Controversial Treatment of Atherosclerotic Renal Vascular Disease

The Cardiovascular Outcomes in Renal Atherosclerotic Lesions Trial

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Atherosclerotic renal artery stenosis (RAS) is a relatively common problem, affecting from 1% to 5% of patients with hypertension.1,2 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. Autopsy data demonstrate that the incidence of RAS increases with age affecting 18% of individuals between the ages 65 to 74 years and >40% of those more than age 75.3 RAS is also common in individuals with vascular disease in other beds and is present in ≤40% of those with overt coronary artery disease, aortoiliac disease, or peripheral vascular disease.4–6 At present, the best treatment for RAS is unknown, and, in particular, whether or not revascularization, typically accomplished by angioplasty and stenting, improves clinical outcomes for patients with RAS is unclear. Nevertheless, it is estimated that ≈40 000 renal artery angioplasties procedures are performed in the United States each year, which, depending on whether or not the procedure is beneficial, is either far too many or far too few. The purpose of this article is to review current knowledge about atherosclerotic RAS and to discuss the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial, which is examining the best treatment for this disease.

Pathophysiology and Natural History

The pathophysiology of hypertension is different in patients with unilateral and bilateral RAS. In both, a drop in perfusion pressure to a kidney distal to a stenosis induces an increase in the activity of the renin–angiotensin–aldosterone system (RAAS). Salt and water retention and vasoconstriction contribute to the initial rise in systemic blood pressure, which tends to raise perfusion pressure of the poststenotic kidney toward normal. In patients with unilateral disease, perfusion pressure also rises in the contralateral, nonstenotic kidney to supra normal levels, inducing a pressure natriuresis response. Salt and water excretion increase in the nonstenotic kidney promoting a return of extracellular volume toward normal.7,8 In this setting, at least initially, hypertension depends on ongoing activation of the RAAS, and such patients may experience marked reductions in blood pressure in response to RAAS blockade.9 Although the initial pathogenic processes are similar in subjects with bilateral stenosis, when both kidneys are distal to hemodynamically significant stenoses, the increase in systemic pressure is never transmitted to a kidney, there is no pressure natriuresis, and salt and water retention can persist. Systemic hypertension and volume expansion return renal perfusion pressure toward normal, suppressing activity of the RAAS, and RAAS-blocking drugs may fail to reduce blood pressure effectively in these patients.10 Ultimately, 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 help to sustain hypertension.11–13 Regardless of whether the disease is unilateral or bilateral, revascularization may fail to cure hypertension when stenosis is longstanding and these secondary processes dominate.

Although atherosclerotic renal artery lesions tend to progress with time, relatively few arteries go to complete occlusion within a 5-year period.14 Furthermore, progression of the anatomic lesion is not always associated with changes in blood pressure or in kidney function, and there is often poor correlation between the degree of anatomic stenosis and glomerular filtration rate (GFR). Patients with unilateral RAS can have GFRs that range from normal to stage 5 kidney disease.15 Nuclear studies in patients with unilateral stenosis reveal that GFR is the same or even lower in the nonstenotic kidney as in the kidney distal to a stenosis.16 This lack of correlation between the severity of renal arterial disease and kidney function may explain why filtration rate often fails to improve significantly after revascularization. In one large series of >300 patients with RAS and impaired kidney function who underwent surgical revascularization, sustained reductions in serum creatinine were only observed in ≈25% of patients. Serum creatinine was essentially unchanged in more than half the subjects and markedly increased in ≈20% so that there was no net improvement in kidney function for the group as a whole.17

Cardiovascular Disease and RAS

A challenging feature of the care of these patients is that there is an extremely high incidence of adverse cardiovascular events in patients with atherosclerotic renal vascular disease as compared with age-matched subjects with normal renal arteries. In a large
group of patients in whom renal arteriography was performed at the time of cardiac catheterization, those with RAS had a much higher incidence of adverse cardiovascular events as compared with patients without renal vascular disease.\textsuperscript{18} Furthermore, there was a direct correlation between the degree of stenosis and survival. Patients with narrowings $>95\%$ had only approximately a 40\% 4-year survival as compared with 80\% in those with normal arteries. These findings were independent of whether or not the patients underwent revascularization.

The explanation for the increased risk of adverse cardiovascular events in RAS is uncertain. Some suggest that the cardiovascular morbidity and mortality seen in patients with RAS may be attributable to concomitant atherosclerosis found in other vascular beds, including the coronary and cerebral circulations.\textsuperscript{19–25} An alternative hypothesis is that neuroendocrine systems activated by renal ischemia have deleterious cardiovascular and renal effects. In addition to raising blood pressure, evidence suggests that angiotensin II has direct adverse effects on multiple tissues. Increased levels of angiotensin II are implicated in smooth muscle proliferation, plaque rupture, endothelial dysfunction, and inhibition of fibrinolysis. Angiotensin II also promotes medial and cardiac myocyte hypertrophy,\textsuperscript{9,26–33} which may persist even when blood pressure is controlled.\textsuperscript{34} Angiotensin II interacts with other peptides, such as endothelin, transforming growth factor $\beta$, and platelet-derived growth factor, each of which is implicated in end-organ damage, ventricular hypertrophy, and vascular hypertrophy.\textsuperscript{33,33,35} Renal dysfunction, mild or severe, is also associated with increased rates of cardiovascular events\textsuperscript{36–39} and increased cardiovascular mortality.\textsuperscript{40,41} and this is particularly true for patients with RAS.\textsuperscript{42,43} Thus, there may exist a pathogenic pathway wherein renal ischemia leads to neuroendocrine activation, hypertension, and renal insufficiency. These factors then combine to accelerate atherosclerosis and promote thrombosis, renal dysfunction, and left ventricular hypertrophy, all culminating in adverse events, including congestive heart failure, myocardial infarction, stroke, progressive renal insufficiency, and, ultimately, death.

The high rate of adverse cardiovascular events in patients with RAS presents both a challenge and a potential opportunity. On the one hand, by the time patients present for revascularization, there may be such a large burden of atherosclerotic disease that it is too late for an intervention in a single vascular bed to significantly alter outcomes. On the other hand, there is the possibility that an effective intervention, even at this late stage, might reduce the incidence of adverse events in these patients. In fact, whether or not revascularization prevents adverse cardiovascular events in patients with RAS has not been examined in a randomized, controlled clinical trial. Previous trials have all lacked sufficient power to examine this question and have tended to focus on surrogate end points like blood pressure or serum creatinine.

**Clinical Trials**

There are 3 published randomized prospective clinical trials comparing revascularization, usually angioplasty with or without stenting, to medical therapy in patients with atherosclerotic RAS.\textsuperscript{44–46} Most would agree that all 3 of the studies are severely flawed. Typically, the primary end point was blood pressure, a surrogate that may impact on survival and on cardiovascular and renal events but is unlikely to be the only factor driving these outcomes. The definition of clinically important renal vascular disease in these trials was probably overly inclusive. In the largest study, the Dutch Renal Artery Intervention Cooperative (DRASTIC) trial,\textsuperscript{44} 106 patients with a $\geq 50\%$ stenosis were enrolled; the exact proportion with mild stenoses in the 50\% to 70\% range was not specified. In contrast, most practitioners believe that lesions $<70\%$ are often clinically insignificant. The studies were also marred by a high crossover rate, $\approx 40\%$ in the DRASTIC study within the first 3 months. Nevertheless under intention to treat, patients were still analyzed as part of the group to which they were initially randomly assigned, undermining the power of the study to detect a beneficial effect of the intervention. Comparatively less attention was paid to the medical regimen that patients received; however, this regimen needs to be robust so as not to bias the data in favor of the intervention. Finally, there was no careful analysis of the impact of the intervention on cost or quality of life, important considerations when selecting a therapy for such a common clinical problem.

Recognizing these serious limitations, it is still the case that none of the studies showed a clear benefit of revascularization over medical therapy either in terms of a significant reduction of blood pressure or better preservation of kidney function. At best, the number of antihypertensive medications needed to control blood pressure tended to decline, although almost all of the patients continued to require medication. 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. Also of note is the significant complication rate with angioplasty and stenting, reported to be from 7\% to 15\% and including such adverse outcomes as death and rapid progression to end-stage renal disease.\textsuperscript{47,48} More recently, uncertainty regarding the benefits of revascularization has been compounded by advances in medical therapy that may further improve outcomes for patients managed conservatively. These include: (1) reduction in cardiovascular mortality associated with effective blockade of the RAAS; (2) potent agents to lower low-density lipoprotein (LDL) cholesterol levels to very low values that may be associated with regression of atherosclerosis in some settings; (3) newer hypoglycemic agents that improve diabetes control; and (4) highly effective antiplatelet regimens. Nevertheless, although there is no clear evidence that revascularization improves outcomes, procedures are often performed in patients with uncontrolled hypertension, declining or impaired kidney function, and/or recurrent episodes of congestive heart failure.

**The CORAL Study**

Given the current state of uncertainty; the size of the population at risk; and the substantial health, social, and economic consequences of this problem, the CORAL study was conceived. CORAL is a multicenter, randomized, unblinded, 2-arm clinical trial designed to test the hypothesis that medical therapy with stent placement of hemodynamically significant atherosclerotic RAS in patients with refractory systolic hypertension reduces the incidence of adverse cardiovascular and renal events compared with optimal medical therapy alone (Figure). A total of 1080 patients will be randomly assigned and closely monitored for blood pressure control and management of other risk factors for...
Summary of CORAL protocol. The trial will randomly assign 1080 subjects with resistant hypertension defined as a systolic blood pressure ≥155 mm Hg and angiographically defined, atherosclerotic narrowing of a renal artery by ≥60%. Patients will be treated with angioplasty, stenting, and optimal medical therapy alone and followed for ≥5 years. Survival free from a composite of clinically important events, including cardiovascular or renal death, myocardial infarction, stroke, admission for congestive heart failure, progression of renal disease, or the need for renal replacement therapy, will be compared. Cost-effectiveness and quality of life will also be examined.

a minimum of 3 years. A subgroup of 400 patients will undergo renal artery duplex ultrasound at baseline, 1 year, and termination for measurement of renal-resistive indexes and evaluation of stenosis. All of the patients will have quality-of-life measures performed, and data will be collected for cost-effectiveness analyses.

Participants will have a history of refractory stage II hypertension defined as a systolic blood pressure ≥155 mm Hg while taking ≥2 antihypertensive medications. Subjects must also meet angiographic criteria for significant stenoses, which is defined as a narrowing of the renal artery of 60% to 80% with a systolic pressure gradient of ≥20 mm Hg, or a >80% narrowing without a gradient requirement. This somewhat rigorous definition of anatomic stenosis was based on the desire to only enroll patients in whom hypertension was likely to be the direct result of atherosclerotic renal artery disease. Nevertheless, patients with hemodynamically insignificant lesions will fail to benefit from stent placement. Patients with recent myocardial infarction, stroke, admission for congestive heart failure, or a serum creatinine >3 mg/dL are excluded from entry, but, otherwise, CORAL casts a fairly wide net and, therefore, should be broadly applicable to the spectrum of affected patients seen in clinical practice.

Study End Points
The primary end point for CORAL is event-free survival from composite cardiovascular and renal adverse events, including cardiovascular or renal death, stroke, myocardial infarction, hospitalization for congestive heart failure, progressive renal insufficiency defined as doubling of serum creatinine, or the need for permanent renal replacement therapy. As discussed, previous studies have used a variety of surrogate end points; however, none are sufficiently robust to guide patient treatment. In CORAL, all of the elements of the composite end point are clinically important in their own right, translate into reduced survival, and each potentially can be attributed mechanistically to RAS and hypertension. In addition to the primary composite end point, 12 prespecified discrete secondary end points will be examined, including all-cause mortality and a number of subgroup interactions, including men versus woman, black versus nonblack, diabetes versus nondiabetes mellitus, global versus partial ischemia, longitudinal kidney function, systolic blood pressure, durability of renal artery patency, renal resistive index as an indicator of microvascular renal function, correlation between stenosis severity and kidney function, quality of life, and cost-effectiveness. In summary, CORAL defines a population with clinically significant atherosclerotic RAS, and inferences made from the CORAL study should be highly applicable to a broad population of patients with RAS and hypertension.

Optimal Medical Therapy for RAS
In CORAL, 2 active treatment groups will be compared: an optimal medical management group and a renal stent with distal protection plus optimal medical management group. Optimal medical management of patients with RAS is not established; however, by analogy to patients with vascular disease in other beds, it should include antiplatelet therapy, angiotensin inhibition, blood pressure control, cholesterol management, blood glucose control in diabetics, smoking cessation, diet, and exercise.

Antihypertensive Therapy
Although antihypertensive therapy is proven to be effective in preventing adverse events in patients with essential hypertension, there are no data on its effects on outcomes in patients with RAS. Likewise, the optimal target blood pressure has not been established in these patients; however, based on Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure VII recommendations, a target blood pressure of <140/90 mm Hg is recommended for individuals without other comorbidities. A lower goal of <130/80 mm Hg is recommended for patients with hypertension and diabetes or renal disease. Whether or not this lower blood pressure target would also be beneficial for all patients with hypertension and significant atherosclerosis has not been carefully examined and will not be studied in CORAL but is certainly open for consideration in clinical practice.

In the CORAL study, all of the patients will receive an angiotensin II type 1 receptor antagonist (ARB) as the first-line antihypertensive agent. Because the RAAS is activated in many patients with renal vascular disease, drugs that block the system are often highly effective in controlling blood pressure in this population. In addition, RAAS-blocking drugs are the only agents proven to slow progression to end-stage renal disease in any setting. Nevertheless, use of RAAS-blocking drugs is controversial in patients with RAS. Of particular concern is the risk of acute renal failure. With hemodynamically significant RAS, renal artery perfusion pressure is reduced distal to the stenosis. Renin and angiotensin levels are increased in the poststenotic kidney, constricting the postglomerular, efferent arteriole, which,
in turn, helps to support glomerular capillary hydraulic pressure and filtration rate. Blocking the system can cause precipitous declines in glomerular transcapillary filtration pressure and filtration rate in the poststenotic kidney, which may cause significant acute renal failure if the RAS affects both kidneys or a solitary functioning kidney. \(^{53,54}\) That 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 in patients with RAS is quite low, affecting <5% of patients. \(^{55}\) In addition, acute renal failure in this setting is usually immediately reversible on cessation of the medication and, therefore, without long-term adverse effects.

Additional concerns regard the possible effects of renin–angiotensin system blockade to promote progression of chronic renal insufficiency in the poststenotic kidney. Consistent with this view are animal studies in which severe fibrosis developed in the kidney on the side of the clipped renal artery. On the other hand, angiotensin-converting enzyme inhibitors (ACEIs) and ARBs may actually help preserve glomerular structure and function in the contralateral kidney in patients with unilateral RAS. \(^{53}\) Experimental data demonstrate that angiotensin II is not only a potent vasoconstrictor but also stimulates cell hypertrophy and proliferation. \(^{9,27,31,33}\) Thus, high levels of angiotensin II may contribute to vascular hypertrophy, proliferation associated with atherosclerosis, and progressive glomerular sclerosis. Finally, in the poststenotic kidney, one animal study suggests that renal blood flow and GFR may be better preserved with ARBs than ACEI. \(^{56}\) With regard to cardiovascular disease, Losito et al. \(^{27}\) reported that angiotensin-converting enzyme inhibition was associated with improved clinical outcomes, suggesting that renin–angiotensin–aldosterone blocking drugs should be used preferentially in these patients. Taken together, these data suggest that renin–angiotensin system inhibition may have important therapeutic benefits in patients with renovascular disease independent of the effect on blood pressure.

Based on these considerations, the antihypertensive drug treatment algorithm in CORAL includes an ARB as the first-line agent. If the ARB is not tolerated as a result of allergy or adverse effects, an ACEI is substituted. If the ARB or ACEI produce a significant decline in GFR, then an alternative initial agent may be selected. If a patient’s blood pressure is not controlled with an ARB alone, a thiazide diuretic is added, unless the serum creatinine is >2 mg/dL, in which case a loop diuretic is to be prescribed. Calcium channel blockers, vasodilators, \(\beta\)-blockers, and \(\alpha\)-blockers are all available as third-line agents, and selection may be influenced by the presence of specific comorbidities. There is no limit on the number or class of additional antihypertensive drugs that patients can receive, and forced titration of medication occurs until goal blood pressure is reached.

Serum creatinine and potassium concentration should be closely monitored when administering ACEIs or ARBs to patients with RAS. Of note, modest increases in serum creatinine may be observed in any patient with hypertension and renal insufficiency as systemic blood pressure is reduced, and this can occur with drugs from any class. In practice, increases in creatinine of <1 mg/dL that are not progressive may be well tolerated and do not necessarily require stopping of a particular drug. Greater elevations in creatinine are unusual and should prompt evaluation for causes of acute renal failure, including global ischemia with dependence of GFR on angiotensin II or other drug-associated causes of acute renal failure. Significant elevations in potassium that necessitate stopping an ARB or ACEI are also likely to be uncommon based on clinical experience with these drugs in other settings, such as diabetic nephropathy. Nevertheless, patients should be monitored for the development of either hyperkalemia or hypokalemia during treatment with ACEI, ARB, and diuretics.

**Dyslipidemia**

Data suggest that LDL-lowering therapy reduces total mortality, coronary mortality, major coronary events, and strokes in persons with established congestive heart disease. Although no specific evidence exists for patients with RAS, according to the guidelines established by the National Heart, Lung, and Blood Institute, including those in Adult Treatment Panel III, RAS is considered a coronary artery disease equivalent in terms of cardiovascular risk. Thus, just as with established coronary heart disease, an LDL cholesterol at least <100 mg/dL is the goal of therapy. Recent clinical trial data suggest additional incremental benefits for cardiovascular event reduction and prevention of atherosclerosis progression with more aggressive LDL lowering to values <80 mg/dL. \(^{57,58}\) This goal can be reached using therapeutic lifestyle changes including diet and exercise; however, if these measures fail, patients should be started on 1 lipid-lowering medication including statins, nicotinic acids, and/or fibrates.

**Diabetes Mellitus**

Patients with atherosclerotic RAS are an older population, and a significant percentage will have diabetes, predominantly type 2. In addition to controlling blood pressure to a lower target than recommended in hypertensives without diabetes, evidence-based guidelines, such as those outlined within "American Diabetes Association Clinical Practice Recommendations 2002" \(^{39}\) regarding glucose control, should be followed. There is clear evidence that tight glucose control to an HbA1c of <7 is associated with reductions in microvascular and macrovascular complications in both type 1 and type 2 diabetes. \(^{59,61}\) In addition, 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**

Many patients with RAS have some degree of renal insufficiency, and this may progress over time. In elderly patients, elevation in serum creatinine is a relatively insensitive marker for reductions in GFR and one of the published formulas (Modification of Diet in Renal Disease or Cockcroft-Gault) should be used to more accurately assess GFR in affected patients. If renal functional impairment is present, practitioners should follow the guidelines established by the National Kidney Foundation Kidney Disease Quality Initiatives in treating the complications of chronic renal disease. Treatment of hypertension, diabetes, and lipid disorders is specifically addressed above. Dietary modifications as outlined in the Disease Quality Initiatives guidelines may be needed as GFR declines. Anemia
commonly develops as renal disease progresses even before the need for renal replacement therapy, and this should be treated with erythropoietin when the hemoglobin falls below $\approx 11\ g/dL$. Many patients will also require either oral or parenteral iron supplements once therapy with erythropoietin is initiated.

**Smoking**

Smoking cessation is an important, but underemphasized component of therapy for atherosclerotic RAS. Smoking triggers vascular spasm, reduces the anti-ischemic effects of $\beta$-blockers, and increases mortality after acute myocardial infarction. Smoking may accelerate the course of RAS via promotion of atherosclerosis and cholesterol emboli. In normotensive, nondiabetic, elderly patients with normal GFR, smoking worsened atherosclerotic disease. This was associated with lower renal plasma flow, which likely resulted from ischemic nephropathy. Smoking cessation reduces progression of vascular disease and the rates of reinfarction and death within 1 year after quitting. Unfortunately, many patients who initially quit smoking relapse within 6 to 12 months. Practitioners treating patients with RAS should adapt an aggressive approach to encourage and assist patients in smoking cessation.

**Antiplatelet Agents**

The long-term use of aspirin in hypertensives with vascular disease and patients after myocardial infarction results in a significant reduction in subsequent cardiovascular events and mortality. In 6 randomized, placebo-controlled trials in which patients were randomly selected between 1 week and 7 years after a myocardial infarct, meta-analysis reveals a reduction in vascular mortality of 13% among those assigned to aspirin with a reduction in nonfatal reinfarction of 31% and nonfatal stroke of 42%. Although all of these trials involved the use of aspirin in doses ranging from 300 to 1500 mg/day, a trial of patients with hypertension in which aspirin 75 mg/day was used demonstrated a significant 15% reduction in cardiovascular events. This suggests that long-term use of aspirin in a dose as low as 75 mg/day is effective. Thus, although there are no direct data in patients with RAS, administration of an antiplatelet agent is recommended for all of the patients with RAS. Thienopyridines, such as clopidogrel or ticlopidine, may also be useful for the prevention of cardiovascular events, either as alternatives to aspirin or in addition to aspirin.

**Perspectives**

Published randomized clinical trials provide little support for the notion that angioplasty with stenting significantly improves blood pressure or preserves kidney function in patients with atherosclerotic RAS. Whether revascularization reduces the incidence of adverse cardiovascular events, such as sudden death, myocardial infarction, severe congestive heart failure, or stroke, is also unknown. In contrast, advances in medical therapy continue to improve outcomes for patients with hypertension and vascular disease, making it possible that revascularization, no matter how well performed, will provide little additional benefit to many patients. Until additional data are available, physicians should be conservative in recommending angioplasty and stenting. If patients are screened, magnetic resonance angiography, computerized tomography angiography, or duplex ultrasonography are the most useful screening tests; the gold standard is still the renal arteriogram. If an intervention is performed, angioplasty with stenting seems to be the procedure of choice for most patients. Whether or not patients undergo revascularization, an aggressive medical regimen that addresses the multiple risk factors for cardiovascular disease is indicated. This includes smoking cessation, tight control of blood pressure, tight glycemic control in diabetic patients, treatment of dyslipidemia, and the administration of antiplatelet agents. Given the current uncertainty regarding the use of revascularization, practitioners should consider referring patients into a clinical trial like CORAL that is examining the effects of revascularization versus medical therapy on clinical outcomes in patients with RAS. Contact information for CORAL is available at the study web site (http://www.coralclinicaltrial.org).

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**Disclosures**

None.

**References**


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