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Role of Renin-Angiotensin System Blockade in Atherosclerotic Renal Artery Stenosis and Renovascular Hypertension

Daniel G. Hackam, J. David Spence, Amit X. Garg, Stephen C. Textor

Current management of atherosclerotic renal artery stenosis (ARAS) remains controversial. A major issue is the condition's functional significance; specifically, what is the contribution of ARAS to a specified patient's heart failure, hypertension, or progressive renal disease? Clinicians will often consider whether revascularization of ARAS is likely to alter a patient's symptoms or prognosis. Yet, even when ARAS is incidentally detected, patients are at high risk for future cardiovascular events and death. This suggests that regardless of the clinical scenario, intensive medical therapy should be provided to all patients in whom ARAS is discovered. Here we review evidence that angiotensin inhibitors (angiotensin-converting enzyme [ACE] inhibitors and angiotensin receptor blockers [ARBs]) may improve the prognosis of ARAS. To place this evidence into context, it is important to first review the prognosis of this condition.

Cardiovascular Risk Associated With ARAS

Natural history studies indicate that patients with ARAS are at high risk for myocardial infarction, stroke, and cardiovascular death (Table 1). In a recent analysis of patients with ARAS, the annual incidence of coronary events, stroke, heart failure, and death was 30%, 18%, 19%, and 17%, respectively.¹ The presence of this disease decreases long-term survival by 2- to 4-fold.¹⁻³ An impaired prognosis is also evident in healthy patients with incidentally discovered ARAS. In a cohort of unselected community-dwelling Americans older than 65 years of age, baseline ARAS increased the risk of events by \approx 3-fold (hazard ratio [HR]: 2.92; 95% CI: 1.53 to 5.57).⁴ After adjusting for risk factors, renal function, subclinical cardiovascular disease, and medications, the risk conferred by ARAS remained significant (HR: 1.96; 95% CI: 1.00 to 3.83; $P=0.05$).

ARAS is also linked to heart failure and, in particular, a variant characterized by frequent decompensation.⁵ In a sample of elderly patients with chronic systolic heart failure, the prevalence of ARAS was 34%.⁶ Patients with ARAS had worse renal function and were much more likely to have concomitant peripheral artery disease. The presence of ARAS

in patients with heart failure worsens overall prognosis and is occasionally associated with recurrent pulmonary edema.⁷

The Pathophysiology of Cardiovascular Risk in ARAS

Several mechanisms link renovascular disease with atherothrombotic events. Many patients with ARAS have widespread atherosclerosis. In 1 recent study of patients with ARAS, extrarenal atherosclerosis was documented in 82% of the cohort, with peripheral artery disease, coronary artery disease, and cerebrovascular disease present in 68%, 45%, and 27%, respectively.⁸ Similarly, many patients undergoing coronary or peripheral angiography have ARAS on renal angiography.⁹ Thus, ARAS may be a marker of global atheroma burden, reflecting disease in other vascular beds.

However, additional mechanisms likely magnify the risk of events and death, because ARAS predicts risk even after adjusting for subclinical and clinical atherosclerosis.⁴ Patients with renovascular hypertension exhibit a greater degree of target organ damage (left ventricular hypertrophy, arrhythmias, renal injury, and retinopathy) than those with other forms of hypertension.¹⁰⁻¹² Individuals with ARAS manifest platelet activation, sympathetic tone, oxidative stress, and endothelial dysfunction.¹³⁻¹⁶ Of additional importance is the renin-angiotensin system (RAS), activation of which drives blood pressure elevation in renovascular hypertension. Sustained increases in angiotensin II and aldosterone induce vascular and myocardial remodeling, endothelial dysfunction, inflammation, and plaque vulnerability.

Angiotensin Inhibitors in Animal Studies of ARAS

Animal models have played a major role in dissecting the pathophysiology of ARAS. Seminal animal studies by Goldblatt et al,¹⁷ in particular, are among the most highly cited reports in experimental medicine. After the development of ACE inhibitors in the 1970s, it became possible to test whether selective interruption of the RAS favorably affects ARAS in animals. Studies by Rubin and colleagues^{18,19}

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Table 1. Studies of the Long-Term Prognosis of Renal Artery Stenosis

Study	Sample	Prognosis Related to ARAS
Mui et al ³	550 patients with PAD, including 129 with ARAS	Higher crude mortality (OR: 3.76; $P < 0.0001$) and adjusted mortality (OR: 1.62; $P = 0.005$)
Kalra et al ¹	1 085 250 seniors, including 7434 with ARAS	High annual rates of coronary events (30%), CHF (19%), stroke/TIA (18%), death (17%), and renal replacement therapy (3%), all significantly greater than patients without ARAS ($P < 0.0001$ for each)
Edwards et al ⁴	834 community-derived seniors, including 57 with ARAS	Higher crude (HR: 2.92; 95% CI: 1.53 to 5.57) and adjusted (HR: 1.96; 95% CI: 1.00 to 3.83; $P = 0.05$) risk for coronary events
Uzu et al ⁶²	44 patients with vascular disease, including 22 with ARAS	Higher annual mortality for unilateral ARAS (12.7%) and bilateral ARAS (18.1%) than patients without ARAS (4.4%); $P = 0.006$
Conlon et al ²	3987 patients undergoing aortic angiography, including 191 with ARAS	Higher crude mortality (RR: 3.91; $P < 0.001$) and adjusted mortality (RR: 2.01; $P < 0.001$) in patients with ARAS
Losito et al ⁴⁰	195 patients with ARAS and no control subjects	High annual rates of nonfatal coronary events (11.3%), fatal coronary events (5.3%), and dialysis (2.3%)
Johansson et al ⁶³	169 patients with renovascular hypertension, matched with the general population	Higher overall mortality (RR: 3.3; 95% CI: 2.4 to 4.5) and cardiovascular mortality (RR: 5.7; 95% CI 3.9 to 8.0) in patients with ARAS
Chabova et al ⁶⁴	68 patients with renovascular hypertension undergoing medical therapy and no control subjects	High annual rates of mortality (8.6%) and end-stage renal failure (2.7%)
Baboolal et al ⁶⁵	51 patients with bilateral ARAS and no control subjects	High annual rates of mortality (10.4%) and end-stage renal failure (2.7%)
Connolly et al ⁶⁶	94 patients with ARAS and no control subjects	High annual rates of mortality (12.3%) and end-stage renal failure (5.1%)
Kennedy et al ⁶⁷	261 patients with ARAS undergoing stenting and no control subjects	High annual rates of mortality (16.0%) and cardiovascular events (21.2%)
Losito et al ⁶⁸	61 patients with ARAS and no control subjects	High annual rates of mortality (7.7%) and end-stage renal failure (2.9%)

Data presented as risk ratios for controlled studies and annualized event rates for uncontrolled studies. Some prognostic data were recalculated from the original studies. CHF indicates congestive heart failure; HR, hazard rate ratio; OR, odds ratio; PAD, peripheral artery disease; RR, relative risk; TIA, transient ischemic attack.

showed that captopril (but not hydralazine or hydrochlorothiazide) reduced long-term mortality in ARAS by nearly two thirds. Later work observed improved survival for a range of ACE inhibitors, as well as ARBs, despite some evidence of fibrosis in the clipped kidney (Figure 1).^{20–28} In comparisons between various agents, angiotensin-inhibiting drugs were

more effective at preventing death than other antihypertensive agents.^{18–22}

Several mechanisms may account for these findings. In most models, improved survival correlated with reductions in blood pressure, with angiotensin inhibitors typically more efficient than other agents at improving systemic hemody-

ACE inhibitors

- Atkinson et al
- Battle et al
- Brilla
- Capdeville et al
- Dellsperger et al
- Dussaule et al
- Fein et al
- Jackson et al
- Morgan et al
- Nakata et al
- Rubin et al
- Wenzel et al
- Subtotal: OR 0.14 (0.08 – 0.25)**

Angiotensin receptor blockers

- Garcia et al
- Hilgers et al
- Morgan et al
- Subtotal: OR 0.20 (0.04 – 0.93)**

Total: OR 0.15 (0.09 – 0.25)

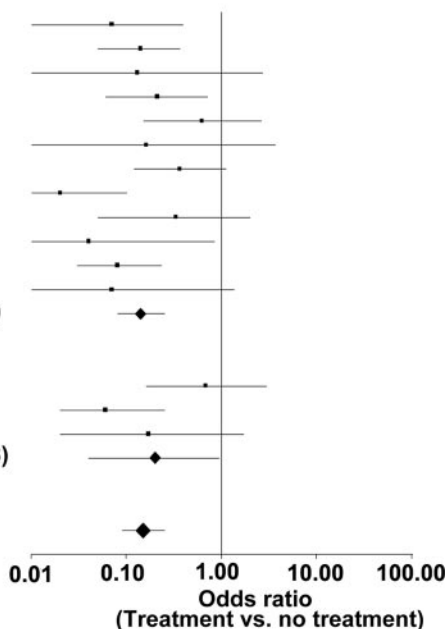


Figure 1. Random-effects meta-analysis of animal studies of mortality in relation to angiotensin inhibitors, with analyses stratified by treatment with ACE inhibitors or ARBs. Point estimates are shown as ORs with 95% CIs as whiskers. Data are plotted on a logarithmic scale. We found no evidence of heterogeneity between studies ($P = 0.08$; $I^2 = 36.1\%$). OR indicates odds ratio.

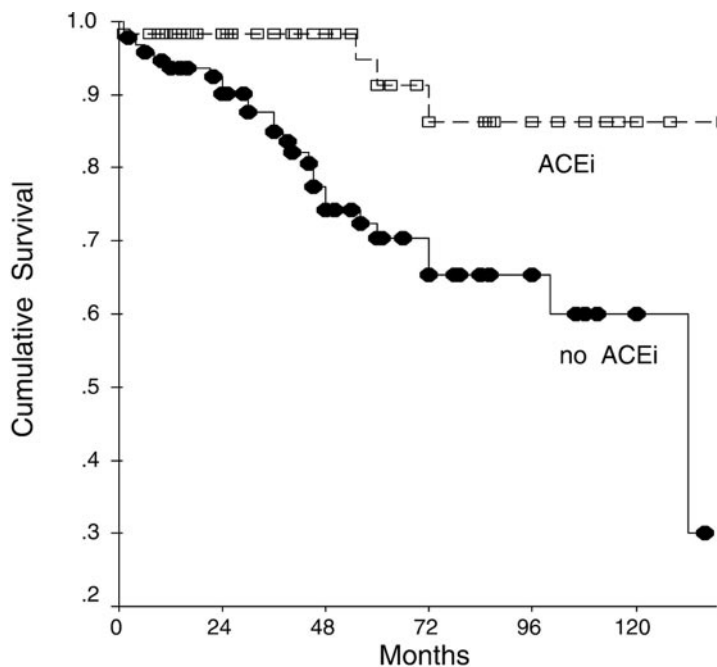


Figure 2. Kaplan–Meier survival analysis from a prospective observational cohort study comparing patients treated ($n=62$) or not treated ($n=133$) with ACEs inhibitors (mean follow-up: 4.5 years). Log rank $P=0.0026$ for the difference between survival curves. ACEi indicates ACE inhibitors. Reproduced from: Losito A, Errico R, Santirosi P, Lupattelli T, Battista-Scalera G, Lupattelli L. Long-term follow-up of atherosclerotic renovascular disease. Beneficial effect of ACE inhibition. *Nephrol Dial Transplant*. 2005;20:1604–1609 by permission of Oxford University Press.

Number at risk

On ACEi	62	45	33	18	12	6
Without ACEi	12	112	66	38	22	6

namics. Angiotensin inhibitors normalized left ventricular hypertrophy to a greater extent and reduced myocardial fibrosis and structural changes in the arterial wall.^{29–31} In a recent study of valsartan in rats with 2-kidney 1-clip hypertension, improved survival in the treatment group was accompanied by reductions in interstitial collagen accumulation, macrophage infiltration, and monocyte chemoattractant protein-1 expression.²⁴ Enhanced survival and reduced structural damage were seen with both low-dose and high-dose valsartan, although blood pressure was not decreased in the low-dose group.

Angiotensin Inhibitors in Human Studies of ARAS

Before the introduction of agents that specifically interrupt the RAS, effective therapy for renovascular hypertension in patients was limited. Available therapies targeted the sympathetic nervous system (including centrally active drugs, eg, methyldopa, reserpine and clonidine, and peripheral ganglion blocking agents, eg, guanethidine) or were diuretics, β -blocking drugs, and vasodilators. Not only were these drugs difficult to tolerate, they were often ineffective in patients with accelerated hypertension, some of which was because of ARAS.³² Several reports describe patients with recurrent, life-threatening episodes of hypertension for whom it was considered necessary to perform bilateral nephrectomy as a life-saving measure.^{33,34}

Starting in the early 1980s, trials began to evaluate ACE inhibitors in patients with renovascular hypertension.^{35–39} These studies showed that ACE inhibitors were more effective in controlling blood pressure than previously available therapy. For example, Franklin and Smith³⁵ compared combination therapy with enalapril plus hydrochlorothiazide

against triple therapy based on hydrochlorothiazide, timolol, and hydralazine in 75 patients with renovascular hypertension. The enalapril-hydrochlorothiazide group had greater decrements in mean systolic blood pressure and higher rates of target blood pressure attainment (96% versus 82%, respectively; $P<0.05$). Achievement of blood pressure goals with ACE inhibitors in other trials ranged from 80% to 100%.^{36–39} Reassuringly, discontinuation rates because of rising creatinine levels were low, ranging from 0% to 3.5%. In aggregate, these data suggest that RAS interruption is highly effective for controlling blood pressure in patients with renovascular disease.

Two limitations of these studies are the inclusion of potentially healthier patients and a lack of data on definitive cardiovascular end points. The association of ACE inhibitors with survival was studied in an observational cohort that enrolled consecutive patients with documented ARAS. ACE inhibitors were associated with decreased mortality over 4.5 years (HR: 0.24; 95% CI: 0.08 to 0.71), which was consistent in multivariable analyses and in subgroups receiving revascularization or medical therapy alone (Figure 2).⁴⁰ Improved survival may relate to the robust decline in blood pressure commonly seen with angiotensin interruption in ARAS. Accordingly, Tullis et al⁴¹ showed that only ACE inhibitors, and not other antihypertensive classes, were associated with reductions in systolic and diastolic blood pressure in this setting.

Acute Renal Failure and Angiotensin Inhibition

The occasional development of acute renal insufficiency from angiotensin inhibition in ARAS likely prevents greater diffusion of this therapy to otherwise eligible patients. However, this complication may be less frequent than previously

thought. Among some 10 000 patients referred to a large hypertension clinic, including >400 patients with renovascular hypertension, we have seen only 18 patients with acute renal failure with angiotensin blockade; all were reversible. Furthermore, van de Ven et al⁴² reported a careful prospective evaluation of renal function in 93 patients with ARAS; in this study, controlled initiation of enalapril did not precipitate acute renal insufficiency, although 67 patients had significant increases in creatinine ($\geq 20\%$ above baseline levels). Most of these elevations were seen in the subgroup with high-grade bilateral ARAS or unilateral RAS to a solitary functioning kidney; in all of the cases, creatinine levels normalized on drug cessation.

In patients with unilateral ARAS, an additional concern is the possibility of long-term loss of renal mass in the stenotic kidney in the face of overall normal renal function. Whether angiotensin inhibitors amplify or contribute to this process is currently unclear. In an often-cited prospective analysis of patients with ARAS followed by duplex ultrasonography for a mean of 33 months, the use of ACE inhibitors was not associated with loss of renal mass; conversely, higher blood pressure (both at baseline and during follow-up) and a greater degree of stenosis were associated with atrophy.⁴³ Animal data also suggest that angiotensin inhibitors do not have selectively profibrotic effects over other antihypertensive agents in this setting.⁴⁴

Multiple series suggest that acute deterioration in renal function is mainly confined to cases in which the entire renal mass is subject to renovascular obstruction.^{42,45–49} In such cases, angiotensin blockade can be considered a form of “medical nephrectomy.” Additional risk factors for acute renal failure in this setting include severe congestive heart failure, use of high-dose loop diuretics, volume contraction, and poor baseline renal function.^{48–50} In the data published to date, azotemia usually remitted on discontinuation of the drug, and most patients did not require long-term dialysis. In a number of series and case reports, moreover, renal revascularization allowed reintroduction of angiotensin inhibitors without further episodes of azotemia.^{5,51–54} Accordingly, some authors suggest that acute renal failure stemming from initiation of angiotensin inhibitors in patients with ARAS represents an indication for renal revascularization.^{55,56}

Heterogeneity of Patient Subtypes

ARAS is a complex clinical entity that requires individualized care from treating physicians. The disease runs from the full spectrum from asymptomatic disease discovered on imaging to high-grade bilateral disease complicated by recurrent pulmonary edema, severe hypertension, and progressive renal failure. Complicating the picture, recent studies suggest that the age and comorbidity of patients with ARAS have increased dramatically over the past few decades.⁵⁷ Such comorbidities typically include diabetes, chronic lung disease, renal impairment, stroke, and hypertension. The implications of this are 3-fold: (1) patients with ARAS frequently die as a result of their comorbidities rather than ARAS itself; (2) therapeutic regimens must be tailored to account for clinical complexity and the potential for drug interactions; and (3) randomized trials with relatively small samples can be

Table 2. Unanswered Questions Concerning the Use of Angiotensin Inhibition for Renal Artery Stenosis

Do angiotensin inhibitors decrease mortality and cardiovascular events in patients with ARAS and no known indications for this treatment (such as heart failure or asymptomatic left ventricular dysfunction)?
Do angiotensin inhibitors reduce progression to end-stage renal disease in patients with ARAS?
What are the risks of angiotensin inhibitors in patients with ARAS encountered in primary care settings?
How common is hyperkalemia in patients with ARAS who are treated with angiotensin inhibitors?
Should patients with ARAS who are treated with angiotensin inhibitors be followed with serial imaging to track changes in kidney size?
Are there important outcome-related differences among ACE inhibitors, ARBs, and renin inhibitors in patients with ARAS?

compromised by asymmetries in the prevalence of comorbidities and other important factors.

In addition to activation of the RAS, other pathologic processes play an important role in the genesis of ARAS and its sequelae. In keeping with other atherosclerotic states, independent risk factors for ARAS include smoking, dyslipidemia, diabetes mellitus, hypertension, advanced age, and male sex. Platelet activation and inflammation are also active players. Limited animal and human data suggest a potential role for antiplatelet agents and statins in ARAS.^{58–60}

Future Perspectives

The accumulated evidence from animal studies, small clinical trials, and cohort studies is persuasive but does not prove that angiotensin inhibitors effectively reduce the risk of cardiovascular events and death in patients with ARAS. Indeed, because of the limited nature of this evidence base, firm recommendations regarding the use of these agents in ARAS cannot yet be made. Other questions remain unanswered, such as the relative equivalence of ACE inhibitors and ARBs, the true incidence of angiotensin inhibitor-induced renal failure in primary care (rather than in secondary or tertiary care), the intensity of follow-up required in this setting, and the risks of iatrogenic hyperkalemia (Table 2). Despite these uncertainties, it is reasonable to monitor renal function and electrolytes in patients with renovascular disease in whom angiotensin inhibitors are initiated. In addition, angiotensin inhibitors are likely safest in patients with unilateral ARAS (and good function in the contralateral kidney) or in those with low-grade bilateral disease. The respective roles of RAS inhibition and revascularization as therapeutic approaches in ARAS remain to be defined.

Ultimately, only a hypothesis-driven randomized trial with definitive end points can fully determine the long-term risks and benefits of angiotensin inhibition in this setting. Such a study could also tell us whether angiotensin inhibition improves the long-term renal prognosis of ARAS, reducing progression to end-stage renal failure as such agents are known to do in chronic nephropathy of other causes. The trial would likely need to exclude patients with strong indications for angiotensin inhibitors, such as chronic heart failure or previous myocardial infarction, given that the mortality

benefit of these agents has already been proven in these settings. Given the high baseline risk of patients with ARAS (Table 1), we estimate that such a trial would need to enroll ≈ 900 patients and have a follow-up of 3 years to exclude a 20% relative-risk reduction with therapy (2-tailed $\alpha=0.05$ and $\beta=0.20$). An important subset in this trial would consist of patients with a history of renal revascularization, so that the interaction of angiotensin inhibitors and mechanical intervention might be better defined.

Ongoing trials in this field are mainly focused on the role of renal artery stenting for improving prognosis. In the largest such study, the Cardiovascular Outcomes in Renal Atherosclerotic Lesions Trial, all of the enrolled patients will receive candesartan as part of optimal medical therapy.⁶¹ We believe that a major opportunity will be lost if randomized trials are not performed to evaluate whether angiotensin inhibitors are indeed an essential component of optimal medical therapy in this setting.

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