



ACCEL: Renal Artery Intervention: Who Gets What and When?
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Abstract

Patients with renal artery stenosis (RAS) may develop poorly controlled hypertension, progressive renal insufficiency, or renal atrophy, all of which are usually asymptomatic in the early stages. In recent years, RAS has been a widely discussed, hotly debated topic in cardiovascular medicine. There are many reasons for the increased interest and ongoing debate, including an aging population, improved imaging methods that suggest RAS is more common than previously thought, and conflicting data regarding treatment options.

Less debatable is the seriousness of RAS. In a 2-year period, about one-third of patients with ischemic renal disease will experience a cardiovascular event and the risk of mortality is directly related to the severity of atherosclerotic RAS: The more severe the stenosis, the higher the mortality risk (Slide 1).¹

Despite its association with renal function, about 90% of the serious events associated with RAS are cardiovascular in nature, including death, heart failure, myocardial infarction (MI), and stroke. Given that the presence of coronary artery disease (CAD) independently doubles these patients' risk of mortality, the detection of atherosclerotic RAS, even if not hemodynamically significant, provides information that should affect patient management.¹

Incidence and Detection

The incidence of RAS is about 0.1% in the general population, 4.0% in a hypertensive population, and 10-20% in individuals with hypertension and CAD.²⁻⁴ For patients with peripheral vascular disease, the prevalence of atherosclerotic RAS has been estimated to be 30-50% in most studies.⁵ Overall, ischemic nephropathy may be responsible for 5-22% of advanced renal disease in patients older than 50 years.

There has been considerable debate regarding the value of routine renal arteriography at the time of coronary arteriography. In the largest series of patients undergoing such screening, 1,235 unselected, consecutive patients had both coronary arteriography and abdominal aortography.⁶ Thirty percent of patients had some evidence of atherosclerotic RAS and 15% had lesions with $\geq 50\%$ diameter stenosis.

In a 2006 science advisory, the American Heart Association noted that the increased prevalence of atherosclerotic RAS in patients with CAD and the poor prognosis of these patients support a need for greater awareness and earlier detection of RAS.⁷ The authors noted, "It is reasonable to perform screening renal arteriography at the time of cardiac catheterization in patients at increased risk for (atherosclerotic) RAS (Slide 2) who are candidates for revascularization."

Managing RAS

RAS can be managed by medication alone (often using multiple antihypertensive therapies) or with revascularization of the stenosed artery or arteries. Despite the proven efficacy of surgical revascularization, endovascular therapy is increasingly being performed using percutaneous transluminal renal angioplasty (PTRA) and endoluminal stenting. Yet, the value of PTRA remains the source of considerable debate.

At the end of 2006, investigators published a systematic review of prospective studies evaluating medical therapy versus interventional therapy for RAS.⁸ No study directly compared aggressive medical therapy with angioplasty and stent placement. Observational studies of medical therapy demonstrated deterioration in renal function over time while of the 22 cohort studies of angioplasty, two demonstrated improvement, two worsening, and the remainder no change in renal function. Two randomized trials of renal angioplasty versus medical therapy did not demonstrate superiority of either strategy with respect to preservation or improvement of renal function.

The two randomized trials, as well as most of the comparative studies, found some evidence of greater improvement in blood pressure after angioplasty than medical treatment. After PTRAs, patients required almost half as many antihypertensive drugs as those in the medical arm. Furthermore, a small subset (18%) was totally cured of their hypertension.

In this systematic review, renal interventions were associated with a high incidence of complications, including a 30-day mortality of up to 3%, transient deterioration of kidney function in 1-13%, renal artery or parenchymal injury in up to 5%, and periprocedural MI in up to 3%. The incidence of renal arterial restenosis is high and ranged from 10-21% (17 studies) during 3-40 months of follow-up.

In general, the authors noted, the studies had poor methodologic quality and limited applicability to current practice. Overall, they reported no robust evidence from which to draw conclusions and no one treatment approach that was clinically superior to another for patients with atherosclerotic RAS.

Even differences in quality-of-life (QOL) measures are minimal. Krijnen et al. for example, studied patients with hypertension, significant atherosclerotic RAS, and normal or mildly impaired renal function who were randomized to immediate balloon angioplasty or drug therapy followed by angioplasty after 3 months, if needed.⁹ Based on 1-year follow-up, immediate angioplasty was beneficial only for patients with bilateral stenosis. Moreover, both groups reported similar physical complaints and QOL. There was a decrease in the number of antihypertensive drugs required after intervention, but the change was too small to lead to a detectable improvement in QOL.¹⁰

The ASPIRE-2 study was a large multicenter registry, which followed hypertensive patients with suspected renovascular hypertension and a presumed RAS $\geq 70\%$.¹¹ Stent placement was successful in 80% of lesions and the 9-month binary restenosis rate was 17%. There was an approximately 20-point decline in systolic blood pressure associated with the procedure that was maintained over 24 months (Slide 3). There was a small but statistically significant effect on the number of antihypertensive medications used during follow-up (Slide 4). At 2 years, the cumulative rate of major adverse events was 20% (Slide 5), with most events being target lesion revascularization.

Interestingly, only 47% of the ASPIRE-2 study cohort experienced a significant lowering of blood pressure. While this may be due to several factors, the mean renal artery percent diameter stenosis reported by the angiographic core lab was 61.5%. This suggests that patients with moderate, not severe, RAS were enrolled and many may have had primary as opposed to renovascular hypertension. The authors noted that the inconsistent blood pressure response to renal stenting highlights the importance of appropriate patient selection, particularly in light of the observed 20% risk of major adverse events at 2-year follow-up.

The most recent data come from the 2008 SCAI-ACC i2 Summit where investigators presented the results of the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial. Patients with significant renal artery stenosis, in whom the investigators were unsure of appropriate therapy, were randomized to PTRAs (angioplasty and/or stenting) plus medical therapy (n = 403) or medical therapy alone (n = 403). Of the medically treated group, 4.4% were crossed over to renal revascularization and 93% of all revascularized patients received a stent. The primary endpoint — an improvement in renal function — was no different in the two patient groups. There were only trends suggesting benefits associated with intervention in terms of cardiovascular mortality or hospitalization for fluid overload or heart failure (Slide 6). There also was no difference in serum creatinine, systolic blood pressure, time to first renal event, or overall vascular event during follow-up (p = ns for all outcomes).

Current guidelines suggest that revascularization may benefit specific subgroups of patients, including those with hemodynamically significant RAS and recurrent, unexplained congestive heart failure or unexplained, sudden-onset or "flash" pulmonary edema (class 1 recommendation). Percutaneous revascularization is reasonable (class IIa) for patients with hemodynamically significant RAS and unstable angina or accelerated hypertension, resistant hypertension, and malignant hypertension. It is also

reasonable for patients with RAS and progressive chronic kidney disease with bilateral RAS, or RAS to a solitary functioning kidney, and for patients with RAS and chronic renal insufficiency with global renal ischemia.

It should be noted that none of those recommendations are based on data from multiple randomized clinical trials or meta-analyses (level of evidence A), but rather emerge from single randomized trials or nonrandomized studies (level B) or from consensus opinion of experts, case studies, or standard-of-care (level C). Eventually, better evidence may emerge from the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial. This large, randomized, prospective trial is comparing angioplasty with stenting and optimal medical therapy versus medical therapy alone on a composite of adverse cardiovascular and renal events. CORAL is a National Institutes of Health-sponsored trial and uses medical therapy that includes tight control of blood pressure, treatment of dyslipidemia and diabetes, smoking cessation, administration of an antiplatelet agent, and attention to the complications of renal insufficiency. The findings from this trial will not be available until 2010.

This interview for ACCEL features Michael R. Jaff, DO, FACC, co-author of the ASPIRE-2 study and co-chair of the writing committee that prepared the 2006 AHA advisory detailing the indications for renal arteriography at the time of coronary arteriography. He discusses specifics regarding the detection and management of patients with RAS and which patients are candidates for intervention.

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