemic Therapy (NITER) trial randomized ARAS individuals into two arms: OMT alone versus OMT and PTRAS. The patients selected had stable chronic kidney disease (GFR >30 mL/min/m²), hypertension and hemodynamically significant renal luminal lesion greater than 70% diagnosed by DUS and confirmed by MRA.⁴⁹ The clinical endpoints include: initiation of dialysis, reduction of GFR by greater than 20% and death. The other trial is the Medical and Endovascular Treatment of Atherosclerotic Renal Artery Stenosis (METRAS), which had a similar intervention arm and enrolled similar participants from the ARAS population. Their main clinical endpoint is the GFR value in the ischemic kidney determined by renal scintigraphy. Additional endpoints include: reduction in blood pressure reading, improvement in quality of life and prevention of cardiovascular events.⁵⁰

Overall, published randomized control trials did not show differences in cumulative endpoint outcomes such as: blood pressure reduction, cardiovascular and cerebrovascular events, and change in renal function (decline, stabilization, improvement) or death compared to the observational trials. This is likely due to several factors. First of all, there was selection bias starting with the low-risk patients enrolled in the randomized trials. For example, participants in the ASTRAL trial had stable underlying chronic kidney disease, baseline eCrCl of 40 mL/min/1.73 m² and it is not surprising to see that there were no significant changes in renal function in either groups. Moreover, these patients did not have resistant hypertension and the inclusion criteria for blood pressure management varied considerably with blood pressure readings and number of medications used. Also, individuals with severe ARAS may not always have clinical manifestations. This was seen in the patient population of the ASTRAL trial who were asymptomatic and majority had ARAS incidentally diagnosed. That is why there is no justification for PTRAS of incidentally discovered ARAS. Additional factors that limited the application of these randomized control trials findings include: small sample size and short time interval with follow-up. Since these were intention to treat designed trials, the increased cross-over rate from the conservative therapy arm also influenced the overall results. See [Table 4](#) for summary of the top three clinical trials regarding PTRAS among the ARAS patient population.

Renal Revascularization

Renal revascularization using PTRAS in select groups of individuals with severe ARAS has proven to be beneficial.

Table 4 Comparison of Randomized Control Trials for OMT versus PTRAS in ARAS

Name of Clinical Trial	ASTRAL ⁵ (806 Participants)	STAR ⁶ (140 Participants)	CORAL ⁷ (947 Participants)
Severity of ARAS	Any degree of ARAS (confirmed by DUS, CTA, MRA and renal angiography)	At least 50% ARAS (seen on CTA, MRA and renal angiography)	At least 80% ARAS (seen on DUS, CTA or MRA)
Inclusion Criteria of Blood Pressure	Uncontrolled or resistant hypertension	Stable BP <140/90 mmHg on medication	Systolic BP greater than 155 mmHg, on two anti-hypertensive medications
Inclusion Criteria of Renal Disease	Any degree of unexplained renal dysfunction	CrCl <80 mL/min/1.73 m ²	eGFR of less than 60 mL/min/1.73 m ²
Exclusion Criteria	<ul style="list-style-type: none"> -Surgical renal revascularization required or high likelihood will be needed within 6 months -Previous revascularization for renal artery stenosis -Nonatheromatous cardiovascular disease 	<ul style="list-style-type: none"> -Proven cholesterol embolization at previous interventions -Any known cause of renal failure other than ischemic nephropathy -Pulmonary edema in the presence of bilateral renovascular disease in combination with intolerance of ACE-I or angiotensin-II antagonist defined as a decline in eCrCl > 20% -Myocardial infarction or cerebrovascular accident less than 3 months -Renal artery diameter < 4 mm 	<ul style="list-style-type: none"> -Renal artery stenosis due to fibromuscular dysplasia -CKD from another cause besides ischemic nephropathy -CKD associated with a serum creatinine level greater than 4 mg/dL or kidney length less than 7 cm -Renal artery stenosis lesion that could not be treated with the use of a single stent
Follow-Up	34 months	24 months	43 months
Endpoints	Primary: change in renal function Secondary: blood pressure control, time to first renal event, time to first cardiovascular event and mortality	Primary: reduction in creatinine clearance greater than 20% compared to baseline Secondary: safety, cardiovascular morbidity and mortality	Primary: composite of cardiovascular or renal death, myocardial infarction, stroke, hospitalization for ADHF, progressive renal insufficiency and need for dialysis
Results	-The rate of progression of renal impairment was lower in the revascularization group.- Blood pressure readings decreased but without significant difference between the two groups.	Approximately 16% in the PTRAS group and 22% in the OMT alone group had a 20% or greater decrease in creatinine clearance.	-No significant difference in rate of primary end points or all cause mortality was seen.-There was a difference in systolic blood pressure seen in the PTRAS group.
Limitations	-Approximately 25% of study participants in each group had normal renal function at the entry of the trial. -Some participants identified as having 50–70% stenosis in actuality had stenosis of <50%. -There was a high complication rate (9% in the first 24 hours) after PTRAS. -It was a non-blinded trial so observer and selection bias was present. -Nearly 6% of the study participants crossed over from OMT to intervention group. -There was low power to detect difference in subgroups.	-Study participants were falsely identified with ARAS by non-invasive imaging and some did not require stenting. -Complication rates were high.	-Study participants were not medically optimized on their blood pressure medications. -Participants with severe ARAS were withdrawn from study. -ARAS was not confirmed to have hemodynamic significance. -Participants with mild stenosis were also included and randomized to PTRAS.

Table 5 Procedural Complications Seen with PTRAS⁵⁶

Procedural Complication	Percentage of Patients Affected
30 day mortality	1%
Worsening of renal function	4%
Acute renal failure	2%
Segmental kidney infarction	1–2%
Need for surgical intervention for either nephrectomy or salvage	2%
Groin hematoma and puncture site trauma	3–5%
Occlusion of the renal artery	2–3%
Symptomatic embolization	3%
Death	1%

Note: Data from Ruzsa et al.⁵⁶

Severe ARAS is defined as a luminal stenosis of >70%, or if the stenosis is between 50% and 70% a trans-stenotic peak pressure gradient greater than 20 mmHg or mean pressure gradient greater than 10 mmHg is required.^{26,27} Clinical guidelines support stenting ARAS in individuals with an established indication for renal revascularization. Revascularization in patients with severe ARAS is indicated in the following individuals: (i) cardiac destabilization syndromes: flash pulmonary edema with severe hypertension, (ii) resistant (refractory) hypertension and (iii) rapidly progressive ischemic nephropathy, chronic kidney disease with GFR less than 45 cc/min/m² and global renal ischemia.^{26,51} Observational studies have shown that after renal revascularization, ARAS individuals

have improvement in their New York Heart Association (NYHA) functional class and fewer hospitalizations for ADHF.^{29,52} These individuals also have better controlled blood pressure. Renal revascularization in addition to coronary intervention for individuals with cardiac destabilization syndromes results in significant improvement in their left ventricular filling pressure.^{29,30}

PTRAS with drug-eluting stents (DES) were studied in The Palmaz Genesis Peripheral Stainless Steel Balloon Expandable Stent in Renal Artery Treatment (GREAT) trial that compared sirolimus DES to bare-metal stents (BMS).⁵³ They observed no procedural complications, stent implantation failure/displacement or need for additional stent implantation in patients with ARAS who underwent PTRAS. The binary restenosis rate was 6.7% for DES versus 14.6% for the BMS (p=0.30).⁵³ With regard to the long-term procedural success of PTRAS, it is important to look at the long-term patency rates. Stent restenosis is 10–20% after 5 years of follow-up.^{54,55} Factors that promote long-term stent patency include short stent length and good implantation technique.

The reported rate of procedural complications with PTRAS in the first 30 days is low in experienced operator hands (Table 5).⁵⁶ The CORAL trial reported renal artery dissection in 2.2%, branch-vessel occlusion in 1.2% and distal embolization in 1.2%.⁶ Other complications associated with PTRAS include: stent misplacement, access-vessel damage, stent embolization, renal artery thrombosis or occlusion and

Table 6 American College of Cardiology Appropriate Use Criteria for Treatment of ARAS

Clinical Scenario*	Percutaneous Renal Artery Stenting	Class and Level of Evidence
Sudden presentation of flash pulmonary edema	Appropriate	Class I, LOE B
Bilateral ARAS or a solitary viable kidney with ARAS along with declining renal function	Appropriate	Class IIa, LOE B
Failure to control blood pressure on three maximally treated medications (one of which is a diuretic)	May be appropriate	Class IIa, LOE B
Recurrent ADHF requiring hospitalization despite being on maximal medical treatment	May be appropriate	Class I, LOE B
Unilateral ARAS with declining renal function	May be appropriate	Class IIb, LOE C
ACS while being on OMT	May be appropriate	Class IIa, LOE B
Well controlled blood pressure on two or more antihypertensive medications	Rarely appropriate	
Uncontrolled blood pressure on less than three antihypertensive medications	Rarely appropriate	
Incidentally discovered unilateral ARAS (severe ARAS 70–99% stenosis or 50–69% stenosis with hemodynamic significance)	Rarely appropriate	
Incidentally discovered bilateral ARAS or solitary kidney (severe ARAS 70–99% stenosis or 50–69% stenosis with hemodynamic significance)	Rarely appropriate	
Unilateral ARAS, bilateral ARAS or a solitary kidney with borderline (50–69% stenosis without hemodynamic confirmation of severity)	Rarely appropriate	

Notes: *Significant ARAS = moderate (50%–70%) ARAS with a resting/hyperemic translesional mean gradient of ≥ 10 mm Hg, systolic gradient ≥ 20 mm Hg/or severe (>70%) ARAS. Data from Bailey et al.⁵¹

death.⁶ Alternative access sites (such as: radial and brachial artery) to femoral artery access are preferred due to most individuals with ARAS having concurrent peripheral artery disease and the associated risk with femoral vascular complications.⁵⁷ A “no-touch” technique has been adopted for PTRAS where a second 0.035-inch J wire is placed within the guide catheter that is sitting within the renal artery to minimize contact between the guide catheter and atherosclerotic plaque.⁵⁸ This ultimately prevents cholesterol embolization.⁵⁸

Percutaneous renal artery interventions are also associated with the risk of distal embolization. Preventative measures include the use of embolic protection device (EPDs). The Renal Artery Stenting With or Without Distal Protection Device and Use of a Platelet Aggregator Inhibitor (RESIST) were a prospective-randomized study that evaluated the safety and efficacy of PTRAS along with glycoprotein IIb/IIIa inhibitor (abciximab) and EPD on renal function. Platelets secrete soluble CD40 ligand (sCD40L) which promotes platelet activation. GP IIb/IIIa inhibits platelet activation. In this study, participants were randomized to one of the four groups: (1) EPD only, (2) no EPD and no abciximab, (3) abciximab only and (4) EPD and abciximab. Of those study participants who received EPD with renal revascularization, 26% of them had captured emboli in their filter.⁵⁹ Participants that were randomized to the EPD and abciximab showed significant decrease in sCD40L after PTRAS. Findings revealed that individuals that received abciximab and EPD during their renal artery stenting had stable or improved renal function compared to the controls.⁵⁹

Intravascular ultrasound (IVUS) is commonly utilized with PTRAS to aid in stent sizing and confirming apposition of the stent to the arterial wall. IVUS can reveal detailed information on the plaque morphology and accurately measure vessel diameter so operators of PTRAS can predict in advance which lesions are at risk for complications after interventions.⁶⁰ In a large case series study conducted at a single center site, the role of IVUS with PTRAS was evaluated. ARAS cases where IVUS was performed in conjunction with PTRAS and achieved good angiographic result required only additional therapeutic interventions in 23.5% of the cases.⁶⁰ This could be explained by 14.4% of the stents having incomplete stent apposition/expansion, 5.2% of renal arteries having dissections and 3.9% of the stents not covering the ostia.⁶⁰ Additional stenting was needed in 4.5% of the arteries that were treated. It is found that restenosis most often occurs in renal arteries with a diameter of less than 4.5 mm¹⁰. IVUS allows for successful placement of these stents while

minimizing the risk of vessel wall rupture.⁸ Overall, IVUS is used to achieve optimal stenting results by safely delivering the appropriate size stent with hopes of reducing future occurrence of developing renal artery restenosis.⁶⁰

Follow-Up

Patients should be followed clinically in terms of blood pressure control with laboratory results to monitor renal function, and surveillance DUS imaging is recommended to evaluate stent patency. DUS is the recommended imaging technique to screen for in-stent restenosis (ISR). DUS surveillance monitoring for renal stent patency should take into account that a stented artery is less compliant than a native artery and that peak systolic velocity (PSV) and systolic renal to aortic ratio (RAR) obtained by DUS are higher for any given degree of arterial narrowing within the stent; therefore, obtaining a post-procedure DUS is reasonable to establish a new baseline PSV.⁶¹ ISR based on DUS is defined as greater than 70% stenosis and peak systolic velocity (PSV) greater than 395 cm/s.⁶¹ Patients should have routine 30-day, 3-month, 6-month, 12-month and annual clinical, laboratory, and DUS follow-up for surveillance of ISR.⁶¹

Guidelines and Appropriate Use Criteria (AUC)

The ACC/AHA guidelines for treating ARAS stem from the peripheral artery disease guidelines created in 2006.^{27,28} These recommendations are based on expert opinion, and observational studies. In 2018 Society for Cardiovascular Angiography and Interventions (SCAI) produced an appropriate use criteria (AUC) statement for renal artery stenting. They reported stenting as an appropriate treatment in specific groups of individuals with ARAS with severe stenosis.²⁸ See Table 6 for summary of AUC for treatment of ARAS.^{27,28}

Conclusion

The clinical outcome of individuals with ARAS depends on both the degree of underlying renal parenchymal damage and atherosclerotic burden. In randomized control trials, the recruited patients had low-risk ARAS with <70% stenosis and underlying normal to mildly reduced renal function.⁶² The selection of low-risk participants impacted the results of the trials. The subanalysis of the trials showed that participants with ARAS of 80% or greater along with acute presentation of ADHF, unstable angina, rapid deterioration of renal function and severe uncontrolled hypertension significantly benefited from renal revascularization in addition to OMT.⁶²

It may be worthwhile determining which ARAS patients have hibernating renal parenchyma along with functionally significant stenosis that can truly benefit from renal revascularization. Long-term outcomes of individuals with ARAS can be improved potentially from interventions such as, stem cell therapies that can inhibit oxidative injury and inflammation to the renal parenchyma and cardiovascular system.⁶³ These adjunct therapies could change the natural disease progression and improve their morbidity and mortality rate in individuals with ARAS. However, further investigative studies will need to prove that these therapies provide a renoprotective benefit.

Disclosure

There are no relationships with industry. The authors report no conflicts of interest in this work.

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