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STATE-OF-THE-ART REVIEW

When and How Should We Revascularize Patients With Atherosclerotic Renal Artery Stenosis?

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ABSTRACT

Atherosclerotic renal artery stenosis is the leading cause of secondary hypertension and may lead to resistant (refractory) hypertension, progressive decline in renal function, and cardiac destabilization syndromes (pulmonary edema, recurrent heart failure, or acute coronary syndromes) despite guideline-directed medical therapy. Although randomized controlled trials comparing medical therapy with medical therapy and renal artery stenting have failed to show a benefit for renal artery stenting, according to comparative effectiveness reviews by the Agency for Healthcare Research and Quality, the trials may not have enrolled patients with the most severe atherosclerotic renal artery stenosis, who would be more likely to benefit from renal stenting. Because of limitations of conventional angiography, it is critical that the hemodynamic severity of moderately severe (50% to 70%) atherosclerotic renal artery stenosis lesions be confirmed on hemodynamic measurement. The authors review techniques to optimize patient selection, to minimize procedural complications, and to facilitate durable patency of renal stenting. The authors also review the current American College of Cardiology and American Heart Association guidelines and the Society for Cardiovascular Angiography and Interventions appropriate use criteria as they relate to renal stenting. (J Am Coll Cardiol Intv 2019;12:505–17) © 2019 by the American College of Cardiology Foundation.

Renal artery stenosis (RAS) may result in resistant (refractory) hypertension (HTN), progressive decline in renal function, and cardiac destabilization syndromes, including "flash" pulmonary edema, aortic syndromes, stroke, recurrent congestive heart failure (CHF), and acute coronary syndromes (ACS). Despite prospective clinical trial evidence for the safety and efficacy of percutaneous transluminal renal artery stenting (1–3), randomized controlled trials (RCTs) have shown no difference in outcomes with guideline-directed medical therapy (GDMT) and percutaneous transluminal renal artery stenting compared with GDMT alone (4–7). However, these trials had significant design flaws (variability in inclusion and exclusion criteria, inconsistent definitions of improvement, mixtures of HTN and renal function endpoints), making the selection of patients for renal artery stenting a controversial topic, as acknowledged by a comparative effectiveness review of management strategies for renal artery stenosis by the Agency for Healthcare Research and Quality (8,9).

We believe that the best strategy to approach the treatment of atherosclerotic renal artery stenosis (ARAS) is to identify which patients are most likely to benefit from renal artery stenting and to optimize the safety and durability of the procedure. Our discussion focuses on those patients most likely to clinically benefit from revascularization, considering that this subset of patients may not have been well represented in RCTs. The most reliable predictor of clinical benefit from renal artery revascularization is

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

ARAS = atherosclerotic renal artery stenosis

AUC = appropriate use criteria

BMS = bare-metal stent(s)

CHF = congestive heart failure

CKD = chronic kidney disease

CTA = computed tomographic angiography

EPD = embolic protection device

FMD = fibromuscular dysplasia

GDMT = guideline-directed medical therapy

HSG = hyperemic systolic gradient

HTN = hypertension

ISR = in-stent restenosis

IVUS = intravascular ultrasound

MRA = magnetic resonance angiography

PSV = peak systolic velocity

RAS = renal artery stenosis

RCT = randomized controlled trial

RFC = renal frame count

RFFR = renal fractional flow reserve

confirmation of the hemodynamic severity of the ARAS in the context of clinical event (refractory HTN, flash pulmonary edema, ischemic nephropathy) as well as the condition of the kidneys. We also review the current American College of Cardiology and American Heart Association guidelines (10) and Society of Cardiovascular Angiography and Interventions appropriate use criteria (AUC) (11) as they relate to renal artery stenting.

PREVALENCE

RAS is predominantly due to atherosclerosis (>90%) in the adult population, with fibromuscular dysplasia (FMD) being more common in younger female patients (12). The prevalence of ARAS depends on the population that is screened. Among patients with HTN, ARAS is the most common (2% to 5%) secondary cause of HTN but does not imply causation (13,14). In 834 Medicare-age subjects (mean age 77 years), renal duplex screening demonstrated ARAS (>60%) in 6.8% (13). In an autopsy series, ARAS (≥50%) was found in 27% of patients ≥50 years, rising to 53% if there was a history of severe diastolic HTN (>100 mm Hg) (15). Among patients beginning dialysis treatment, 10% to 15% will have ARAS, with approximately 25% of elderly patients with chronic kidney disease (CKD) found to have unsuspected ARAS (16). In patients undergoing cardiac catheterization for suspected coronary artery disease, the prevalence of ARAS ranged from 25% to 30% (17–21), while peripheral arterial disease or abdominal aortic aneurysm is associated with ARAS in 30% to 40% (22,23). ARAS is more common in patients who have atherosclerosis involving any other vascular bed (24).

FMD is a nonatherosclerotic congenital condition with potential flow-limiting fibroplasia of an artery predominantly affecting carotid arteries, femoral arteries, and visceral (renal) arteries (25). FMD usually involves the mid to distal portion of the renal artery and is angiographically characterized by the "string of pearls" appearance. Renal artery FMD is often found incidentally in asymptomatic individuals but has a prevalence estimated from about 2% to about 6% (26–29), with a female preponderance, and can lead to HTN, which is preferentially treated with balloon angioplasty (30).

CLINICAL MANIFESTATIONS OF RENAL VASCULAR DISEASES

HTN. In patients with hemodynamically significant ARAS, the renin-angiotensin-aldosterone system is thought to be activated, leading to HTN, but there are very few data in humans. In some patients, there may be a component of renovascular HTN superimposed on a background of essential HTN. Unilateral RAS results in vasoconstrictor-mediated HTN, while bilateral or solitary kidney RAS results in HTN with volume overload. Refractory HTN is present when 3 different classes of maximally tolerated blood pressure medications, including a diuretic agent, that when taken fail to achieve target blood pressure (6,7). Predicting which patients with refractory HTN with ARAS are most likely to respond to renal artery stenting with improved blood pressure has been controversial (3,31–33).

CARDIAC DESTABILIZATION SYNDROMES. Uncontrolled HTN and volume retention associated with ARAS play an important role in the destabilization of patients with ACS or CHF. The Pickering syndrome, sudden onset, "flash," pulmonary edema, is a commonly recognized destabilization syndrome resulting from ARAS (33,34). The presence of these syndromes should prompt an investigation for RAS.

ISCHEMIC NEPHROPATHY. ARAS, if hemodynamically significant, may cause ischemic nephropathy and CKD. Nephropathy implicates loss of renal mass, loss of glomerular and filtration surface, and extensive fibrosis of parenchyma; this is a marker of adverse outcome for virtually all HTN, renal, and cardiovascular outcomes. It is important to determine if the patient has intrinsic renal disease, ischemic nephropathy, or both (35). The evaluation of nephropathy may include urinalysis for proteinuria, serum creatinine, and renal imaging to assess the renal dimensions, renal resistive indexes, as well as the renal arteriolar patterns. Advanced nephropathy that is not likely to benefit from revascularization has been described by proteinuria >1 g/day, kidney pole-to-pole length of <7 cm, or hemodialysis for >3 months (11,12,35,36). If the cause of CKD is ischemic nephropathy, this is potentially reversible. Some studies suggest that as many as 12% of patients with end-stage renal disease have CKD attributable to progressive ischemic nephropathy from ARAS (37,38). Atrophy of the kidney occurs as a consequence of the progression of ARAS (12,39). In patients with CKD and severe ARAS, renal artery stenting is most beneficial in those with a more rapid rate of decline (40,41).

DIAGNOSIS OF ARAS

NONINVASIVE STENOSIS ASSESSMENT. Renal Doppler ultrasound (duplex) imaging is an excellent initial choice for the diagnosis of ARAS. A peak systolic velocity (PSV) of >200 cm/s is associated with 95% sensitivity and 90% specificity for >50% stenosis. A ratio of renal artery PSV to the PSV of the aorta of >3.5 has 92% sensitivity for >60% diameter stenosis (11,42). Duplex imaging is dependent on the skill of the sonographer, the body habitus of the patient, and the presence of bowel gas. If duplex imaging is unable to confirm the hemodynamic severity of ARAS, then noninvasive cross-sectional imaging with computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) is the next option.

The sensitivity and specificity of CTA have been shown to be 90% to 100% and 97% for stenosis >50%. The sensitivity of MRA is 92% to 97%, with specificity of 73% to 93% (42). However, in patients with poor renal function, these tests may be unattractive, as CTA requires the use of iodinated contrast with the associated potential risk for contrast-induced nephropathy (43,44), and MRA requires gadolinium-based contrast, which has been associated with nephrogenic systemic fibrosis (45). MRA is preferred in heavily calcified arteries, which can be a greater challenge for CTA. MRA and CTA are very useful for assessment of renal branching patterns, accessory vessels, and orientation of the vessels.

The affected kidney with unilateral severe ARAS will have a decline in function, while the contralateral nonobstructed kidney will compensate by hyperfiltering, so that no net decline in systemic renal function may be detected. Split renal function is a nuclear imaging technique to assess the impact of hemodynamically significant unilateral ARAS on overall renal function. Split renal function using ^{99m}Tc diethylenetriaminepentaacetic acid renal scintigraphy was performed before and after endovascular therapy for unilateral ARAS. Following successful renal artery stenting, ambulatory systolic and diastolic blood pressures significantly decreased from 145 to 138 mm Hg, diastolic blood pressure decreased from 80 to 77 mm Hg ($p = 0.005$), and the estimated glomerular filtration rate increased in the stented kidney from 22 to 26 ml/min/1.73 m^2 and normalized in the hyperfiltering, nonstenotic kidney from 37 to 34 ml/min/1.73 m^2 ($p < 0.026$) (46). This technique may be helpful in determining who may benefit from revascularization when a significant unilateral stenosis is detected but glomerular filtration rate is normal and entails very little risk to the patient. The noninvasive measurements should be performed prior to invasive measurements.

INVASIVE STENOSIS ASSESSMENT. Digital subtraction angiography is a two-dimensional imaging modality that suffers from relatively poor discrimination of renal artery lesion severity because these stenoses are often located in tortuous, overlapping arteries. A "string sign," 99% lesion, may be easy to identify, but more commonly there is a mild to moderate aorto-ostial stenosis, whose hemodynamic consequences are uncertain. By consensus of experts, an angiographic ARAS >70% diameter stenosis is severe or significant, and diameter stenoses of 50% to 70% are considered moderately severe, of uncertain hemodynamic significance. For moderately severe stenoses, confirmation of the hemodynamic severity of the RAS is recommended prior to stenting (11). A resting or hyperemic translesional systolic gradient of ≥20 mm Hg, a resting or hyperemic mean translesional gradient of ≥10 mm Hg, or a renal fractional flow reserve (RFFR) ≤0.8 will confirm hemodynamically severe ARAS (11). The translesional pressure gradient should be measured using a nonobstructive catheter or a 0.014-inch pressure wire. Hyperemia may be induced with an intrarenal bolus of papaverine at a dose of 40 mg (47) or an intrarenal bolus of 50 μg/kg dopamine (32). It is important to note that papaverine will precipitate in heparinized saline solutions commonly used for catheterization laboratory flush solutions.

Investigators have shown that a ratio of aortic and translesional pressures (Pd/Pa) demonstrates a threshold for hemodynamically significant with ipsilateral renal vein renin release. hemodynamic gradients. Renal artery Pd/Pa and ipsilateral selective renal vein renin measurements were made with incremental renal artery balloon inflation to simulate an arterial obstruction. When the resting Pd/Pa ratio was >0.9, there was no ipsilateral renin release, but when the resting Pd/Pa ratio was <0.9, ipsilateral renin was released, with a maximal increase noted with Pd/Pa ratio ≤0.5 (48).

We compared conventional angiography with RFFR and with translesional pressure gradients to determine ARAS stenosis severity (47). There was a poor correlation between the angiographic stenosis and RFFR ($r = -0.18$; $p = 0.54$) as well as to the translesional pressure gradient ($r = 0.22$; $p = 0.44$). However, the correlation between RFFR and the resting translesional pressure gradient was excellent ($r = 0.76$; $p = 0.0016$).

TABLE 1 Current Society for Cardiovascular Angiography and Interventions Appropriate Use Criteria and American Heart Association/American College of Cardiology Recommendations (11,35,39)

Scenario	SCAI Appropriate Use Criteria	AHA/ACC Recommendations
Cardiac disturbance syndromes (flash pulmonary edema, unstable angina, or ACS) with hypertension with moderate RAS with a resting translesional mean gradient of ≥10 mm Hg and/or severe RAS	Appropriate	Class I, Level of Evidence: B; Class IIa, Level of Evidence: B (unstable angina)
CKD stage IV with bilateral moderate RAS with a resting translesional mean gradient of ≥10 mm Hg with a kidney size >7 cm in pole-to-pole length	Appropriate	Class IIa, Level of Evidence: B
CKD stage IV and global renal ischemia (unilateral severe RAS with a solitary kidney or bilateral severe RAS) without another explanation	Appropriate	Class IIb, Level of Evidence: B
Resistant hypertension (uncontrolled hypertension having failed maximally tolerated doses of at least three antihypertensive agents, one of which is a diuretic agent) and bilateral or solitary severe RAS	Appropriate	Class IIa, Level of Evidence: B
Recurrent CHF with unilateral moderate RAS with a resting translesional mean gradient of ≥10 mm Hg	May be appropriate	Class I, Level of Evidence: B
Resistant hypertension (uncontrolled hypertension having failed maximally tolerated doses of at least three antihypertensive agents, one of which is a diuretic agent) and unilateral severe RAS	May be appropriate	Class IIa, Level of Evidence: B
Asymptomatic, unilateral, bilateral, or solitary kidney with hemodynamically significant RAS	Rarely appropriate	Class IIb, Level of Evidence: C

ACC = American College of Cardiology; ACS = acute coronary syndrome; AHA = American Heart Association; CHF = congestive heart failure; RAS = renal artery stenosis; SCAI = Society for Cardiovascular Angiography and Interventions.

Limitations to conventional angiography include radiation exposure and the use of iodinated contrast, which poses a risk for potential contrast-induced nephropathy similar to CTA in patients with decreased renal function. Adequate hydration and limiting contrast volume are helpful in preventing the development of contrast-induced nephropathy (49). If the risk for exposure to iodinated contrast is deemed prohibitive, then CO_2 angiography may be a safer option (50), acknowledging that because CO_2 is a negative contrast agent, bowel gas and motion artifact can compromise image quality (50,51).

TREATMENT OF ARAS

INDICATIONS FOR REVASCULARIZATION (GUIDELINES AND AUC). Patients most likely to benefit from revascularization. The American College of Cardiology and American Heart Association guidelines and SCAI AUC recommend that patients most likely to benefit from renal artery stenting have hemodynamically significant ARAS and 1) recurrent CHF or sudden-onset, "flash," pulmonary edema (Class I, Level of Evidence: B; AUC: appropriate). Patients with hemodynamically significant ARAS with refractory ACS (Class IIa, Level of Evidence: B; AUC: appropriate); 2) those with refractory HTN who fail or are intolerant of GDMT (Class IIa; Level of Evidence: B; AUC: appropriate) (32); and 3) patients with progressive CKD due to bilateral or solitary ARAS (Class IIa; Level of Evidence: B; AUC: appropriate), or with unilateral ARAS (Class IIb; Level of Evidence: C; AUC: appropriate) (10,11,39) (Table 1).

Patients not likely to benefit from revascularization. There is no indication for the treatment of ARAS in asymptomatic patients (11). The initial treatment of symptomatic ARAS, as demonstrated in the CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial, is GDMT (6). When evaluating a patient with ARAS, it is important to determine whether his or her symptoms are caused by renal hypoperfusion or if ARAS is an innocent bystander. ARAS may be found on routine abdominal imaging when evaluating a patient for other problems. However, if ARAS is not causing a clinical problem, there is no role for revascularization. Also not likely to benefit from renal artery stenting are patients with uncontrolled blood pressure who are not on maximally tolerated GDMT including a total of 3 antihypertensive agents, including a diuretic agent. Last, patients with ischemic nephropathy unlikely to benefit from revascularization include those with chronic CKD stage III to stage IV and a pole-to-pole kidney size of ≤7 cm or

TABLE 2 Summary of Recent Trials

Trial	STAR	ASTRAL	CORAL
Year	2009	2009	2014
Number of patients	140	806	947
Inclusion criteria	Impaired renal function (CrCl <80) Ostial ARAS of ≥50% (CTA, MRA, DSA) Controlled BP <140/90 mm Hg	Renal artery atherosclerotic disease in ≥1 renal artery amenable to revascularization Clinician unsure if revascularization would provide clear benefit	Severe RAS angiographically defined as ≥60% but <100%, and hypertension with systolic BP ≥155 mm Hg on ≥2 agents or CKD defined as GFR <60 ml/min/1.73 m^2
Exclusion criteria	Renal size <8 cm Renal artery <4 mm CrCl <15 Diabetes with proteinuria >3 g/day Malignant hypertension	Disease needing surgical revascularization High likelihood of needing revascularization in 6 months Nonatheromatous disease Prior RAS revascularization Lack of informed consent	FMD CKD from causes other than ischemic nephropathy Cr >4 Kidney size <7 cm Lesions that could not be treated with 1 stent
Primary endpoint	Worsening renal function >20% decrease of CrCl	Slope of the reciprocal of Cr over 5 yrs	Time to major renal or cardiovascular event (stroke, heart attack, CHF hospitalization, progressive renal insufficiency, need for dialysis)
Limitations	Patients had controlled BP Considerable number of participants had <50% stenoses	Rate of complications much higher than reported Smaller number of antihypertensive agents used in intervention group Diagnosis of RAS made with noninvasive imaging without functional studies Patients with kidney size <6 cm included in study Patients with insignificant lesions included	Patients were not optimized on antihypertensive therapy Inclusion of patients with mild stenosis Only moderate correlation between angiography and hemodynamically significant stenoses

ARAS = atherosclerotic renal artery stenosis; BP = blood pressure; CKD = chronic kidney disease; Cr = creatinine; CrCl = creatinine clearance; CTA = computed tomographic angiography; DSA = digital subtraction angiography; FMD = fibromuscular dysplasia; GFR = glomerular filtration rate; MRA = magnetic resonance angiography; other abbreviations as in Table 1.

patients on hemodialysis for ≥3 months (10,11) (Table 1).

CONTEMPORARY TRIALS

NONRANDOMIZED TRIALS. There have been multiple nonrandomized clinical trials evaluating the outcomes of renal artery stenting in ARAS. In the ASPIRE-2 (Evaluation of the Safety and Effectiveness of Renal Artery Stenting After Unsuccessful Balloon Angioplasty) study, balloon-expandable stents were used as a revascularization strategy after balloon angioplasty failed to achieve <50% stenosis in patients with aorto-ostial ARAS causing HTN. Systolic and diastolic blood pressure decreased from 168 ± 25/82 ± 13 mm Hg to 149 ± 25/77 ± 12 mm Hg at 24 months ($p < 0.001$) (1). A safety and effectiveness study of the HERCULES (Herculink Elite Renal Stent to Treat Renal Artery Stenosis) trial also demonstrated a significant reduction in systolic blood pressure in patients with significant ARAS and uncontrolled HTN (mean 3.4 hypertensive medications) who underwent renal artery stenting. Brain natriuretic peptide was also measured in this series and was not predictive of a reduction in blood pressure after renal artery stenting (3).

RANDOMIZED TRIALS. There have been 3 recent RCTs investigating renal artery stenting for ARAS. STAR (Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function: A Randomized Trial) enrolled patients with ARAS with stenoses >50% and creatinine clearance <80 ml/min/1.73 m^2. GDMT alone was compared with GDMT and renal artery stenting, and renal artery stenting had no effect on progression of CKD; however, a major limitation of this study was that 30% of the patients randomized to the revascularization arm had ARAS <50% and were not candidates for revascularization (4). The ASTRAL (Angioplasty and Stenting for Renal Artery Lesions) trial reported no benefit of revascularization over medical therapy with regard to blood pressure, renal function, cardiovascular events, or mortality. However, the revascularization group was on fewer antihypertensive medications than the medical group (2.77 vs. 2.97; $p = 0.03$). The major criticisms include that only 60% of the patients had >70% ARAS, using only ultrasound as the modality used to measure the severity of stenosis, so that many of the patients in the trial may not have been candidates for revascularization (5,7).

The CORAL trial enrolled patients with HTN, defined as systolic blood pressure of ≥155 mm Hg

despite taking ≥2 antihypertensive medications, which by definition included patients without refractory HTN. Because the hemodynamic lesion severity of moderate (50% to 70% diameter stenosis) lesions was not hemodynamically confirmed, it is very likely that patients with nonobstructive ARAS were enrolled in the trial (6).

A 2016 comparative effectiveness analysis concluded that there was low strength of evidence for the relative benefits and harms of percutaneous transluminal renal artery balloon angioplasty and renal artery stenting versus GDMT alone in patients with ARAS (9). The CORAL trial as well as the ASTRAL trial demonstrated that in patients with moderate ARAS (50% to 70% diameter stenosis) and unconfirmed hemodynamic severity of RAS and HTN, there was no benefit of revascularization over GDMT alone. In both of these trials, many patients had moderate or indeterminate degrees of ARAS. As pointed out in the Agency for Healthcare Research and Quality comparative effectiveness statement on renal artery stenting, selection bias may have prevented the enrollment of patients who would likely benefit from revascularization, that is, those with very severe stenoses and uncontrolled blood pressure, recurrent sudden-onset, "flash" pulmonary edema, or refractory HTN (6,7,9). There may well have been equipoise for patients with borderline, uncertain ARAS permitting their randomization, but there may not have been equipoise for patients with the most severe ARAS. This is a common problem for many RCTs, which could have been addressed with a parallel registry but unfortunately was not (6).

In a meta-analysis of 678 patients, the renal artery stenting procedure success rate was 98%, but clinical improvement in HTN was only about 70%, and improvement in renal function occurred in 30% of patients, with stabilization in 38% (52). These discrepant data suggest that either non-flow-limiting ARAS lesions were treated or their symptom of HTN or CKD was unrelated to the ARAS (**Table 2**).

RENAL REVASCULARIZATION TECHNIQUE

Early attempts to revascularize ARAS were limited to renal artery bypass surgery. Because of the associated morbidity and mortality of open surgery, renal artery stenting is now the preferred technique. Because ARAS is often due to bulky aorto-ostial plaque, balloon angioplasty alone is frequently ineffective because of the recoil associated with these bulky plaques, making renal artery stenting the preferred method of treatment (53).

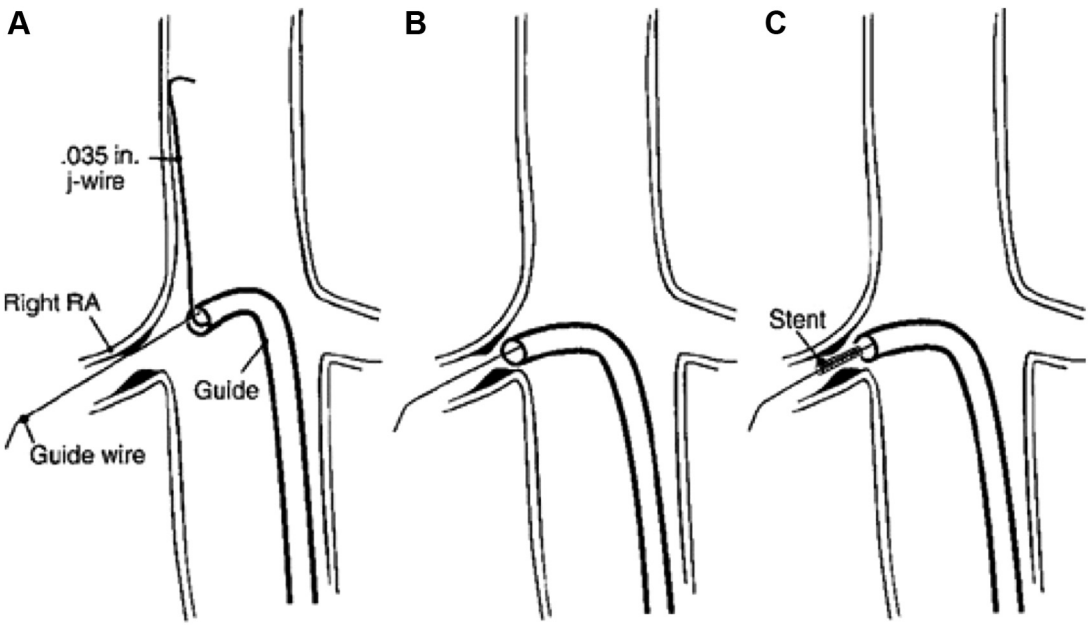
MINIMIZING COMPLICATIONS. For renal artery stenting performed by experienced operators, the complication rate approaches 2%, with the most common complications related to femoral access (hematoma, pseudoaneurysm, arteriovenous fistula), but atheroembolism, retroperitoneal hematoma, renal artery rupture, aortic and renal artery dissection, contrast nephropathy, renal infarction, and death have also been reported (1,11). Some technical issues one should consider in order to reduce complications include radial artery vascular access, embolic protection devices (EPDs), catheter-in-catheter technique, no-touch technique, stent sizing with intravascular ultrasound (IVUS), and hydration before and after angiography is performed.

VASCULAR ACCESS. Careful vascular access should be performed, though there should be strong consideration for radial artery access. Radial artery access is associated with reduced vascular access bleeding complications and patient discomfort compared with femoral access (54). For renal intervention, either radial artery may be used. The left radial artery may have a shorter distance to the renal arteries depending on aortic arch tortuosity and therefore may be preferred in taller patients, but the right radial artery is more comfortable and exposes the operator to less radiation. More recently, the use of distal left radial access in the anatomic snuffbox has been proposed to allow ergonomically easier access of the left radial artery. This provides more patient and operator comfort for the procedure (55). In patients with tortuous aortas or taller patients, the use of standard 100-cm-long guide catheters and 135-cm-long balloon or stent catheters may need to be replaced with 125-cm-long guiding catheters and 150-cm balloon or stent catheters (56).

ATHEROEMBOLISM REDUCTION. Atheroembolism can complicate renal artery stenting, leading to increased morbidity and a significant decrease in 5-year survival (54% vs. 85%; $p = 0.011$) compared with patients with no evidence of periprocedural atheroembolization (57). Some suggested ways to prevent atheroembolism are EPDs as well as the no-touch technique during intervention. EPDs have been investigated in renal artery interventions to mitigate the risk for atheroembolism, particularly in patients with reduced renal function.

A small ($n = 100$) RCT compared four groups, renal stent alone, stent plus an EPD, stent plus a glycoprotein IIb/IIIa inhibitor, and stent with both an EPD and a glycoprotein IIb/IIIa inhibitor, and demonstrated that stenting alone, stenting plus EPD, and stenting plus the glycoprotein IIb/IIIa inhibitor

FIGURE 1 **No-Touch Technique**



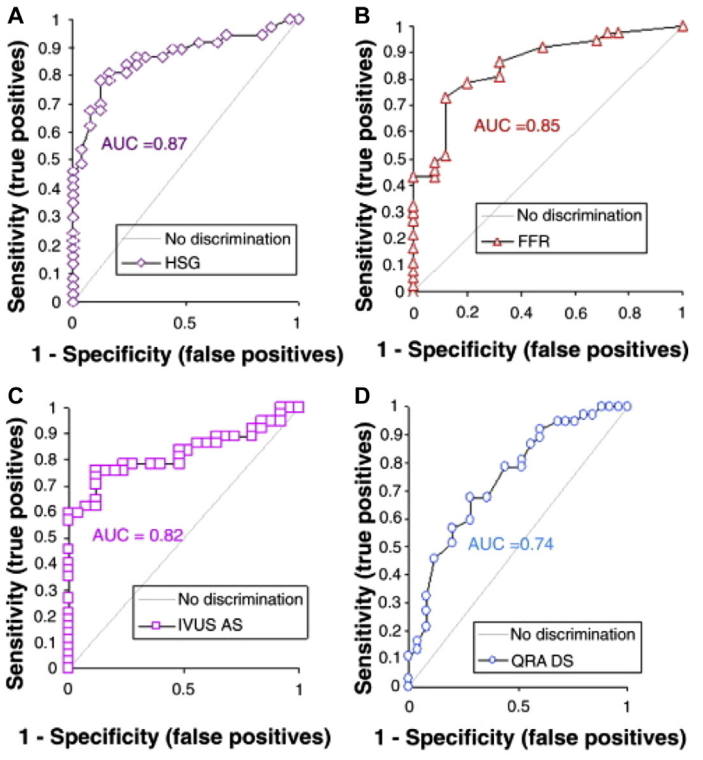
Placing a 0.035-inch J-wire through the guiding catheter helps prevent the guide from scraping the aortic wall and minimizes the risk for plaque embolization. A 0.035-inch J-wire is placed through the guide catheter during initial engagement **(A)**. The entire system is cleared of blood and debris and flushed with saline prior to the guide catheter reaching the level of the renal artery (RA). The 0.035-inch guidewire prevents the guide catheter from scraping the wall of the abdominal aorta. When the renal artery is engaged, a guidewire is inserted alongside the 0.035-inch J-wire and advanced into the target vessel **(A)**. Once the guidewire is in position across the target lesion, the 0.035-inch guidewire is removed **(B)**, and the percutaneous intervention is completed according to conventional techniques **(C)**. Reprinted with permission from Feldman et al. (60).

showed no benefit. In the group that received the stent with both the EPD and the glycoprotein IIb/IIIa inhibitor, there appeared to be a benefit with no decline in renal function ($p < 0.01$) (58).

Angiographic renal frame counts (RFCs), which are a surrogate marker for renal blood flow (the lower the RFC the better), were measured both before and after renal artery stenting. The before and after RFCs in the control group were 30.4 ± 12.1 and 23.7 ± 9.9 ($p = 0.002$) and in the EPD group 42.6 ± 12.6 and 28.3 ± 9.2 ($p < 0.0001$). The EPD group had a greater improvement in RFC (14.2 ± 15.2 vs. 6.7 ± 11.7; $p = 0.03$) compared with the control group, suggesting that EPD may be effective in preventing renal atheroembolic injury (59). There are insufficient data to recommend routine use of EPDs and glycoprotein IIb/IIIa inhibitors, but they may be considered in patients with renal insufficiency as a strategy to prevent worsening renal function related to atheroembolism as a result of renal artery stenting.

To prevent catheter manipulation and embolization of plaque within the aorta, no-touch and catheter-in-catheter techniques have been proposed. Before proceeding with either technique, selective renal angiography should be preceded by nonselective abdominal aortography to identify accessory renal arteries unless CTA or MRA has been performed. The no-touch technique requires a 0.035-inch J-wire resting on the wall of the aorta during engagement of the renal artery. This J-wire prevents the tip of the guide catheter from scraping the wall of the aorta during maneuvering. Once the artery is engaged, an angioplasty guidewire is introduced with the J-wire and advanced past the target lesion and, the J-wire is then removed (60). The catheter-in-catheter approach is also used to prevent excessive manipulation. In this technique a 4- or 5-F diagnostic catheter is placed inside a guiding catheter that is 2-F larger. Once cannulation of the renal artery is achieved, a 0.014-inch wire is used to cross the target lesion, and the guide is then advanced over the diagnostic catheter. When the guide is in correct position, the diagnostic catheter is removed (61) (**Figure 1**).

FIGURE 2 Chart Showing Sensitivity and Specificity Among Invasive Measurements to Determine Hemodynamic Significance and Improvement of Blood Pressure After Stenting



AUC = area under the curve; FFR = fractional flow reserve; HSG = hyperemic systolic gradient; IVUS AS = intravascular ultrasound assessment; QRA DS = renal angiography diameter stenosis. Reproduced with permission from Leesar et al. (63).

STENT SIZING WITH IVUS. Oversizing stents leads to increased procedural complications, and undersizing stents increases restenosis (62). The use of IVUS offers a more precise measurement of vessel luminal diameter than two-dimensional angiography, which improves the operator's ability to safely maximize stent size. IVUS enhances better stent apposition and can reduce the amount of contrast used. However, the use of IVUS is not a current recommendation, because it has not been proved to improve outcomes in renal stenting (63).

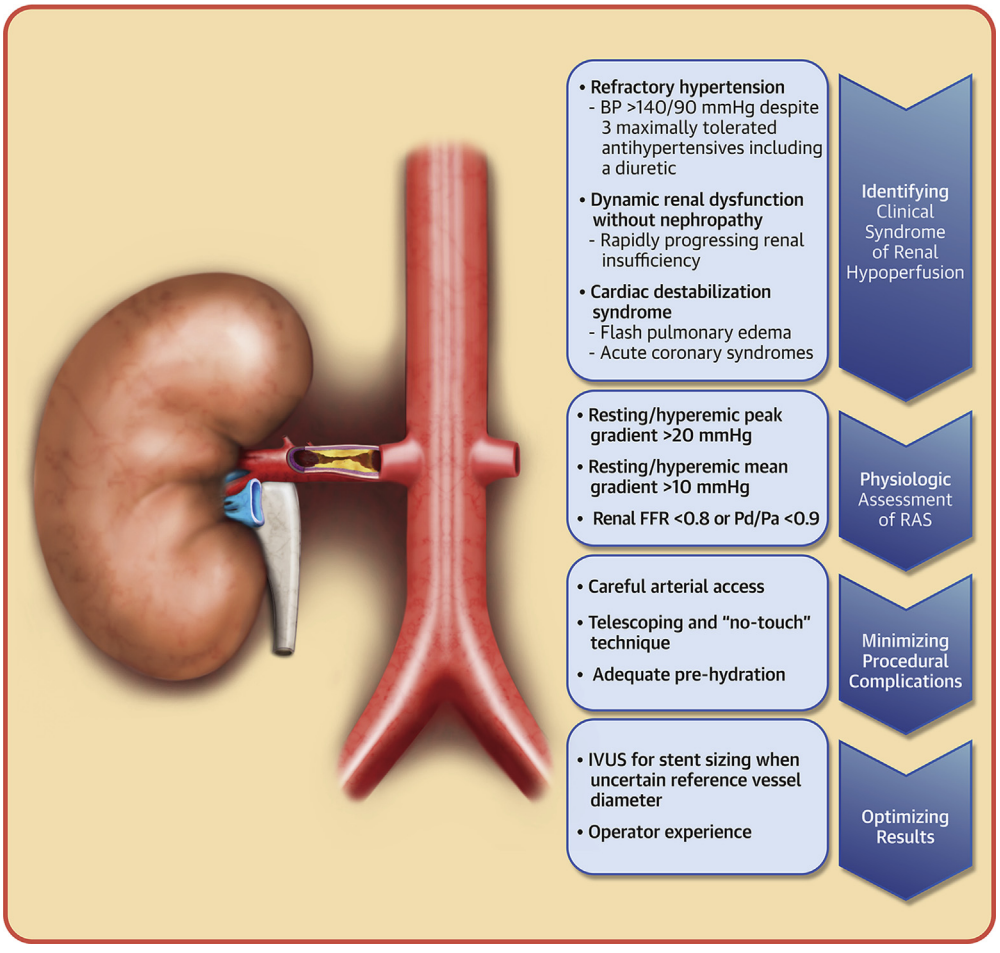
EFFECTS OF INTERVENTIONS ON OUTCOMES. There appears to be no effect of renal artery stenting on blood pressure, renal function, cardiac destabilization syndromes, and outcomes (death, renal failure) according to the recent RCTs. However, the Agency for Healthcare Research and Quality comparative effectiveness document suggests that there is low strength of evidence and that these trials are applicable only to patients for whom there is clinical equipoise between the 2 treatments. There were many flaws in these trials, including extraordinary variability in inclusion and exclusion criteria, inconsistent definitions of improvement, and mixtures of HTN and renal endpoints. There have been many observational trials suggesting that patients in need of renal artery revascularization (worsening renal function, refractory HTN despite medical therapy, or flash pulmonary edema) are more likely to improve blood pressure and renal function after stenting (9).

BLOOD PRESSURE IMPROVEMENT. Determining which patients' blood pressure will improve with renal artery stenting has been controversial. Investigators have described a threshold translesional resting or hyperemic mean gradient of >10 mm Hg associated with improved blood pressure after renal artery stenting (32). A hyperemic systolic gradient (HSG) of ≥21 mm Hg predicted better blood pressure response after renal artery stenting, for which it was noted that 84% patients with HSGs ≥21 mm Hg had significantly improved blood pressure, whereas only 36% of patients with HSGs <21 mm Hg had significant changes in blood pressure at 12 months ($p < 0.01$). It was also noted that patients with HSGs ≥21 mm Hg were controlled on fewer blood pressure medications after renal artery stenting, 2.30 ± 0.90 versus 3.40 ± 0.50 for patients with HSGs <21 mm Hg ($p < 0.01$) (63). Abnormal RFC and renal blush grade have been reported to predict blood pressure improvement after renal artery stenting (64,65). RFFR <0.8 has also been correlated with improvement in blood pressure after renal artery stenting (31,33) (**Figure 2**).

Four-year follow-up of 1,058 successful renal artery stenting patients demonstrated significant improvement in systolic (168 ± 27 to 147 ± 21 mm Hg; $p < 0.05$) and diastolic (84 ± 15 to 78 ± 12 mm Hg; $p < 0.05$) blood pressures, and the number of antihypertensive medications also significantly decreased (2.4 ± 1.1 to 2.0 ± 1.0; $p < 0.05$). Renal function also improved, as serum creatinine significantly declined (1.7 ± 1.1 to 1.3 ± 0.8 mg/dl; $p < 0.05$). Overall survival was 74 ± 3% at 4 years (66).

In a post hoc analysis of the CORAL trial, it was noted that when renal artery stenting was performed in patients with urine albumin/creatinine ratios of ≤22.5 mg/g, there was better event-free survival (73% vs. 59%; $p = 0.02$), lower cardiovascular disease-related death (85% vs. 93%; $p \leq 0.01$), less ongoing renal failure (77% vs. 91%; $p = 0.03$), and higher overall survival (89% vs. 76%; $p \leq 0.01$) (67).

CENTRAL ILLUSTRATION **Flow Chart to Identify, Determine Significance, Minimize Complications, and Maximize Results**



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BP = blood pressure; FFR = fractional flow reserve; IVUS = intravascular ultrasound; RAS = renal artery stenosis.

CARDIAC DESTABILIZATION OUTCOMES. We reported outcomes in 48 patients with HTN refractory to medical therapy (blood pressure ≥140/90 mm Hg despite 3 maximally tolerated antihypertensive medications including a diuretic agent) and severe ARAS (>70% diameter stenosis) who presented with ACS (n = 20) or decompensated CHF (n = 28) and underwent successful renal artery stenting (68). Regardless of any coronary revascularization, renal artery stenting improved the clinical status of 88% (42 of 48). In patients with ACS, angina class improved significantly (3.1 ± 1.8 to 1.5 ± 0.9; $p < 0.05$), with an improvement in blood pressure, and in the patients with CHF, New York Heart Association class improved (2.8 ± 0.9 to 1.7 ± 1.2; $p < 0.05$), also with a significant improvement in blood pressure. After 8 months of follow-up, sustained improvement was present in 72.5% (29 of 40). The mean angina class, New York Heart Association CHF class, blood pressure, and number of cardiac medications all improved at the time of follow-up (68).

These results, in cardiac destabilization syndromes, were confirmed in 207 patients with decompensated CHF from the Cleveland Clinic, 19% of whom were found to have severe ARAS. Successful renal artery stenting resulted in a significant decrease in CHF admissions, diminished CHF symptoms, reduced incidence of sudden-onset pulmonary edema, and better tolerance of angiotensin-converting enzyme inhibitors (38).

ISCHEMIC NEPHROPATHY OUTCOMES. The reversibility of ischemic nephropathy with renal artery stenting remains a topic of debate. Because many patients with ARAS also have other comorbidities such as diabetes and essential HTN, which adversely affect renal function, it is difficult to determine if revascularization will improve renal function. There are many reports of improved renal function with renal stenting (41,69-72) but also some reports of worsening renal function after renal artery stenting (73-75). In some patients with end-stage renal disease, successful renal artery stenting permits discontinuation of dialysis treatments (76). There are currently no randomized control trials indicating benefit of renal artery stenting over medical therapy for improvement of renal function.

POST-RENAL ARTERY STENTING FOLLOW-UP. There are no standards for duplex or imaging follow-up unless mandated clinically and no standards for repeat revascularization for in-stent restenosis (ISR). When duplex imaging is performed after renal stent placement, it is necessary to adjust the velocity parameters for a stented artery compared with a native vessel, as decreased compliance due to the stent will result in higher velocities (42). ISR of >70% can be confirmed with PSV >395 cm/s (77). If duplex suggests restenosis, one should confirm the recurrence of clinical symptoms before reintervention is performed (42). If duplex imaging is inconclusive, CTA would be the next best test for determining stent patency. The quality of MRA is affected by metal artifact (78). If ultrasound and CTA are still inconclusive and the patient has recurrent clinical symptoms, angiography with hemodynamic confirmation of the severity of the ISR is indicated.

RESTENOSIS. Restenosis as a measure of continued patency could be improved with optimal stent sizing. Larger diameter target vessels with a larger acute gain (post-stent minimal luminal diameter) yield lower restenosis rates than smaller diameter vessels with smaller acute gain. In a series of 363 patient undergoing renal artery stenting, with 102 (34%) having 1-year follow-up angiography, the restenosis rate was 36% for vessels with diameters <4.5mm, 16% for vessels with diameters of 4.5 to 6 mm ($p = 0.068$), and 6.5% in vessels with diameters >6 mm ($p < 0.01$) (62). Bare-metal stents (BMS) have excellent long-term patency rates, demonstrating a 5-year primary patency rate of ≥80% and a secondary patency rate of ≥90% (79).

ISR. If there is a concern about ISR, CTA is preferred to avoid the metal artifact that affects the quality of MRA (78,80). Repeat stenting is the preferred technique over balloon angioplasty alone, as there was a 58% reduction in recurrent restenosis ($p = 0.02$) (81). The treatment of recurrent ISR was evaluated in 31 patients with at least their second occurrence of ISR. Seven lesions were treated with balloon angioplasty alone, 7 were treated with BMS, 6 lesions were treated with covered stent, 3 lesions were treated with cutting balloons, and 10 lesions were treated with oversized coronary drug-eluting stents. The restenosis rates were 71% in the balloon angioplasty group, 43% in the BMS group, 18% in the covered stent group, 100% in the cutting balloon group, and 0% in the drug-eluting stent group. The only significant predictor of recurrent ISR was the use of a cutting balloon ($p < 0.0001$), which was ineffective (82). Covered stents have been used for intraprocedural complications such as perforation or vessel rupture (83). The caveat to keep in mind with the use of coronary DES, with thinner struts than peripheral stents, is the risk for stent compression due to the bulky nature of renal artery plaque.

CONCLUSIONS

For symptomatic ARAS in patients in whom GDMT fails, that is, those patients with hemodynamically significant RAS causing resistant (refractory) HTN despite GDMT, those with declining renal function, and those with cardiac destabilization syndromes are reasonable candidates for renal artery stenting. Screening with duplex ultrasound, CTA, or MRA is recommended. A moderately severe (indeterminate) ARAS stenosis (50% to 70%) should have the lesion's hemodynamic significance confirmed. Renal artery stenting with an optimally sized BMS is the revascularization procedure of choice. Overall this is a safe and effective treatment for patients most likely to benefit, with a procedure complication risk of about 2% in experienced hands. Treating hemodynamically significant ARAS in patients with the indications described here results in better blood pressure control and better clinical outcomes (**Central Illustration**). However, this hypothesis has not been proved in any RCT, because of limitations in trial design (8,9,84). In the current era, in which objective evidence of end-organ ischemia is the main driver of revascularization, we have no reason to believe the renal vasculature should be treated differently.

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KEY WORDS **renal artery stenosis, renovascular hypertension, stent**