The 3 clinical syndromes related to atherosclerotic renal artery stenosis (RAS) are (1) renovascular hypertension; (2) ischemic nephropathy; and (3) cardiac disturbance syndromes (ie, sudden-onset pulmonary edema, refractory heart failure, or unstable angina). Clinical improvement after treatment of RAS will depend on the efficacy of reperfusion and the safety of the procedure. Controversy exists among experts regarding the most appropriate utilization of percutaneous renal intervention (PRI) as the treatment for significant RAS. Despite the acknowledged uncertainty in this area, clinicians must make treatment decisions for patients who are considered potential candidates for revascularization of atherosclerotic RAS.

Procedural efficacy is defined by both technical and clinical end points. Technical success occurs when stent deployment results in anatomic and physiological relief of the obstruction to renal blood flow. Progressive equipment and device evolution (including down-sizing from the peripheral vascular 0.035-in systems to the coronary 0.014-in systems and new renal guiding catheter shapes) and advanced balloon-expandable stent designs (many are off-label devices Food and Drug Administration-approved for other anatomic regions) have led to excellent technical success rates for PRI in the hands of skilled operators (Table 1).

A key principle is that clinical benefit from PRI will result from correcting renal hypoperfusion caused by significant RAS. Published meta-analyses suggest that a high PRI technical success rate (>95%) is accompanied by surprisingly modest and inconsistent clinical improvement. The discordance between the high technical success and the inconsistent clinical response to revascularization suggests that (1) successful PRI procedures were performed on nonobstructive RAS (not causing symptomatic renal hypoperfusion); or (2) that the clinical syndrome being treated was not caused by renal hypoperfusion. Improvement in discriminating ischemia-producing RAS lesions from nonschemia-producing lesions would be expected to increase the clinical response rate of PRI.

The purpose of this article is to review recent developments that may help to guide the clinical practice of PRI by improving case selection of significant RAS and to optimize procedural techniques aimed at improving safety for patients undergoing catheter-based therapy of renovascular disease.

### Procedural Efficacy

#### Hypertension

The current American Heart Association/American College of Cardiology guideline indications for PRI in hypertensive patients with hemodynamically significant RAS and a viable kidney (linear length $>7$ cm), includes (1) accelerated hypertension; (2) refractory hypertension (failure of 3 appropriate drugs, 1 of which should be a diuretic); (3) hypertension with a small kidney; or (4) hypertension with intolerance to medications (class IIa, level of evidence B). By convention, a hemodynamically significant lesion requires demonstration of a $\geq 70\%$ RAS by visual estimation, $\geq 70\%$ RAS by intravascular ultrasound measurement, or a $50\%$ to $70\%$ RAS with a systolic gradient of $\geq 20$ mm Hg or a mean gradient of $\geq 10$ mm Hg.

#### Angiographic Assessment

The “Achilles heel” of PRI is the inaccuracy of the angiographic determination of the severity of RAS. The traditional “gold” standard for determining the severity of RAS has been invasive angiography. Even with quantitative measurement, angiography may be unable to discriminate between nonobstructive RAS and clinically significant RAS (Figure 1). Most would agree that interventionalists are able to identify “critical” stenoses in renal arteries, but for mild to moderately severe RAS, physiological confirmation is necessary.

Atherosclerotic RAS usually involves the ostial and proximal portion of the main renal artery. These lesions are morphologically complex and can be difficult to visualize with 2D angiography. The errors made with angiography are increased when interventionalists rely on “visual estimation” as the only means to determine lesion severity. Under the best of circumstances, visual estimation of angiographic stenoses lacks reproducibility and precision (Figure 2).

There has been interest in angiographic measurements of renal blood flow by using renal frame counts (RFC) and renal blush grades for microvascular flow. Healthy patients can be differentiated from patients with fibromuscular dysplasia of the renal arteries with RFC (Figure 3). Building on that work, Mahmud et al confirmed that hypertensive patients with RAS have decreased renal perfusion as measured by RFC and renal blush grades. They were able to separate hypertensive patients without RAS (RFC=$20.1\pm5.4$) from...
hypertensive patients with RAS (RFC=26.6±9.1) that normalized following stent placement (RFC=21.4±6.7) (Table 2).19 Clinical responders tended to have higher baseline RFCs than nonresponders and had greater improvement in their RFC values after PRI. Three quarters of the blood pressure responders had a baseline RFC ≥25, and if the RFC improved by >4, then 79% were responders to PRI.

Biomarkers

The original biomarker for renovascular hypertension was renin. Renin may be measured invasively, from the renal veins or in peripheral blood, usually after a stimulatory test with captopril. Although renin release is a result of hypoperfusion of the kidney, it has been a difficult tool to use in clinical practice. Measurements of plasma renin activity have been plagued by a lack of sensitivity and specificity for renovascular disease.20 Invasive renal vein renin measurements can detect unilateral increases of renin, but to improve accuracy, all medications that affect renal renin secretion must be stopped for weeks, including all antihypertensive agents, diuretics, and nonsteroidal anti-inflammatory drugs. Renin measurement is further complicated by the patient’s volume status, the degree of renal insufficiency, and whether they have unilateral or bilateral disease. Selective renal vein renin measurements were used to demonstrate a threshold pressure gradient for renin release (Figure 4).21 However, there remain too many confounders in clinical medicine to support the use of renin in everyday practice.

Brain natriuretic peptide (BNP) is a neurohormone released from the myocardium under conditions of myocardial volume or pressure overload.22–24 BNP promotes diuresis, natriuresis, arterial vasodilation, and antagonizes renin.22 BNP is increased in patients with renovascular hypertension, with activation of the renal angiotensin system and the release of angiotensin II. BNP is increased in patients with severe (>70%) RAS and an increased BNP level of >80 pg/mL correlated with a blood pressure response to PRI.25

These data are supported by results from the Renal Artery Angioplasty in Patients with Renal Insufficiency and Hypertension Using a Dedicated Renal Stent Device (PRECISION) study in which 55 patients with severe RAS were treated with a new stent.26 The baseline BNP was increased at 251±282 pg/mL (range, 5 to 1300) and significantly decreased after successful intervention to 188±219 pg/mL (range, 10 to 758; P=0.046). There was a trend for higher levels of BNP in blood pressure responders (BNP=202±240) compared with patients who did not respond (BNP=85±89, P=0.2).

Hemodynamic Assessment

The important work of De Bruyne et al21 established a firm in vivo relationship between a threshold hemodynamic gradient (Pd/Pa <0.9) and ipsilateral renal vein renin release (Figure 4) and provided a fundamental understanding of the threshold hemodynamic value for RAS. The next step, to close the loop, will be to show that patients with Pd/Pa <0.9 have a reduction in blood pressure after successful PRI.

<table>
<thead>
<tr>
<th>Table 1. Technical Success Rate and Complications of PRI</th>
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<td>Reference</td>
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</tr>
<tr>
<td>Tuttle et al5</td>
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<tr>
<td>Rocha-Singh et al6</td>
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<td>Blum et al6</td>
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<tr>
<td>White et al8</td>
</tr>
<tr>
<td>Dorros et al9</td>
</tr>
<tr>
<td>Ivanovic10</td>
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<tr>
<td>Zeller11</td>
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<td>Total/average</td>
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Major Comp indicates major complication (death, myocardial infarction, emergency surgery, need for dialysis, or blood transfusion).

Figure 1. There is a poor correlation of quantitative angiographic diameter stenosis with baseline mean translesional pressure gradient (BPG; left), hyperemic mean translesional pressure gradient (HPG; middle) and renal fractional flow reserve (right). Reprinted from Catheterization and Cardiovascular Intervention, vol 64, Subramanian R, White CJ, Rosenfeld K, Bashir R, Almagor Y, Meerkin D, Shalman E, Renal fractional flow reserve: a hemodynamic evaluation of moderate renal artery stenoses, pp 480–486, © 2005, with permission from Wiley-Liss, Inc., A Wiley Company.
Neither resting baseline gradients nor hyperemic pressure gradients were able to separate blood pressure responders from nonresponders after successful PRI in our series. However, we were able to demonstrate that an abnormal renal fractional flow reserve (<0.8) did predict a beneficial blood pressure response after PRI. In contrast, Leesar et al. published a larger series and showed that although renal fractional flow reserve was a useful discriminator, the strongest correlation for blood pressure improvement was the hyperemic translesional pressure gradient. In 62 patients with RAS, who also had angiographic and intravascular ultrasound measurements performed, they found that a hyperemic systolic gradient of >21 mm Hg measured with an 0.014-in pressure wire after intrarenal injection of 30 mg of papaverine was the best predictor of improved blood pressure response after PRI. Hypertension improvement at 1 year occurred in 84% of those with hyperemic pressure gradient of ≥21 mm Hg compared with 36% with a gradient of <21 mm Hg (P < 0.01). Once again, these data need to be validated in a larger series of patients before widespread clinical adoption, but it does seem to be encouraging.

Renal Function Preservation

The current American Heart Association/American College of Cardiology Guideline recommendation for catheter-based therapy to preserve renal function concludes that PRI is reasonable for patients with RAS and progressive chronic kidney disease with bilateral RAS or a RAS to a solitary functioning kidney. (Class IIa, level of evidence B) PRI may also be considered on an individual basis for patients with RAS and chronic renal insufficiency with unilateral RAS (class IIb, level of evidence C).

Patient Selection

Ischemic nephropathy, its incidence and its reversibility, continues to be a source of debate among experts. The number of patients with atherosclerotic RAS requiring dialysis therapy is increasing. Opponents of aggressive revascularization of patients with RAS with renal insufficiency contend that the kidney is supplied with an excess of nutrient blood flow and therefore few kidneys will benefit from revascularization. The literature is replete with patient series in which PRI improves renal function as well as counterbalancing reports of worsening of renal failure after successful PRI. There are no large randomized studies demonstrating benefit of revascularization over medical therapy alone for improving renal function. Unfortunately, there are several poorly done studies such as the recently completed STAR (STent placement and blood pressure and lipid lowering for the prevention of progression of renal dysfunction caused by Atherosclerotic ostial stenosis of the Renal artery) trial. STAR compared PRI plus best medical therapy (BMT) to BMT alone in patients with RAS and impaired renal function. Unfortunately, methodological problems, such as enrolling study patients with mild (<50%) RAS and allowing significant treatment crossover (30% of the stent group did not get a stent) weakened this “intention to treat” trial. The RAS lesions (in both groups) were milder than expected, which means that PRI would not be helpful, and the BMT-only group would not be expected to experience any progressive decline because of the mild nature of the RAS. Once again, as was the case for the DRASTIC (Dutch

![Figure 2. Poor lesion selection: Visual versus QCA for renal angiography: Top: Quantitative angiographic stenosis (Medis, Leiden, Netherlands) compared with visual estimation of peripheral arterial stenosis. Middle: Quantitative angiographic stenosis (Medis, Leiden, Netherlands) compared with quantitative angiographic stenosis (Toshiba). Bottom: Visual estimation of peripheral arterial angiographic stenosis compared with quantitative angiographic stenosis (Toshiba). Reprinted from Journal of American College of Cardiology: Cardiovascular Intervention, vol 2, Safian RD, Madder RD, Refining the approach to renal artery revascularization, pp. 161–174, ©2009, with permission from The American College of Cardiology Foundation and Elsevier.]
Renal Artery Stenosis Intervention Cooperative study group) trial, the methodological errors inflated the benefits of “conservative” therapy and biased this trial against revascularization therapy.

The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial was a randomized comparison of PRI plus BMT versus BMT-alone in patients with the unusual enrollment criteria of having an “uncertain indication” for renal revascularization. The primary end point, loss of renal function measured by the slope of the reciprocal of the serum creatinine level, favored PRI with an improvement of $0.06 \times 10^{-3} \text{ L} \cdot \mu\text{mol}^{-1} \cdot \text{yr}^{-1}$ versus $-0.07 \times 10^{-3} \text{ L} \cdot \mu\text{mol}^{-1} \cdot \text{yr}^{-1}$, 95% CI, -0.002 to 0.13; $P=0.06$). Compared with the BMT-only group, there was a significant reduction in blood pressure medications in the PRI group (2.77 versus 2.97; $P=0.03$).

ASTRAL has serious methodological problems creating a bias against PRI. There was a selection bias that favored enrollment of mild to moderate RAS (41% had ≤70% stenosis and no pressure gradients were used to determine severity of borderline lesions). Almost half (41%) of the patients did not meet the American Heart Association/American College of Cardiology criteria for revascularization (50% to 70% stenosis with a hemodynamic gradient of 20 mm Hg). With the end point progressive loss of renal function, why would enroll a majority of unilateral RAS with 25% of patients having normal renal function and another 15% with mildly impaired renal function? It would be difficult for PRI to make patients with such mild RAS with normally functioning kidneys better. In their intention-to-treat analysis, 17% of the PRI group never received a stent, and 6% of the medical group crossed over to stent, further weakening any benefit from the PRI group. ASTRAL did not use any core laboratories to adjudicate the results of imaging or biological tests, which certainly falls below accepted “best practice” for modern multicenter clinical trials. The major procedural complication rate for the ASTRAL interventionists (9%) was a bit higher (3- to 4-fold higher) than that reported for renal stenting in major trials (Table 1). In summary, the sweeping negative conclusions of the ASTRAL investigators were not supported by their data and should have been restricted to cautioning against PRI in mild RAS lesions.

### Table 2. Renal Frame Count and Renal Blush Grade Before and After PRI

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>RAS Baseline</th>
<th>RAS Stent</th>
</tr>
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<tbody>
<tr>
<td>RFC</td>
<td>20.1±5.4</td>
<td>26.6±9.1</td>
<td>21.4±6.7*</td>
</tr>
<tr>
<td>RBG</td>
<td>2.33±0.66</td>
<td>1.63±0.71</td>
<td>2.13±0.85**</td>
</tr>
</tbody>
</table>

*RBG indicates renal blush grade.

$P<0.001$; $P<0.03$ compared with baseline.
Two European centers demonstrated a dramatic benefit for PRI versus BMT in the patients with the most severe renal disease in a large cohort study.42,43 One center offered patients (n=182) BMT only, and the other center offered PRI plus BMT (n=348). Patients were matched for the degree of renal dysfunction, and outcomes were compared over 5 years. Patients who underwent PRI had a marked reduction in mortality (RR 0.55 [95% CI: 0.34 to 0.88]; \( P = 0.013 \)) by multivariate Cox regression analysis. When analyzed according to the degree of renal impairment, there were striking improvements in renal function after PRI for the patients with moderate to severe renal impairment (Figure 5). The authors concluded that patients with RAS and advanced chronic kidney disease (stages 4 to 5) benefit from PRI with improved renal function and had a survival advantage.

Currently, there are several parameters that suggest that a patient is likely to improve renal function after revascularization. First, there must be an obstructive RAS causing hypoperfusion of the kidney. Patients with rapidly declining renal function, as opposed to those with stable renal failure, have the most to gain from revascularization.34,44 The more renal tissue at risk, the more likely there will be a response or improvement with PRI. Patients with bilateral RAS and solitary kidney RAS are traditionally thought to be most likely to improve. Patients with small kidneys (<7 cm) and those with significant proteinuria are less likely to benefit.45

Contrary to conventional teaching, there is now a significant body of literature supporting revascularization of unilateral RAS to improve renal function.46–48 For chronic renal insufficiency to manifest in a patient with unilateral RAS, there must be impaired function of the nonstenotic kidney resulting in decreased overall renal function. Multiple clinical trials have demonstrated improvement in overall renal function in patients with unilateral RAS.11,26,34 PRI in patients with unilateral RAS has been shown to improve the split-renal function of the stenotic kidney.46,48,49 Hyperfiltration in the nonstenotic kidney was also corrected after successful unilateral PRI, resulting in decreased proteinuria from hyperfiltration on the nonstenotic side.46,48

The rate of decline of renal function, determined as the slope of the regression line of serum creatinine over time, is a strong predictor of benefit with PRI.54 A multivariate analysis demonstrated the only significant predictor of benefit after PRI was the rate of decline of renal function that preceded the procedure. Baseline creatinine, the presence of proteinuria, renal size, and diabetes were not significant predictors of improvement in this study.

**Procedural Safety**

**Vascular Access**

The predominant access site for PRI is the femoral artery. PRI trials report femoral vascular access complications ranging from 4.4% to 28%.7,39,50–52 The most common vascular complication (4.6%) was pseudoaneurysm formation. The adoption of smaller 6 Fr guiding catheters with 0.014-in systems to replace the traditional 8 Fr guiding catheters and larger 0.035-in wire systems should further lower the rate of vascular access complications.

One “secret” among coronary interventionalists wishing to avoid vascular access complications is to use radial artery access. The coronary interventional literature has demonstrated a marked reduction in vascular access complications with radial artery access compared with both brachial and femoral artery access.53 The ability to use 6 Fr guiding catheters for PRI allows the radial artery approach to be a viable option (Figure 6).54 In addition to few vascular access complications, the radial artery approach has other advantages, including increased patient acceptance and improved guiding catheter engagement due to the downward or caudal orientation of most renal arteries. The radial approach does require some investment in time by the interventionalist switching from a femoral approach, as there is a minor learning curve. The undeniable benefit of the radial access
approach, however, is a major reduction in the vascular access-related complications.55

Atheroembolization
Renal atheroembolism in individuals with no aortorenal intervention or surgery performed has been described in autopsy studies in up to 20% of patients with severe atherosclerosis.56 Clinically evident acute atheroembolic renal disease has a dramatically negative effect on prognosis.57,58 However, the majority of atheroembolic renal disease is subclinical rather than acutely catastrophic.59 With the reported frequency of visible atherosclerotic debris recovered after PRI with embolic protection devices (EPDs) well above 50%, it is not surprising that 25% of successfully revascularized kidneys show a decline in renal function.60–68

One approach to reducing renal atheroembolization is to avoid catheter trauma to the aorta or scraping the aorta during engagement of the renal ostium.69 This is particularly relevant for RAS associated with bulky aorto-ostial atheromatous disease. The likelihood of trauma to the aorto-ostial plaque during direct guiding catheter engagement is high. There are 2 approaches to reduce guiding catheter trauma. The first is the telescoping guide or exchange technique, with a 4-Fr diagnostic internal mammary catheter is placed within a 6-Fr guiding catheter, with its tip protruding. The 4-Fr angiographic catheter and the guide catheter are advanced over a 0.035-in wire to the level of the target renal artery. The soft, atraumatic angiographic 4 Fr catheter is used to engage the renal ostium. A guide wire is advanced across the lesion and safely into distal renal artery. The guide catheter is then telescop ed (advanced) over the 4-Fr catheter, allowing the larger catheter to atraumatically engage the renal artery ostium.

The second technique is the “no touch” technique (Figure 7).69 A 0.035-in J-guide wire is advanced into the descending thoracic aorta above the renal arteries. The renal guide catheter is advanced over the J-wire wire until it is near the renal ostium. By gently manipulating (advancing and/or withdrawing) the 0.035-in J-wire in the aorta, the tip of the guide catheter can be steered nearer to the renal artery ostium. When the guide is near the renal artery ostium, a 0.014-in steerable guide wire is advanced through the guide catheter (along side the 0.035-in wire) and exiting the guide catheter near the ostium to enter into the renal artery and cross the stenosis into the distal portion of the renal artery. As the 0.035-in guide wire is withdrawn, the guide catheter will atraumatically engage the renal ostium over the 0.014-in wire.

During carotid stenting, it has been documented that embolic signals are produced with every manipulation of the stenosis.70 The in vitro work of Hiramoto et al71 leaves little doubt that atheroemboli are also a common accompaniment of PRI. Multiple trials and registries describing the performance of the several EPD confirm the high frequency of embolic material that can be recovered during PRI.60–68

There are no EPDs specifically approved for use in the renal artery. Furthermore, there is disagreement among clinical experts and government regulators regarding how much additional data are required to demonstrate the safety and efficacy of EPDs in the kidney. Do we need a randomized
controlled trial to prove that removal of atheroembolic debris is better than allowing atherosclerotic debris to flow downstream to the kidney during PRI? Randomized trials were not necessary to gain approval for carotid EPDs by the Food and Drug Administration and EPDs are a requirement for reimbursement by Medicare. If safety of the devices can be established in registry trials, why not use EPDs to prevent or reduce renal atheroembolization?

A small, nicely done, randomized trial compared 2b3a antiplatelet antagonists, EPDs, both, and neither during PRI. There was no benefit for the EPD or 2b3a antiplatelet agent alone; however, there was benefit for the 2b3a antiplatelet antagonists and the EPD together. The reasons for this interaction are speculative, and because the number of patients studied was small, will require confirmation in larger numbers of patients.

It is interesting to note that in patients with coronary disease, 2b3a antiplatelet antagonists are beneficial for native coronary interventions, whereas the reverse has been true for EPDs. Is it possible that PRI shares elements of both procedures? The aorto-ostial plaque is similar to the bulky plaque found in saphenous vein grafts, and the kidney’s microvascular bed may be sensitive to embolic injury similar to the native coronary arteries. Further work in this area is needed; however, it is tempting to offer patients with underlying renal dysfunction (estimated glomerular filtration rate ≤60 mL/min) the empirical protection of an off-label EPD if their renal artery anatomy is suitable.

Conclusion

There are 3 primary clinical syndromes related to RAS, renovascular hypertension, ischemic nephropathy, and cardiac disturbance syndromes (ie, sudden-onset pulmonary edema, refractory heart failure, or unstable angina). Each of these, are correctable with revascularization. The response to treatment will depend on the adequacy of relief of the obstruction, the remaining viable kidney tissue, and the safety of the procedure. Current technology has advanced such that successful renal artery stent placement is achievable in >95% of the attempts (Table 1). Despite this tremendous technical success, clinical response (cure or improvement) in hypertensive patients with RAS is only ≈70%. Clinical improvement in renal function after successful stent placement for RAS is ≈25%, with renal function remaining stable in ≈50%, and deteriorating in 25%.

The discordance between the high rate of successful PRI and the moderate clinical response can make it difficult to construct a risk versus benefit argument. With more predictable clinical benefit, most would accept the risk of infrequent serious procedural complications. However, when the likelihood of clinical benefit is uncertain, many patients may be unwilling to accept the risk of infrequent serious complications.

Without large randomized trials to guide case selection, physicians become prisoners of the anecdote. Interventionalists are convinced that “open arteries are better than closed arteries,” but other caregivers are not so sure. Nephrologists and hypertension experts counsel that significant harm may come to a patient undergoing PRI, which is true. Despite the relatively low rate of serious complications, in their experience, the uncertainty of predicting individual benefit from PRI makes the risk versus benefit calculation, unattractive.

Interventionalists engaged in renal revascularization must embrace the need to further develop an evidence base on which to guide appropriate utilization of PRI. It will be necessary for all of us to willingly participate and enroll our patients in clinical trials, just as we have done in establishing...
"best practices" for managing coronary artery disease. It is incumbent on us, the interventionalists, to lead the way, by generating the data that justifies the risk versus benefit calculation for individuals who are potential candidates for PRI. I firmly believe that "open renal arteries are better than closed renal arteries," but it is clear to me that we interventionalists will need to prove it.

Disclosures

None.

References


Optimizing Outcomes for Renal Artery Intervention
Christopher J. White

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