Atherosclerotic renal artery stenosis (RAS) is more common than has been previously appreciated and is an independent predictor of death regardless of the presence, severity, or method of revascularization of coronary artery disease.3–5 Among 1235 patients undergoing diagnostic coronary angiography, multivariate analysis demonstrated that RAS (>50%) was a stronger independent predictor of all-cause mortality (relative risk [RR], 2.9; 95% confidence interval [CI], 1.7 to 7.0) than congestive heart failure (RR, 2.3; 95% CI, 1.3 to 4.1), elevated left ventricular ejection fraction (RR, 1.7; 95% CI, 1.2 to 2.2), or decreased renal function (serum creatinine) (RR, 1.3; 95% CI, 1.1 to 1.5).3 A subsequent expansion of that study group, extended to 3987 patients undergoing abdominal aortography at the time of diagnostic cardiac catheterization, identified an incremental effect of the severity of RAS on the 4-year mortality rates. They found that a mild-to-moderate (50%) RAS was associated with a 30% 4-year mortality rate, which almost doubled (52%) with severe (>95%) RAS.4

The cause-and-effect relation between RAS and death is uncertain. It is possible that the presence of RAS is simply a marker for more diffuse or extensive atherosclerosis, which would result in more vascular-related deaths. However, there is one study5 that raises the possibility that the treatment of RAS with a renal stent in patients with renal insufficiency can improve mortality rates. In this trial, patients who improved their renal function after renal stent placement had significantly better survival rates compared with those whose renal function did not improve.

A dedicated educational effort aimed at improving the diagnosis and treatment of peripheral arterial disease, including RAS, has been supported over the past 10 years by several professional societies.6–8 There is now objective evidence from the Medicare database that this effort to increase the number of patients with RAS who receive treatment has been successful, particularly among invasive cardiologists.9 Defining the appropriate strategy for screening high-risk populations, determining the risk-to-benefit ratio for treatment, and avoiding complications of percutaneous renal revascularization is a continuously evolving process.

An ultrasound screening study in 834 free-living Medicare patients, with a mean age of 77 years, found significant (>60%) RAS in 6.8%.6 There were almost twice as many men (9.1%) as women (5.5%, P=0.053), with an even distribution among white (6.9%) and black (6.7%) participants. In a series of unselected autopsies in 221 patients older than 50 years, the prevalence of RAS (>50%) was 27%.11 The prevalence of RAS rose to 53% if there was a history of a diastolic hypertension (>100 mm Hg).

Renovascular hypertension is the most common secondary cause (=5%) of hypertension, and there are several clinical subsets of patients, particularly those with known atherosclerotic vascular disease, who have an increased incidence of RAS.12,13 In patients undergoing diagnostic coronary angiography for suspected coronary artery disease, the prevalence of significant (=50% diameter stenosis) renal artery stenosis ranges from 25% to 34% (Table 1).14–19 In patients with documented lower-extremity atherosclerotic arterial disease, the prevalence of concomitant RAS is greater than 30%.20–22 It is apparent that atherosclerosis is a systemic disorder and affects multiple vascular beds in any given individual.

Atherosclerotic RAS is a progressive disease.23 Progression of the severity of RAS, over time, has been documented in multiple studies.23–25 Progression to occlusion, usually associated with irreversible ischemic death of the kidney, is more likely with more severe stenoses.26 In a modern randomized trial comparing medical therapy with balloon angioplasty for RAS, over a 1-year period, progression to renal artery occlusion occurred in 16% of the medical therapy group compared with none in the angioplasty group.27 Others have demonstrated that progressive worsening of RAS occurs despite medical therapy that effectively controls blood pressure.24,25

Atherosclerotic renal artery disease has been estimated to be the cause of end-stage renal disease in approximately 15% of patients over age 50 beginning dialysis each year.28–30 There is a general consensus that intervention to prevent loss of renal function should be performed before there has been...
a clinically evident decline in renal function. Successful implementation of this strategy requires an efficient and accurate method of screening for RAS in patients at risk for this disease.

**Screening for Renal Artery Stenosis**

Screening for renal artery stenosis is appropriate in patients at increased risk for this disease (Table 2). A distinction should be made between aggressively making the diagnosis of RAS, which aids in patient treatment, and selecting patients for revascularization, which requires a risk-to-benefit analysis and should be done more carefully and judiciously. Whenever possible, screening tests for RAS should be performed noninvasively. Noninvasive tests that are inconclusive, or require clarification, should be resolved with invasive angiography, including hemodynamic assessment of the translesional pressure gradient if necessary.

Doppler ultrasound imaging, although technician-dependent for its accuracy and reproducibility, is the most cost-effective tool available. The next choice is either magnetic resonance angiography (MRA) or computed tomographic angiography (CTA). The choice of diagnostic test is often dependent on local skills and available equipment. In one comparative trial, there were no statistical differences between the sensitivity of MRA (92% to 93%) and CTA (91% to 92%) or specificity of MRA (99% to 100%) and CTA (99%) for detection of RAS. MRA cannot be used in patients with ferromagnetic implants such as pacemakers and defibrillators. CTA requires the patient be exposed to ionizing radiation and iodinated contrast (Figure 1). Because RAS is frequently bilateral, tests such as radionuclide angiography or captopril scintigraphy, which rely on differences in renal perfusion between the kidneys, are not recommended for screening. Plasma renin measurements have little value in screening patients for renal artery stenosis and are not recommended.

Occasionally, patients will be brought urgently or semi-urgently to the cardiac catheterization laboratory for coronary angiography. If they meet criteria listed in Table 2, then nonselective renal angiography should be performed to rule out RAS. If the nonselective aortogram is not diagnostic, then selective angiography should be performed. Angiographic screening of a subset of high-risk patients at the time of cardiac catheterization is justifiable; in fact, it is good medicine, based on the high prevalence and treatable nature of RAS.

---

**TABLE 1. Incidence of Renal Artery Stenosis at Cardiac Catheterization**

<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Patients, n</th>
<th>Any RAS, %</th>
<th>RAS ≥50%, %</th>
<th>Bilateral, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqel et al14</td>
<td>90</td>
<td>NR</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>Weber-Mzell et al15</td>
<td>177</td>
<td>25</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Rihal et al16</td>
<td>297</td>
<td>34</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Vetrovec et al17</td>
<td>116</td>
<td>29</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>Harding et al18</td>
<td>1302</td>
<td>30</td>
<td>15</td>
<td>36</td>
</tr>
<tr>
<td>Jean et al19</td>
<td>196</td>
<td>33</td>
<td>18</td>
<td>NR</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>2178</td>
<td>30.2±3.6</td>
<td>19±6</td>
<td>17.4±14.2</td>
</tr>
</tbody>
</table>

RAS indicates renal artery stenosis; NR, not reported.

**TABLE 2. Causes of Increased Prevalence of Renal Artery Stenosis**

- Onset of hypertension ≥30 years or ≥55 years
- Malignant, accelerated, or resistant hypertension
- Unexplained renal dysfunction
- Development of azotemia with an ACE inhibitor or ARB medication
- Unexplained size discrepancy of ≥1.5 cm between kidneys
- Cardiac disturbance syndrome (flash pulmonary edema)
- Peripheral arterial disease (abdominal aortic aneurysm or ABI <0.9)
- Multivessel (≥2) coronary artery disease

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; and ABI, ankle brachial index.
of this condition and the lack of any incremental risk associated with a screening aortogram.\textsuperscript{14,16}

**Patient Selection for Renal Revascularization**

When selecting a patient for renal intervention, the treating physician should have a high clinical suspicion that the target renal artery stenosis is causally related to the clinical symptoms. This determination may be based on both functional and anatomic assessments of the RAS. Functional assessments include estimation of the severity of the stenosis from translesional pressure gradients measured with catheters or pressure wires or noninvasively assessed by Doppler ultrasound signals. Other functional assessments include measurement of the kidney size, determination of renal function or perfusion by radionuclide methods or clinical chemistry tests such as selective renal vein renin measurement, and creatinine clearance determinations.

Anatomic assessments include visualization of the stenosis by noninvasive tools such as CTA, MRA, or duplex ultrasound imaging. Invasive imaging options include intravascular ultrasound (IVUS) and the gold standard for imaging renal artery anatomy, angiography. A hemodynamically significant RAS is defined as a moderate (50% to 69%) stenosis with $\geq 10$ mm Hg mean or $\geq 20$ mm Hg systolic translesional gradient, or a severe stenosis with a visually estimated diameter stenosis of $\geq 70\%$.\textsuperscript{36}

Renal artery revascularization is generally indicated for patients with hemodynamically significant renal artery stenosis associated with the clinical conditions of (1) accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with a unilaterally small kidney, and hypertension with intolerance to medication; (2) renal insufficiency; and (3) recurrent congestive heart failure or “flash” pulmonary edema, refractory heart failure, or refractory angina pectoris. Until there is evidence that renal artery stent placement improves long-term renal artery patency and preserves renal function, the treatment of asymptomatic RAS must be individualized and is generally not indicated.

**Renovascular Hypertension**

The overall incidence for blood pressure improvement or cure after renal intervention is approximately 70\%.\textsuperscript{13,37} The high procedure-related success rate (\geq 95\%) and lower rate of blood pressure improvement (70\%) suggest that either the renal artery stenosis is not causally related to the hypertension or the angiographically successful procedure did not relieve the renal hypoperfusion. We have investigated two methods to improve patient selection by measuring (1) the renal fractional flow reserve\textsuperscript{38} and (2) serum brain natriuretic peptide (BNP).

**Physiological Lesion Assessment**

The renal fractional flow reserve (FFR) is an assessment of the severity of the RAS by using maximal vasodilation with papaverine, an endothelium-independent vasodilator.\textsuperscript{39} We demonstrated a poor correlation between quantitatively measured renal angiographic stenosis and hemodynamic parameters (Figure 2) and an excellent correlation between renal FFR and the baseline pressure gradient (Figure 3).\textsuperscript{39} A major limitations of the angiographic evaluation of aorto-ostial renal artery stenosis are the inaccuracy of visual estimation of vessel diameter in these moderately large vessels, the difficulty in obtaining orthogonal views of the stenosis, and the difficulty establishing the normal reference segment of the renal artery (Figure 4). Other characteristics of the stenosis such as length and geometry (lesion eccentricity), in addition to the diameter stenosis, contribute to decreased renal blood flow. These factors cumulatively contribute to the poor correlation between angiographic and hemodynamic parameters of RAS severity.

We measured renal FFR in 17 patients with uncontrolled hypertension. Patients with an abnormal baseline renal FFR ($<0.8$) had a higher rate of blood pressure improvement (86\%) compared with only 30\% in those with a normal baseline FFR ($P=0.04$).\textsuperscript{40} Importantly, the translesional pressure gradient (resting, peak systolic, and hyperemic) did not separate blood pressure responders from nonresponders (Table 3). The sensitivity of an abnormal renal FFR to predict improvement in blood pressure control after renal stenting was 88\%.

**Biomarkers**

The second method of improving patient selection for renal artery revascularization is to measure a biomarker, such as
BNP, which can be related to renovascular hypertension.41 BNP is a neurohormone released from ventricular myocytes under conditions of cell stretching. It promotes diuresis, natriuresis, and arterial vasodilation and antagonizes the renin-angiotensin system and angiotensin II.42 BNP is synthesized and released from glomerular mesangial and epithelial cells.43 Hemodynamically significant renal artery stenosis is known to promote activation of the renin-angiotensin system, leading to increased levels of angiotensin II. In animal experiments, angiotensin II induces synthesis and release of BNP, and the BNP mRNA is upregulated in the setting of RAS.44,45 It would appear that angiotensin II directly stimulates the synthesis and release of BNP independent of cardiac cell stretching and that the BNP mRNA is upregulated in the 2-kidney, 1-clip renal artery stenosis model.44,45

We prospectively studied 27 patients with uncontrolled hypertension who had visually estimated significant atherosclerotic renal artery stenosis (≥70% diameter stenosis) by contrast angiography.46 Patients with other medical conditions associated with elevated BNP levels (congestive heart failure, acute coronary syndromes, and renal failure) were excluded. Procedure success, defined as a ≤30% residual diameter stenosis without a serious complication after renal stent placement, was obtained in all of the patients. For the entire group, hypertension was cured or improved in 70% (19 of 27) of the patients at hospital discharge. Twenty-two (81%) patients with RAS had a baseline BNP ≥80 pg/mL. Hypertension improved in 77% (17/22) of those with elevated BNP, compared with none of the 5 patients with a baseline BNP ≤80 pg/mL (P=0.001). When the posttreatment BNP fell to >30%, 94% (16 of 17 patients) improved their blood pressure control. When the poststent BNP fell by ≤30%, only 1 patient (10%), had improved blood pressure control (P<0.001) (Figure 5).46

Our preliminary data suggest that BNP is increased in patients with refractory hypertension and renal artery stenosis and that this peptide may be useful in predicting which patients will clinically improve their blood pressure after successful renal revascularization. An elevated baseline BNP ≥80 pg/mL strongly correlated with hypertension improvement after 3.5 months of follow-up.

**Resistance Index and Nephrosclerosis**

Nephrosclerosis has been suggested as a factor in reducing the kidney response to revascularization. The renal artery resistive index (RI), measured by Doppler ultrasound, has been suggested as a means to stratify patients who are likely to respond to renal intervention. However, there are conflicting data regarding the ability of RI to predict treatment response in patients with RAS.

A retrospective study, without prespecified end points, in which most patients were treated with balloon angioplasty, not stents, suggested that an elevated RI ≥0.8 was associated with a low probability of improved blood pressure or renal function after revascularization.47 The authors’ reliance on balloon angioplasty as the primary method of treatment further weakens the conclusions.

These data have been challenged by publications by Zeller and colleagues.48,49 A prospective study of renal stent placement in 241 patients demonstrated that patients with an elevated RI achieved a favorable blood pressure response and renal functional improvement at 1 year after renal arterial intervention (Figure 6 and Figure 7).48 The preponderance of evidence and scientific quality of the latter studies favors the conclusion that an elevated RI should not be a contraindication to performing renal artery intervention.

**Renal Function Preservation**

Several clinical trials have demonstrated that in patients with atherosclerotic RAS and renal insufficiency, renal artery stent placement improves or stabilizes renal function. One group

---

**Figure 4.** Top, Quantitative angiographic assessment (Medis, Leiden, the Netherlands) of stenosis compared with visual estimation of peripheral arterial stenosis. Middle, Quantitative angiographic assessment of stenosis using Medis compared with assessment using Toshiba. Bottom, Visual estimation of peripheral arterial angiographic stenosis compared with quantitative angiographic assessment (Toshiba) of stenosis.

**TABLE 3.** Lack of Correlation Between Renal Translesional Pressure Gradients and a Treatment Response After Renal Artery Stent Placement46

<table>
<thead>
<tr>
<th></th>
<th>Peak, mm Hg</th>
<th>Mean, mm Hg</th>
<th>Hyperemic, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>28.6±26</td>
<td>10.6±13.8</td>
<td>15.5±17.9</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>30.7±26.9</td>
<td>9.5±8.1</td>
<td>18.9±10.9</td>
</tr>
<tr>
<td>P</td>
<td>0.88</td>
<td>0.85</td>
<td>0.64</td>
</tr>
</tbody>
</table>

---

White Renal Artery Intervention 1467
found that the best predictor of improvement in renal function after percutaneous revascularization was a rapid rate of decline in renal function.\(^50\) They suggested that the rapid decline in renal function reflected acute injury that was more likely to be reversible. Harden and coworkers\(^51\) reported a series of 32 patients (33 kidneys) with unexplained renal insufficiency and hemodynamically significant renal artery stenosis treated with renal artery stent placement. Most patients had bilateral RAS or a single kidney with RAS, although unilateral disease was present in 7 patients with 2 kidneys each. Improvement or stabilization of renal function was demonstrated by plotting the slope of reciprocal serum creatinine values. The authors concluded that stent placement slowed the progression of ischemic nephropathy.

A more recent study examined patients undergoing successful renal artery stent placement for bilateral or solitary renal artery stenosis (\(\geq 70\%\)) with a baseline serum creatinine between 1.5 mg/dL and 4.0 mg/dL.\(^52\) Using reciprocal creatinine plots, all patients had deteriorating renal function manifested by a negative slope. At follow-up, all had changed to either a positive or less negative slope, indicating improvement of renal function.

**Unilateral Versus Bilateral Renal Artery Stenosis**

Traditional teaching has been that ischemic nephropathy requires RAS of a single solitary kidney or RAS involving bilateral kidneys. Several recent studies have challenged this conventional wisdom and suggested that revascularization of unilateral RAS can improve or stabilize renal function. Two clinical trials have demonstrated improvement in overall renal function in patients with unilateral renal stenosis.\(^49,50\) Revascularization of unilateral renal artery stenosis results in measurable improvement in the split-renal function of the stenotic kidney.\(^33,54\) Restoring flow to the stenotic kidney reversed the hyperfiltration of the nonstenotic kidney, resulting in decreased proteinuria.\(^54\) These data suggest that in patients with abnormal renal function, treatment of a hemodynamically significant unilateral RAS is beneficial in improving and/or stabilizing renal function.

**Cardiac Destabilization Syndromes**

Cardiac disturbance syndromes attributable to RAS include exacerbations of coronary ischemia and congestive heart failure caused by peripheral arterial vasoconstriction and/or volume overload. The most widely recognized example of a cardiac destabilization syndrome is “flash” pulmonary edema.\(^55\) Renovascular disease may also complicate the treatment of patients with heart failure by preventing the administration of angiotensin antagonist therapy.\(^56\)

The importance of renal artery stent placement in the treatment of cardiac disturbance syndromes has been described in a series of patients presenting with either congestive heart failure or an acute coronary syndrome.\(^57\) Successful renal stent placement resulted in a significant decrease in blood pressure and symptom improvement in 88% (42 of 48) of patients. Some patients underwent both coronary and renal intervention, whereas others had only renal artery stent placement because of unsuitability of coronary lesions for revascularization. Assessment of the treatment effects acutely and at 8 months using the Canadian Cardiovascular Society angina classification and the New York Heart Association functional classification demonstrated that those with renal stent placement did as well as those treated with both renal and coronary intervention.

There are multiple benefits for patients with cardiac destabilization syndromes who undergo renal revascularization. Improving renal perfusion reduces renin production, thereby
decreasing angiotensin and aldosterone production, which promotes natriuresis and enables the use of angiotensin antagonists in a population of patients proven to benefit from this therapy.

Technical Issues
Catheter-based therapy for hemodynamically significant renal artery stenosis has largely replaced surgical revascularization in patients with suitable anatomy.59 A recent survey of Medicare patients suggests that the rate of renal surgery decreased by almost half in the year 2000, whereas the rate of catheter-based therapy increased by 2.4-fold.9 The overall procedural success rates for catheter-based therapy are very high (mean 98%; 95% CI, 95% to 100%), the overall complication rates are acceptable (mean 11%; 95% CI, 6% to 16%), and the serious complication rates are low (Table 4).59–63

Medical Therapy Versus Balloon Angioplasty
There have been 3 randomized trials of balloon angioplasty compared with medical therapy for renal artery stenosis and hypertension and/or renal function improvement.27,64,65 These trials are limited by enrollment of small numbers of patients; however, allowing liberal crossover from medical to interventional therapy compromised the intention-to-treat results. Perhaps the best-known and widest-quoted of these studies was the Dutch Renal Artery STenosis Intervention Cooperative (DRASTIC) trial, which randomized 106 patients with renal artery stenosis (>50% diameter stenosis), serum creatinine ≤2.3 mg/dL, and hypertension to balloon angioplasty or best medical therapy.27 At the 3-month follow-up, 22 (44%) patients were failing medical therapy with either uncontrolled hypertension on 3 or more drugs (n = 14) or worsening renal failure (n = 8) and were allowed to receive balloon angioplasty. At the 3-month follow-up visit, (before crossover), there was a statistically significant improvement in systolic (179 ± 25 to 169 ± 28 mm Hg; P < 0.001) and diastolic (104 ± 10 to 99 ± 12 mm Hg; P < 0.001) blood pressure in the angioplasty group, and there was no change in the medically treated group. At 12 months, there was no difference in blood pressure between the groups, largely because almost half of the medical therapy group received balloon angioplasty. Additionally, 16% of the medically treated patients went on to suffer renal artery occlusion, which did not occur in the angioplasty group. Given these data, it is hard to understand the basis for the conclusion that “angioplasty has little advantage over antihypertensive drug therapy.”27

Balloon Angioplasty Versus Renal Stent
Balloon angioplasty has been the traditional treatment of choice for renal artery fibromuscular medial dysplastic lesions.66 Atherosclerotic renal artery stenosis predominantly affects the most proximal or ostial portion of the renal artery. This atherosclerotic plaque is often in continuity with aortic wall plaque. The lesions are typically bulky and calcified. Balloon angioplasty often fails in these lesions predominantly because of recoil of the bulky aortorenal plaque. Balloon angioplasty is associated with a restenosis rate that approaches 50% because of the significant recoil.67,68

Dorros and coworkers69 demonstrated a superior hemodynamic result for stents compared with balloons in atherosclerotic RAS. A randomized trial comparing balloon angioplasty versus stent placement in 85 patients with atherosclerotic RAS and hypertension demonstrated a higher success rate and superior long-term patency rate with stent placement compared with balloon angioplasty.70 At 6 months, the angiographic restenosis rate for the balloon angioplasty group was 48%, compared with only 14% (P < 0.01) for the stent group. The authors calculated that a provisional stent strategy (bailout) would avoid a stent 40% of the time. However, 45% of the patients would ultimately require a second procedure because of restenosis, making the strategy of primary stent placement more efficient. For the balloon group to achieve a 90% patency rate at 6 months, 62% of all patients would ultimately require a stent and 57% of all patients would need a second or third procedure. To obtain a 90% 6-month

<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Patients, n</th>
<th>Death, %</th>
<th>Dialysis, %</th>
<th>Major Complications, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocha-Singh et al62</td>
<td>180</td>
<td>0.6</td>
<td>0</td>
<td>2.6</td>
</tr>
<tr>
<td>Tuttle et al69</td>
<td>148</td>
<td>0</td>
<td>0</td>
<td>4.1</td>
</tr>
<tr>
<td>White et al63</td>
<td>133</td>
<td>0</td>
<td>0</td>
<td>0.75</td>
</tr>
<tr>
<td>Burket et al64</td>
<td>171</td>
<td>0</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Dorros et al65</td>
<td>163</td>
<td>0.6</td>
<td>0</td>
<td>1.8</td>
</tr>
<tr>
<td>Total</td>
<td>795</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

Major complications include death, myocardial infarction, emergency surgery, need for dialysis, or blood transfusion.
patency rate in the primary stent group, only 12% would need a second procedure. This randomized, controlled trial demonstrated the superiority of renal stents over balloons in hypertensive patients with atherosclerotic RAS for procedure success, late patency, and cost-effectiveness.70

A meta-analysis by Isles et al71 that reviewed 10 renal stent studies performed between 1991 and 1997 demonstrated procedural success rates \( \geq 96\% \), with a procedure-related mortality rate of \(<1\%\). The average restenosis rate was 16\%.

A more recent meta-analysis comparing renal stent placement with balloon angioplasty confirmed a significantly higher procedural success rate for stents (98\%) than for balloon angioplasty (77\%, \( P<0.001 \)) and a lower restenosis rate for stents (17\%) than for balloon angioplasty (26\%, \( P<0.001 \)) (Figure 8).37

**Avoiding Complications**

**Adjunctive Pharmacology**

There are no controlled studies or comparative data to suggest that the use of any antiplatelet therapy, other than aspirin, or any anticoagulant therapy, other than unfractionated heparin (activated clotting time \( >250 \) seconds), is beneficial for patients treated with renal stents. Trials that objectively examine the efficacy of clopidogrel, glycoprotein IIa/IIIb receptor blockers, and anticoagulation alternatives to heparin (ie, low-molecular-weight heparins and bivalirudin) need to be done to justify the additional expense of these agents in renal intervention. Long-term therapy with aspirin alone is the standard of care at the present time.

**Restenosis**

Two meta-analyses of renal artery intervention have demonstrated average restenosis rates after stent placement of 16\% and 17\%.37,74 More recent reports suggest that with optimal deployment techniques, restenosis rates of less than 15\% can be achieved.59,62,72,73

Renal artery restenosis after stent placement is related to both acute gain and late loss, similar to restenosis after coronary artery intervention. We performed quantitative angiography on a series of 100 consecutive patients and found that patients with patent renal arteries at 8-month follow-up had significantly larger postprocedure minimal lumen diameter (4.3±0.7 mm versus 4.9±0.9 mm; \( P=0.025 \)) and had significantly less late loss (1.3±0.9 mm versus 3.0±1.4 mm; \( P<0.001 \)).53 The largest single series of 300 consecutive patients and 361 renal arteries treated with stent implantation demonstrated that a larger reference vessel diameter (RVD) and larger acute gain (poststent minimal lumen diameter) after stent deployment were strongly associated with a lower incidence of restenosis. For example, the restenosis rate for small renal arteries (RVD of \(<4.5 \) mm) was 36\%, compared with only 6.5\% for a larger renal artery (RVD of \( \geq 6.0 \) mm).74

The type of stent, or composition of the stent, has an impact on restenosis. The 1-year restenosis rate for gold-coated stents (NIRoyal, BSC, Natick, Mass) was 31\% in 59 patients compared with 16\% (\( P=0.012 \)) for stainless steel stents in 38 patients.75 Two-year patency for the gold-coated stents was 39\% compared with 78\% for stainless steel stents. Using a multivariate analysis, the use of gold-coated stents was the strongest predictor of restenosis (\( P=0.018 \); hazard ratio [HR], 3.3; 95\% CI, 1.2 to 8.7).

Renal stents have been shown to have excellent long-term patency rates, with a reported cumulative primary patency rate of 84.5\% and a secondary patency rate of 92.4\% at 5 years.72 These excellent results were confirmed by Henry and associates,73 who reported a cumulative primary patency rate of 78.8\% and a secondary patency rate of 97.8\% at 6 years (72 to 78 months) of follow-up.

**Atheroembolism and Embolic Protection**

The issue of atheroembolism has been difficult to define. There is no available surrogate biomarker, such as troponin for the heart, to detect renal embolic injury. Atheroemboli associated with carotid intervention have been well documented,76 and it is likely that the same is true for the bulky friable aorto-ostial renal artery plaque.77

In a meta-analysis, Isles and coworkers71 determined that in patients with abnormal renal function who undergo renal artery stent placement, roughly one quarter will have improved renal function, one quarter will have decreased renal
function, and one half will remain unchanged. The two most likely reasons for deterioration of renal function after intervention are contrast-deterioration nephropathy and atheroembolization. The bulky aorto-ostial plaque probably is a source of emboli, but the incidence has been difficult to determine (Figure 9).

Henry and coworkers\textsuperscript{78} placed renal stents in 65 renal arteries in 56 patients, using emboli protection devices. They noted debris retrieval after renal stent deployment in 100% of the patients with distal balloon occlusion (Percusurge \textsuperscript{[n=38]}, Medtronic, Minneapolis, Minn), and in 80% of the filter cases (FilterWire \textsuperscript{[n=26]}, BSC, Natick, Mass, and Angioguard \textsuperscript{[n=1]}, Cordis, Miami, Fla). Interestingly, there was no difference in the size or number of particles regardless of whether or not balloon predilation was performed. There were no dissections or major complications related to the use of the protection device. Holden and colleagues\textsuperscript{79} also reported a retrospective series involving 46 renal stents and 37 patients who had abnormal renal function. This group used the Angioguard filter device and found visible debris present in 65% of the cases.

The recently begun Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial comparing best medical therapy to renal artery stent placement in hypertensive patients with renal artery stenosis will require that an emboli protection device be used if possible in all renal stent patients. Unfortunately, because the great majority of interventional patients will have an emboli protection device used, it will not be possible to determine what benefit, if any, is attributable to the emboli protection device. To determine the risk-benefit relation of emboli protection devices requires an assessment of the disadvantages and potential risks of emboli protection devices. These include the possibility for distal renal artery injury, dissection, or spasm and lack of support for stent delivery that is available with dedicated renal angioplasty guidewires. At present, none of the filter devices has been developed specifically for the renal artery, and using coronary equipment may occasionally lead to undersizing of the filter.\textsuperscript{80} A further limiting feature is the requirement for approximately 2 cm between the distal edge of the deployed stent and the filter, which can be a problem in patients with proximal renal artery bifurcations.

In-Stent Restenosis

The optimal treatment of renal artery in-stent restenosis is uncertain. An initial report\textsuperscript{81} described the feasibility and late follow-up in 20 stents with recurrent stenosis that were treated with either balloon angioplasty (\textsuperscript{n=18}) or restenting (\textsuperscript{n=2}). Follow-up angiography was available in 16 (80%) of the arteries at slightly less than 1 year and showed a restenosis rate of 25%. Other methodologies such as cutting balloons and brachytherapy have also been reported, but there is no evidence to suggest objective benefit.\textsuperscript{82–84} A recurrence rate of 21.7% has been reported at 6 months after balloon angioplasty for renal in-stent restenosis. This was in contrast to a much poorer result 42.3% in matched pairs after balloon dilation for renal artery restenosis after balloon dilation.\textsuperscript{85}

Summary

Catheter-based therapy for symptomatic (hypertension, ischemic nephropathy, or cardiac destabilization, ie, flash pulmonary edema syndromes), hemodynamically significant, atherosclerotic RAS has become the preferred method of revascularization. The discordance between the high (>95%) procedural success and moderate (60% to 70%) clinical response obtained in patients with renal artery stenosis and hypertension probably is due to poor patient selection related to the very difficult process of angiographically assessing the severity of an aorto-ostial renal artery lesion. Preliminary data suggest that the use of physiological lesion assessment (renal FFR) and/or biomarkers (BNP) can enhance lesion selection and result in improved clinical response rates.\textsuperscript{40,46} Further studies are needed to establish their clinical role.

Data from a single randomized trial and 2 meta-analyses comparing stent placement with balloon angioplasty for atherosclerotic RAS demonstrate overall superiority for stent therapy. The conventional wisdom of using an elevated RI to exclude patients as candidates for revascularization and the argument against treating unilateral RAS to improve renal function have been challenged with data from uncontrolled, nonrandomized clinical trials. The need has become clear to prospectively and objectively evaluate these criteria.

Finally, the development of new technologies to further improve the safety and efficacy of renal intervention are on the horizon. The feasibility and safety of embolic protection have been demonstrated by several groups, although trials to determine their efficacy in preserving renal function have not been done. The current restenosis rates are acceptable (<20%), with excellent long-term secondary patency rates (>80%), but there is room for improvement. Given the dependence on acute gain and late loss, it would appear that there is a role in the renal arteries for drug-eluting stents.\textsuperscript{86}

Acknowledgment

The author acknowledges the contributions made to this body of work by Drs Mohammed Awaad, Rajesh Subramanian, and Jason Mitchel.

Disclosures

None.

References


Catheter-Based Therapy for Atherosclerotic Renal Artery Stenosis
Christopher J. White

Circulation. 2006;113:1464-1473
doi: 10.1161/CIRCULATIONAHA.105.540039

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/113/11/1464

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/