Case Against Angioplasty and Stenting of Atherosclerotic Renal Artery Stenosis

Lance D. Dworkin, MD; Kenneth A. Jamerson, MD

Atherosclerotic renal artery stenosis (RAS) is a relatively common problem, estimated to affect between 1% and 5% of patients with hypertension. Given the high prevalence of hypertension, it follows that there are from 2 million to 4 million individuals with RAS in the United States alone. A challenging feature of the disease is the high incidence of adverse cardiovascular events in affected individuals compared with those with normal renal arteries, which also presents a potential opportunity. On the one hand, there may be such a large burden of atherosclerotic disease by the time patients present that it is too late for an intervention in a single vascular bed to significantly alter outcomes. On the other hand, it is possible that an effective intervention might reduce adverse events, which has led some physicians to take an aggressive approach to diagnosing and correcting RAS.

Response by Cooper and Murphy p 276

In fact, although individual patients sometimes appear to benefit, whether renal artery revascularization reduces adverse cardiovascular and renal events is currently unknown. Nevertheless, stenting of RAS is performed commonly, with ≈40,000 procedures reported each year in the United States alone. Most often, revascularization is undertaken in 1 of 3 clinical settings and with a specific goal: (1) in patients with resistant hypertension to achieve better blood pressure control, (2) in patients with renal insufficiency to prevent progression to end-stage renal failure, or (3) in patients with congestive heart failure to prevent recurrent exacerbations requiring hospitalization. The present article discusses these “indications” and reviews the data suggesting that revascularization is no better than medical therapy in these settings. Furthermore, just as interventional techniques progress, advances in medical therapy have significantly improved outcomes for patients treated conservatively, making it less likely that revascularization will provide significant benefits to future patients.

Does Revascularization Reduce Blood Pressure?

There are 3 published randomized prospective clinical trials comparing angioplasty with or without stenting to medical therapy in patients with atherosclerotic RAS3–5 (Table 1). Most would agree that all 3 studies are seriously flawed. First, the definition of clinically important renal vascular disease was overly inclusive. Although most practitioners believe that lesions <70% often are clinically insignificant, patients with only a ≥50% stenosis were enrolled, and the proportion of subjects with mild stenoses in the 50% to 70% range was not specified. The studies also were marred by a high crossover rate. In the largest trial, the Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study, ≈40% of subjects crossed over from the medical to the angioplasty arm within the first 3 months. Nevertheless, under intention to...
pressure medications must be weighed against these risks.10,11

Thus, a few patients benefit while most are either not helped normal to nearly zero when, at most, a 50% reduction might be expected.13 Similarly, nuclear studies in patients with unilateral RAS reveal that glomerular filtration rate in the nonstenotic kidney often is the same as or even lower than that in the kidney distal to a stenosis.14 The lack of correlation between the severity of renal arterial disease and kidney function probably relates to the presence of ischemic damage in the poststenotic kidney and hypertensive injury in the nonstenotic kidney. Thus, in many patients with RAS, intrinsic kidney damage rather than the vascular stenosis per se accounts for the renal functional impairment. This phenomenon also explains why filtration rate often fails to improve significantly after revascularization. Regarding the impact of revascularization on kidney function, observational studies document that kidney function may stabilize or improve in some subjects. On the other hand, angioplasty and stenting may cause immediate and sometimes irreversible declines in kidney function, either from contrast nephropathy or atheroembolic disease. In the largest prospective randomized trial, creatinine clearance tended to improve in patients treated medically or with angioplasty, and there was no difference in kidney function between the 2 treatment groups after 1 year.19

In another retrospective series of >300 patients with RAS and impaired kidney function who underwent surgical revascularization, sustained reductions in serum creatinine were observed in only \( \approx 25\% \) of patients. Serum creatinine was essentially unchanged in more than half the subjects and was significantly increased in \( \approx 20\% \), so there was no net improvement in kidney function for the group as a whole.15 Thus, a few patients benefit while most are either not helped or even harmed. That revascularization reduces the incidence of end-stage renal disease in patients with RAS has never been shown.

### Does Renal Artery Stenting Prevent Exacerbations of Congestive Heart Failure?

Episodes of severe congestive heart failure, so-called flash pulmonary edema, are associated with RAS and sometimes are cited as an indication for revascularization. Gray and coworkers16 examined the number of admissions for congestive heart failure and the New York Heart Association

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects Enrolled, n</th>
<th>Follow-Up, mo</th>
<th>ΔBP, mm Hg</th>
<th>Number of Antihypertensive Drugs Needed to Control BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Webster et al Uni RAS3</td>
<td>Med,13;PTA,14</td>
<td>6</td>
<td>-8/-6</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-9/-5</td>
<td></td>
</tr>
<tr>
<td>Webster et al Bi RAS3</td>
<td>Med,12;PTA,16</td>
<td>6</td>
<td>-2/-2</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-19/-4</td>
<td></td>
</tr>
<tr>
<td>Plouin et al4</td>
<td>Med,26;PTA,23</td>
<td>6</td>
<td>-8/-5</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-12/-10</td>
<td></td>
</tr>
<tr>
<td>Van Jaarsveld et al5</td>
<td>Med,50;PTA,56</td>
<td>12</td>
<td>Same</td>
<td>↓</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; Uni, unilateral; Bi, bilateral; Med, medical therapy; and PTA, percutaneous transluminal angioplasty.

**TABLE 1. Clinical Trials Comparing Renal Artery Angioplasty With Medical Therapy**

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treat, patients were still analyzed as part of the group to which they were initially randomized. Perhaps most important, comparatively less attention was paid to the medical regimen that patients received; however, this regimen needs to be robust so that it does not bias the data in favor of the intervention. In particular, evidence suggests that blockade of the renin-angiotensin-aldosterone system is highly effective in controlling blood pressure and may be critical to improving renal and cardiovascular outcomes as well.6 These drugs were not available, their use was not mandated, or their use was restricted as a result of the fear of acute renal failure in these trials, however.

Given the shortcomings of the data, it is fair to say that these studies are at best not interpretable, neither supporting nor refuting the potential benefits of revascularization. Nevertheless, none of the studies showed a benefit of revascularization over medical therapy in reducing blood pressure. At best, the number of antihypertensive medications needed to control blood pressure tended to decline, and almost all patients continued to require medication. In part, this may relate to the fact that with long-standing hypertension, secondary processes such as vascular remodeling, atherosclerosis, ischemic damage to the poststenotic kidney, and hypertensive injury to the nonstenotic kidney ensue and sustain hypertension.7-9 Revascularization may fail to cure hypertension when stenosis is longstanding and these secondary processes dominate. Also of note is the significant complication rate with angioplasty and stenting, reported to be from 7% to 15% and including outcomes as serious as death or rapid progression to end-stage renal disease. In the final risk-benefit analysis, the advantage of taking 3 as opposed to 4 blood pressure medications must be weighed against these risks.10,11

### Does Renal Artery Stenting Preserve Kidney Function?

Although atherosclerotic renal artery lesions tend to progress with time, relatively few arteries go to complete occlusion within a 5-year period.12 In the absence of complete occlusion, there is little or no correlation between the degree of anatomic stenosis and glomerular filtration rate. In 1 study in patients with unilateral RAS and an apparently normal contralateral kidney, glomerular filtration rate ranged from
functional class in 39 patients who underwent renal artery stenting for recurrent episodes of congestive heart failure. Hospitalizations for congestive heart failure declined significantly in the year after stenting, and New York Heart Association functional class also improved. The number of patients receiving angiotensin-converting enzyme inhibitors also increased from 15% to 50%, however, which may have contributed to the improved outcome. Because the study was uncontrolled, the real impact of revascularization is impossible to determine. At present, there are no prospective randomized data demonstrating that angioplasty and stenting reduce admissions for severe congestive heart failure, or any other cardiovascular event, compared with medical therapy alone.

Reducing the Risk of Cardiovascular Disease in RAS: The Medical Approach

Optimal Medical Therapy of RAS

Optimal Medical Therapy for Atherosclerotic RAS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Recommendation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Target BP $\leq$140/90 mm Hg, ARB as first-line agent; monitor potassium and creatinine</td>
<td>JNC VII 20</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Target LDL $&lt;100$ mg/dL, consider $&lt;70$ mg/dL</td>
<td>28</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Target HgbA1c $&lt;$7 mg/dL; foot and eye care</td>
<td></td>
</tr>
<tr>
<td>Antiplatelet agent</td>
<td>Aspirin, clopidogrel, or ticlopidine</td>
<td>29, 30</td>
</tr>
<tr>
<td>Smoking</td>
<td>Cessation</td>
<td>31, 32</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Tight control of blood pressure, dyslipidemia, diabetes; manage anemia, hyperparathyroidism</td>
<td>NKF DOQI</td>
</tr>
</tbody>
</table>

| BP indicates blood pressure; ARB, angiotensin receptor blockade; LDL, low-density lipoprotein; JNC VII, Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure VII; and NKF DOQI, National Kidney Foundation Disease Quality Initiatives. |

Hypertension Treatment

Although it is well known that lowering blood pressure can prevent adverse cardiovascular events, 2 fundamental questions remain: Is there an ideal blood pressure target that confers maximal cardiovascular protection, and is there a specific antihypertensive regimen that provides cardiovascular benefits beyond just lowering blood pressure?

Is There an Ideal Blood Pressure Target?

Although any method of reducing blood pressure is lifesaving in malignant and accelerated hypertension, clinical trials were needed to demonstrate the value of therapy of less severe hypertension. In 1967, the Veterans Administration Cooperative Study was the first to demonstrate the value of treating elevated blood pressure (diastolic blood pressure $>110$ mm Hg) in preventing cardiovascular morbidity (74% reduction in events per year).17 Subsequent trials have progressively lowered the bar until currently a target pressure $<140/90$ mm Hg is recommended, particularly for hypertensive diabetic patients18 or those with proteinuric renal disease.19 In CORAL, the target blood pressure is $<140/90$ mm Hg overall but $<130/80$ mm Hg for diabetics or those with proteinuric renal disease.20

Use of Angiotensin II Receptor Blockade as Initial Therapy

In CORAL, all patients will receive an angiotensin II type 1 receptor antagonist as the first-line antihypertensive agent. Because the renin-angiotensin-aldosterone system is activated in many patients with renal vascular disease, drugs that block the system are often highly effective in controlling blood pressure.21 The hypothesis that newer drugs could confer additional cardiovascular benefits beyond lowering blood pressure compared with older drugs like diuretics and β-blockers has been tested in recent trials. With few exceptions, it appears that lowering blood pressure with any agent confers benefit, although none of these trials examined patients with known RAS.22,23

The newer generation of hypertension clinical trials tests the impact of combination therapy. In the Anglo-
TABLE 3. Hypertension Drug Algorithm in the CORAL Trial

<table>
<thead>
<tr>
<th>First-line agent</th>
<th>Second-line agent</th>
<th>Third-line agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin receptor antagonist</td>
<td>Thiazide diuretic</td>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>Beta-blocker</td>
<td>Vasodilator</td>
</tr>
<tr>
<td>Begin with low dose and titrate up</td>
<td>Begin with low dose and titrate up</td>
<td>Selection may be based on comorbidities (Table 2)</td>
</tr>
<tr>
<td>Monitor serum creatinine and potassium</td>
<td>Combinations with ARB/ACE may be available</td>
<td>Keep titrating up and adding third-line agents until patient reaches goal</td>
</tr>
<tr>
<td>Monitor serum creatinine and potassium</td>
<td>Use loop diuretics for patients with serum creatinine ≥ 2 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

ARB indicates angiotensin receptor blockade; ACE, angiotensin-converting enzyme.

Scandinavian Cardiac Outcomes Trial (ASCOT), an angiotensin-converting enzyme inhibitor/calcium channel blocker regimen improved cardiovascular mortality compared with a beta-blocker/diuretic. Anticipating that most patients with RAS also will require combination therapy, the blood pressure treatment algorithm in CORAL is a stepped-care approach, with multiple classes of agents added sequentially until the target blood pressure is reached (Table 3).

In addition to preventing cardiovascular events, a number of trials suggest that blocking the renin-angiotensin system reduces proteinuria and delays the onset of end-stage renal disease. In part, the observed risk reductions in progressive nephropathy form the basis for the use of an angiotensin II type 1 receptor antagonist as first-line therapy in CORAL.

Despite the potential benefits, use of renin-angiotensin system–blocking drugs is controversial in patients with RAS. Of particular concern is the risk of acute renal failure. Blocking the system can cause precipitous declines in glomerular filtration rate in the poststenotic kidney, which may cause significant acute renal failure if the RAS affects both kidneys or a solitary functioning kidney. These concerns may be somewhat overemphasized is suggested by the fact that the actual incidence of acute renal failure with renin-angiotensin system–blocking drugs is quite low, affecting <5% of these patients. In addition, acute renal failure in this setting is usually immediately reversible on cessation of the medication and therefore without long-term adverse effects. Also of concern is the risk that renin-angiotensin system blockade will promote progression of ischemic nephropathy in the poststenotic kidney, which has been observed in animal studies. On the other hand, these drugs may actually preserve glomerular structure and function in the contralateral kidney in patients with unilateral stenosis.

Taken together, these data suggest that renin-angiotensin system inhibition may have important therapeutic benefits in patients with renovascular disease that are independent of the effect on blood pressure.

Dyslipidemia Treatment

Although no specific evidence exists for patients with renovascular disease, according to the guidelines, including the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), RAS is considered a coronary artery disease equivalent in terms of cardiovascular risk. Thus, lowering low-density lipoprotein cholesterol to at least <100 mg/dL is the goal of therapy, with some suggesting a target low-density lipoprotein of <70 mg/dL.

Diabetes Mellitus

The CORAL approach to diabetes will acknowledge the clear evidence that tight glucose control to an HbA1c of <7 mg/dL with oral agents and/or insulin is associated with reductions in microvascular and macrovascular complications. Additionally, medical nutrition therapy, multidisciplinary foot care (particularly for patients with peripheral vascular disease, a common comorbidity in RAS), eye care to prevent and treat diabetic retinopathy, and physical activity are recommended.

Chronic Renal Insufficiency

Chronic kidney disease is common in RAS. The guidelines established by the National Kidney Foundation Kidney Disease Quality Initiatives (www.kidney.org/professionals/KDOQI/guidelines.cfm) form the underpinnings to the approach to the management of chronic kidney disease in CORAL.

Antplatelet Agents

Although there are no direct data in patients with RAS, administration of an antplatelet agent is required in CORAL and recommended for all patients with RAS.31,32

Cumulative Impact of the Medical Therapy Intervention

Aggressive treatment of comorbidities and atherosclerotic risk factors has tremendous potential to reduce cardiovascular risk in patients with RAS. Yusuf et al summarize the potential cumulative risk reduction resulting from 4 interventions (aspirin, beta-blocker, ACE inhibitor, statin) for prevention of myocardial infarction. Although the effects of interventions may not be additive in this manner, a multifaceted medical approach is a powerful tool for preventing adverse cardiovascular events.
potential risk reduction that would result from a CORAL-style medical intervention can be estimated from clinical trial data. In the early, placebo-controlled hypertension trials, annualized cardiovascular event rates were as high as 30%. Three decades later in the Heart Outcomes Prevention Evaluation (HOPE) trial, which examined the impact of angiotensin-converting enzyme inhibition, the placebo group received other blood pressure medications, acetylsalicylic acid, and statins and experienced only a 4.3% annualized cardiovascular disease event rate. With more widespread use of statins and antiplatelet therapy, high-risk subjects in the placebo arm of the Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial had only a 1.9% annualized cardiovascular disease event rate. These comparisons suggest that nearly 80% of secondary myocardial infarctions, strokes, and heart failure events can be prevented by an effective medical intervention. With annual event rates of <1.7%, it may be difficult to demonstrate additional benefits of revascularization. In contrast to the robust benefits of medical therapy for cardiovascular event rates, progression to end-stage renal disease actually does not respond very well to medical therapy. Thus, kidney disease may progress despite optimal medical management, and it is possible that revascularization will improve renal but not cardiovascular outcomes.

Conclusions

In summary, published randomized clinical trials provide little support for the notion that angioplasty with stenting significantly improves blood pressure, preserves kidney function, or reduces episodes of congestive heart failure in patients with atherosclerotic RAS. Whether revascularization reduces the incidence of adverse cardiovascular events such as sudden death, myocardial infarction, or stroke is also unknown. In contrast, advances in medical therapy continue to improve outcomes for patients with hypertension and vascular disease. With aggressive medical management of diabetes, chronic renal disease, antiplatelet therapy, more effective antismitizing interventions, and new lower targets for blood pressure and low-density lipoprotein cholesterol, it is quite possible that revascularization, no matter how well performed, will provide little additional benefit to most patients. Therefore, physicians should be conservative in recommending angioplasty and stenting. Given the current uncertainty, practitioners may wish to consider referring patients into one of the large clinical trials that are examining the effects of revascularization versus medical therapy on clinical outcomes in patients with RAS. Contact information for the CORAL trial is available at the study Web site (http://www.coralclinicaltrial.org).

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Disclosures

Dr Dworkin has received honoraria from Pfizer and research grants from the University of Oxford and Medical City Dallas Hospital. Dr Jamerson reports no conflicts.

References

Response to Dworkin and Jamerson

Christopher J. Cooper, MD; Timothy P. Murphy, MD

Drs Dworkin and Jamerson nicely outline limitations in the evidence supporting renal artery stent revascularization for patients with renal artery stenosis while concurrently highlighting the value of aggressive medical therapy. Undoubtedly, blood pressure control, lipid-lowering therapy, antiplatelet therapy, and other medical interventions are critically important in patients with established vascular disease, although the value of these medical therapies remains untested in patients with ischemic renal disease. Where we differ is in our apparent understanding of the potential for stent revascularization in this population. Whereas Drs Dworkin and Jamerson rightly state that medical interventions have markedly reduced event rates in trials of primary and secondary prevention, the risk of patients with ischemic renal disease remains exceedingly high. Furthermore, successful revascularization sits in the tantalizing position of addressing multiple mechanisms that may drive cardiovascular and renal risk: neuroendocrine activation, progressive chronic kidney disease, and hypertension. Despite these interpretative differences, we both reach the same conclusion: The value of stenting needs to be established in patients who are aggressively medically managed and in a setting that avoids the methodological limitations of prior studies. Ongoing studies, including Stenting in Renal Dysfunction Caused by Atherosclerotic Renal Artery Stenosis (STAR) and Angioplasty and Stent for Renal Artery Lesions (ASTRAL), are likely to provide insights into the effect of revascularization on the progression of chronic kidney disease. Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL), which is designed to address clinical events and to avoid the prior design limitations of crossover, patient selection, and treatment without stenting, should move opinions of the medical and interventional communities further toward consensus.
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