# Atherosclerotic Renal Artery Stenosis: Current Status

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**Atherosclerotic renal artery stenosis (ARAS) remains a major cause of secondary hypertension and kidney failure. Randomized prospective trials show that medical treatment should constitute the main therapeutic approach in ARAS. Regardless of intensive treatment and adequate blood pressure control, however, renal and extrarenal complications are not uncommon. Yet, the precise mechanisms, accurate detection, and optimal treatment in ARAS remain elusive. Strategies oriented to early detection and targeting these pathogenic pathways might prevent development of clinical end points. Here, we review the results of recent clinical trials, current understanding of the pathogenic mechanisms, novel imaging techniques to assess kidney damage in ARAS, and treatment options.**



**Key Words:** Atherosclerosis, Renal artery obstruction, Ischemia, Inflammation, Hypertension

## INTRODUCTION

Atherosclerotic renal artery stenosis (ARAS, >60% lumen occlusion) is present in almost 7% of elderly people.[1] Attribution of ARAS as an etiology of ESRD is often difficult, especially in patients with vascular diseases, who often have increased burden of risk factors for parenchymal kidney disease.[2] Nevertheless, experimental and observational cohort studies confirm that ARAS is an important contributor to kidney failure and aggravating hypertension.[3-5] In addition, ARAS with CKD poses a risk for exacerbation of cardiovascular disease and multiple long-term complications.[6] Several cohort and clinical trials suggest that therapeutic regimens, such as angiotensin blockade and statins, may slow the rate of loss of kidney function over time.[7,8] However, subgroups of patients with ARAS experience rapid kidney functional decline,[9] although its determinants are difficult to establish.[10] Several lines of evidence highlight the pathophysiological complexity contributing to kidney and cardiovascular damage in ARAS, which warrant detailed examination and design of effective therapeutic strategies. Recent randomized clinical trials of renal artery revascularization showed no benefit compared with medical treatment.[9,11] Among the troublesome results from these studies was an unrelenting high incidence of clinical end points, implying that more effective strategies of screening, monitoring, and treatment are needed in ARAS. Although small studies reported that renal revascularization sometimes can reverse accelerated hypertension and restore kidney function, how best to identify these subgroups and recognize the potentially "viable kidney" remains unknown. To this end, several imaging methods have been developed in an attempt to probe the poststenotic kidney in ARAS.

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This review highlights conclusions gleaned from recent clinical trials and new understanding of ARAS and cutting edge imaging techniques applied for detecting and monitoring ARAS.

## RECENT CLINICAL TRIALS

Recent randomized clinical trials show that renal artery revascularization does not confer a significant benefit with respect to preservation of kidney function or prevention of adverse kidney and cardiovascular events in ARAS patients. Two randomized treatment trials were published in 2009. The Stent Placement in Patients with Atherosclerotic Renal Artery Stenosis and Impaired Renal Function and Angioplasty and Stenting for Renal Artery Lesions trials failed to detect any benefit regarding glomerular filtration rate (GFR) decline, blood pressure (BP), kidney function, mortality, or cardiovascular events.[9,11] The authors concluded that renal revascularization carries substantial procedure-related complications without adding benefit compared with medical treatment. However, these studies had limitations. The Angioplasty and Stenting for Renal Artery Lesions study restricted participation to patients in whom the treating physicians was uncertain about the appropriate treatment strategy (patients who would definitely "benefit" from renal revascularization were excluded). In addition, about 40% had a likely nonhemodynamically significant stenosis. In the Stent Placement in Patients with Atherosclerotic Renal Artery Stenosis and Impaired Renal Function trial, among 64 patients allocated to stent therapy, 30% did not undergo revascularization because of nonsignificant lesion (<50%) and follow-up loss. These flaws might have underpowered the results of these trials.

The more recent Cardiovascular Outcomes in Renal Atherosclerotic Lesion (CORAL) study published in 2014 was a large, multicenter, open-label, randomized controlled trial comparing optimal medical therapy alone to medical therapy plus stenting.[12] CORAL enrolled and followed 947 patients for a median of 43 months. Optimal medical therapy included an angiotensin receptor blocker (ARB), with or without thiazide-type diuretics, and calcium channel blocker for BP control. Participants also took antiplatelet and a lipid-lowering agent, and

some were also randomized to renal revascularization. The rate of the primary composite end points, including death and major cardiovascular outcomes, did not differ between medical therapy alone and medical and stenting therapy (35.8% and 35.1%, respectively; hazard ratio, 0.94; 95% confidence interval, 0.76-1.17; $P = .58$). Compared with the medical treatment group, a lower systolic BP was observed in the stented group, but the number of antihypertensive medications did not differ between the 2 groups. The authors concluded that renal vascularization with stenting does not have a significant benefit for prevention of clinical events in ARAS patients. However, this well-conducted study had some limitations. Enrollment did not require true renovascular hypertension. Exclusion criteria precluded patients with recent episodes of congestive heart failure, who might have specifically benefitted from stenting. A recent meta-analysis of several ARAS treatment trials including the CORAL study showed that overall patients receiving endovascular treatment required fewer antihypertensive medications, but systolic BP, serum creatinine, and incident cardiovascular event rate were unaffected.[13] This finding is consistent with the conclusions of previous meta-analyses.[14,15]

From these studies, it becomes clear that medical treatment should be the preferred management strategy for ARAS patients and that revascularization should be reserved for carefully selected subgroups of patients. However, how to select patients who stand to benefit from stenting is yet a challenge. Clearly, treatment outcomes of medically treated patients remain suboptimal. Furthermore, in recent trials, BP control was aggressive, whereas in real clinical practice, achieving and sustaining optimal BP levels are challenging. Therefore, development of innovative strategies targeting disease mechanisms activated in ARAS is critically needed.

**CLINICAL SUMMARY**

- Despite intensive treatment, a substantial number of patients with atherosclerotic renal artery stenosis progress to have kidney and cardiovascular events.
- The complex pathogenesis of atherosclerotic renal artery stenosis warrants therapeutic interventions targeting atherosclerosis, hypoxia, and inflammation.

## NEW UNDERSTANDING ON THE PATHOGENESIS OF ARAS

ARAS involves exposure of the poststenotic kidney to coexisting hypoperfusion, atherosclerosis, and cardiovascular risk factors, which in concert aggravate kidney dysfunction and impair kidney architecture. The decline in kidney perfusion and function in patients with ARAS does not correlate with the angiographic degree of stenosis,[16,17] and recent data suggest that its manifestations are far more complex than previously thought. Studies with blood oxygen level-dependent (BOLD) magnetic resonance imaging (MRI) indicate that the kidneys can adapt to substantial reduction in blood flow without developing tissue hypoxia,[18] but extreme vascular compromise overwhelms these adaptations and leads to cortical hypoxia and microvascular injury.[19] Furthermore, regional patches of hypoxia likely develop earlier but are more difficult to detect.[20,21] Well-established animal models and human studies have clarified the pathogenesis of ARAS distal to the stenosis.[1,22-24] ARAS not only induces hypoxia in the kidney but also activates the renin-angiotensin-aldosterone system (RAAS), oxidative stress, inflammation, and microvascular rarefaction, eventuating in kidney failure (Fig 1).

## RAAS ACTIVATION

The RAAS is one of the major control systems for BP and fluid balance. In a hemodynamically significant stenosis, reduced kidney perfusion stimulates release of angiotensin II, which exerts deleterious effects such as oxidative stress, apoptosis, and inflammation.[25] In turn, it activates several mechanisms that promote vascular and tissue remodeling. Angiotensin II exerts a strong stimulatory effect on transcription of profibrotic factors like transforming growth factor-ß (TGF-ß) and plasminogen activator inhibitor-1, leading to accumulation of extracellular matrix. Hence, prolonged activation of angiotensin II can directly lead to kidney fibrosis. Angiotensin II also stimulates nuclear factor kappa B, leading to activation of inflammatory gene transcription.[26] Clinically, RAAS inhibition with either ARB or angiotensin-converting enzyme inhibitors (ACEi) has a favorable impact on the kidney, which is thought to be additive to or independent of lowering BP.[27] Pharmacologic and genetic studies have confirmed that deleterious effects of the RAAS effects are mediated by angiotensin II type 1 receptor (AT1R).[28-30] ACEi decrease production of angiotensin II, whereas ARB block AT1R and, thereby, not only blunt the deleterious effects of angiotensin II but also allow it to bind to the angiotensin II type 2 receptor, which counters the effects of AT1R by inducing vasodilation, antiproliferation, and antiapoptosis.[25] Moreover, angiotensin II type 2 receptor stimulation in this setting reduces organ damage by both inhibiting arachidonic acid synthesis and limiting activation of nuclear factor kappa B.[31] Recently, we demonstrated that ARBs in a swine ARAS model also preserve the microcirculation of both the kidney[32] and heart.[33] The role of angiotensin II in activating the immune system is also under investigation.[34,35]

## OXIDATIVE STRESS

Much evidence implicates reactive oxygen species (ROS) in the pathophysiology of ARAS.[24,32,36,37] Oxidative stress, defined as an excessive production of ROS surpassing existing antioxidative defense mechanisms, plays a critical role in the development and progression of diabetic vascular complications, including nephropathy.[38] Oxidative stress in experimental ARAS has been evidenced by a progressive increase in systemic levels of the oxidative stress markers prostaglandin F2α-isoprostanes associated with decreased endogenous radical scavenger levels in both the stenotic and contralateral kidneys.[24] Activation of the