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Cardiovascular Morbidity and Mortality and Renal Artery Stenosis

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Abstract

Renal artery stenosis (RAS) is a common manifestation of atherosclerosis and is associated with many other atherosclerotic conditions. Cardiovascular morbidity and mortality is increased among patients with RAS. This increase is likely due in part to the associated disease states; however, RAS itself may also contribute. Current strategies to limit cardiovascular morbidity and mortality in RAS include various pharmacologic interventions targeting both RAS atherosclerosis in general. Additionally, revascularization has been advocated; however, clear data are lacking. Ongoing clinical trials such as the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial will ultimately help to determine the best strategies to limit the morbidity and mortality associated with RAS.

Keywords

Renal artery stenosis; Treatment; Mortality; Outcomes

Renal artery stenosis (RAS) is a common manifestation of atherosclerosis. It is frequently associated with other atherosclerotic diseases such as coronary artery disease, cerebrovascular disease, and peripheral vascular disease (Table 1).^{1–17} Given this high prevalence of associated disease, it is not surprising that RAS is associated with significant cardiovascular morbidity and mortality. It is difficult to determine the precise role played by RAS; however, efforts to do so are important because such an understanding may impact treatment strategies for RAS. Although RAS is associated with other forms of vascular disease, there is some evidence that cardiovascular mortality is increased independently by the presence of RAS.^{1,18–20}

Many studies have reported high overall and cardiovascular mortality in patients with RAS. More than 40 years ago, Wollenweber et al¹⁸ reported that the 5-year mortality among patients with RAS was 33%, compared with 8% among patients without RAS. In a study of patients where RAS was detected during cardiac catheterization, Conlon et al¹ reported a 35% mortality rate at 4 years of follow-up, compared with 14% in patients without RAS. In a study of 98 patients with RAS, Wright et al²¹ reported a mortality of 36%, with most

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Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

deaths being due to a cardiovascular etiology. Notably, among the patients reported by Wright et al,²¹ 61% had either no or one comorbid cardiovascular condition. In a large population study of Medicare patients in the United States, adverse cardiovascular event rates, including mortality, were found to be significantly higher among patients with RAS (Table 2).²² Baboolal et al²³ reported that among patients with medically treated bilateral RAS, the mortality was 45% at 5 years, with a very high early mortality rate of 38% within 2 years of renal angiography.

Among patients who have undergone stent placement for RAS, similarly high event rates are seen. In a large multicenter registry, Dorros et al²⁴ reported a 4-year mortality rate of 26%. In SOCRATES, patients were followed for up to 10 years after renal artery stenting, with mortality increasing from 9% at 1 year to 33% at 5 years and ultimately 51% at 10 years.²⁵ Kennedy et al²⁶ reported high adverse event rates, including mortality among patients with RAS treated with renal artery stenting followed for up to 6 years (Table 3). The high rates of cardiovascular events seen among patients with RAS, regardless of treatment strategy, suggest that RAS may be contributing to these events beyond being a “bystander” in patients with other forms of cardiovascular disease.

Mechanisms of increased cardiovascular events

RAS is known to be associated with hypertension, which is a well-established risk factor for many cardiovascular events. In addition, RAS is associated with renal insufficiency, which is known to worsen cardiovascular outcomes.^{8,26–32} RAS is also known to activate the rennin-angiotensin-aldosterone system (RAAS), which in turn has specific deleterious cardiovascular effects.^{33–35}

Renal insufficiency and adverse cardiovascular events

Renal insufficiency, in general, specifically those due to RAS, is associated with increased adverse cardiovascular event rates. Among patients 65 years and older hospitalized with a myocardial infarction (MI), renal function is strongly correlated with mortality. In patients with normal renal function, the 1-year mortality was 24%, whereas it was 46% in patients with mild renal insufficiency and 66% in patients with moderate renal insufficiency.²⁸ It has also been shown that renal insufficiency, ranging from mild to end-stage renal disease, is a stronger predictor of in-hospital mortality after MI than increased Killip class on admission or the development of a mechanical complication of MI.²⁹

Among patients with RAS treated with stenting, Dorros et al²⁴ found impaired renal function at baseline to be associated with increased long-term mortality. Specifically, 4-year mortality increased from 15% in patients with normal renal function to 22% in patients with mild renal insufficiency and 51% in patients with severe renal insufficiency. Similarly, Kennedy et al²⁶ has shown that mortality and other adverse cardiovascular events after renal artery stenting are related to baseline renal function, despite the fact that there were no differences in the rate of coronary artery disease or other comorbid conditions at baseline.

Renin-angiotensin-aldosterone system Activation and adverse cardiovascular events

The RAAS is activated when RAS leads to neuroendocrine activation of renal juxtaglomerular cells triggering the release of renin. Renin then acts upon circulating angiotensinogen to produce angiotensin I. Angiotensin I is then converted to angiotensin II, which has multiple deleterious effects throughout the cardiovascular system.³³ Specific effects of angiotensin II include vasoconstriction, aldosterone release, antidiuretic hormone release, cardiac hypertrophy, increased oxidative stress, increased inflammation, and platelet aggregation.³⁴ In addition, angiotensin II has been shown to increase the oxidation of low-density lipoprotein cholesterol, metallo-proteinase production, and lipid peroxidation.^{34,36–38} Thus, RAS-induced activation of the RAAS leads to progression of systemic atherosclerosis as well as to direct effects upon the cardiovascular system.

Therapeutic targets for reducing cardiovascular events

Given the effects of RAS described previously, treatments aimed at stabilizing or improving renal function or decreasing activation of the RAAS are attractive targets for decreasing cardiovascular events. Specifically, renal artery stenting is often performed with these goals. Yet, the role of renal revascularization and stenting, in particular, remains controversial because many experts advocate for the medical management of RAS.

Renal artery stenting to improve renal function

Many experts advocate for the revascularization of RAS, most commonly with stents, to stabilize or to improve renal function. This has been suggested by several studies; however, these are largely limited by factors such as small study size, single-center, retrospective analysis and registry reports.^{39–41} Conversely, renal function has not been shown to improve with revascularization in larger randomized trials that have been completed, including DRASTIC, EMMA, the Scottish and Newcastle Renal Artery Stenosis Collaborative Group, and ASTRAL (Table 4).^{42–46} Despite this lack of improvement in renal function in randomized trials of renal artery revascularization, this remains an appealing target for improving mortality in RAS. Indeed in each of these trials, renal function outcomes were secondary. Kennedy et al²⁶ has shown that among patients with RAS who have an improvement in renal function after stent placement, there is an improvement in survival. This suggests that if the renal response to revascularization can be predicted with greater accuracy, that patients likely to have improved cardiovascular outcomes could be selected for stenting.

Pharmacologic blockade of the RAAS

Trials such as HOPE and ON TARGET have shown that interruption of the RAAS with angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) reduce multiple cardiovascular adverse events.^{47,48} Although patients with RAS are at high risk for cardiovascular events, RAAS blockade is often avoided. Specifically, ACE-I and ARBs are avoided in RAS because of concerns of worsening renal failure.^{49,50} Clearly, there are patients with both unilateral and bilateral RAS who develop worsening renal function after introduction of an ACE-I or ARB; thus, these agents should be approached with caution in this patient population. However, in these patients, a fall in glomerular filtration

rate is not specific to ACE-I. As a result of lowering of blood pressure, which, in renovascular hypertension, is most effectively achieved with ACE-I, a loss of poststenotic function may occur. Therefore, regardless of the blood pressure regimen, close monitoring of renal function is an essential step during the chronic therapy of hypertension in patients with known RAS. In addition, there is evidence that RAAS blockade can be quite beneficial in patients with RAS.^{51,52}

Losito et al⁵¹ reported on outcomes of patients with RAS treated with ACE-I with long-term follow-up. Most of the patients (71%) underwent a revascularization procedure, and the use of ACE-I was similar between patients treated with revascularization vs medical therapy alone. In this group of patients, ACE-I use was associated with a significant survival advantage.

Hackam et al⁵² recently reported on the use of RAAS blockade in a large patient population.⁵² In this study, approximately half of 3570 patients were treated with either an ACE-I or ARB. This study revealed that RAAS blockade reduced the primary composite end point of death, MI, and stroke and, specifically, also the risk of death. Perhaps not surprisingly, heart failure hospitalizations were also significantly reduced. Although there was an increase in the incidence of acute renal failure and hyperkalemia among patients treated with RAAS blockade, there was no increased risk of long-term dialysis. Indeed, the need for long-term dialysis was significantly reduced among patients receiving RAAS blockade.⁵² Furthermore, these benefits were consistent among patients undergoing revascularization, as well as those who were treated with medical therapy only.⁵²

One of the limitations of the data regarding RAAS blockade in patients with RAS is the lack of large, randomized, controlled trials. The Cardiovascular Outcomes in Renal Atherosclerotic Lesions trial (CORAL) will help provide greater insight into the role of RAAS blockade in patients with RAS.⁵³ In CORAL, all patients receive optimal medical therapy, including treatment with an ARB. Thus, questions about both the safety and efficacy of RAAS blockade, among both medically treated and revascularized patients with RAS, will be answered.

Other pharmacologic strategies

Given the high burden of concomitant atherosclerotic disease among patients with RAS, it seems likely that agents that are useful in these conditions would also be useful for patients with RAS. In recent years, statins have emerged as among the most powerful agents for reducing cardiovascular events. Recently, Silva et al⁵⁴ demonstrated statins to be particularly beneficial in patients with RAS. Specifically, it was demonstrated that statin therapy substantially reduced mortality from 36% to 6%. In addition, the doubling of serum creatinine or progression to end-stage renal disease was reduced from 39% to 7%.⁵⁴ This would suggest that in the absence of a clear contraindication, statins should be administered to all patients with RAS regardless of untreated lipid levels.

Conclusions

RAS is commonly associated with other manifestations of atherosclerotic disease. As such, it is somewhat challenging to determine whether RAS increases the rate of adverse cardiovascular events or simply is a marker of atherosclerotic burden. The truth likely lies somewhere between these ends of the spectrum, with RAS worsening outcomes, at least in some patients. Given the high rates of adverse cardiovascular events, it is essential to identify and use strategies to reduce these event rates. This would include the use of antiplatelet therapies and the control of known cardiovascular risk factors such as hypertension and diabetes. In addition, patients should be counseled to make appropriate lifestyle changes. Current evidence would suggest that RAAS blockade be offered to all patients with RAS; however, this must be accompanied by careful monitoring for hyperkalemia and deterioration of renal function. In addition, all patients with RAS should receive statin therapy regardless of lipid levels. The role of revascularization is much more controversial because no randomized trials have demonstrated a mortality benefit. Although some patients may be selected for revascularization based upon individual circumstances, most patients with RAS should be referred for enrollment in trials such as CORAL, so that the best strategy-reduced events in this high-risk population can be identified.

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Table 1

Prevalence of RAS among patients with other forms of atherosclerosis

	RAS prevalence	Reference
Stroke	10%	[7]
Carotid artery disease	19%	[5]
Coronary artery disease	6%–40%	[9,10]
MI	12%	[8]
Abdominal aortic aneurysm	20%–38%	[4,5,11,13]
Iliac and lower extremity occlusive disease	21%–49%	[5,6,11–13,16]

Table 2

Rates of adverse cardiovascular events among medicare patients in the United States [22]

Event	Incidence among patients with RAS (events per 1000 patient years)	Incidence in the general population (events per 1000 patient years)
Atherosclerotic heart disease	303.9	73.5
Peripheral vascular disease	258.6	52.2
Congestive heart failure	194.5	56.3
Cerebrovascular accident or Transient ischemic attack	175.5	52.9
Death	166.3	63.3

Table 3

Rates of adverse cardiovascular events among patients treated with stenting for RAS [26]

Event	Rate
Congestive heart failure	20%
MI	11%
Stroke	7%
Death	32%

Table 4

Renal outcomes from randomized trials comparing revascularization and medical therapy in RAS [42–44]

Trial	Intervention	Medical therapy	P
DRASTIC			
Serum creatinine (mg/dL)	1.2	1.2	
Creatinine clearance (mL/min)	70	62	.11
EMMA			
Creatinine clearance (mL/s)	1.28	1.23	.73
Scottish and Newcastle			
Serum creatinine (mg/dL)			
Bilateral disease	2.1	1.8	NS
Unilateral disease	1.6	2.3	NS

NS indicates not significant.