Update on intervention versus medical therapy for atherosclerotic renal artery stenosis

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Atherosclerotic renal artery stenosis is known to be one of the most common causes of secondary hypertension, and early nonrandomized studies suggested that renal artery stenting (RASt) improved outcomes. The vascular community embraced this less invasive treatment alternative to surgery, and RASt increased in popularity during the late 1990s. However, recent randomized studies have failed to show a benefit regarding blood pressure or renal function when RASt was compared with best medical therapy, creating significant concerns about procedural efficacy. In the wake of these randomized trial results, hypertension and renal disease experts along with vascular interventional specialists now struggle with how to best manage atherosclerotic renal artery stenosis. This review objectively analyzes the current literature and highlights each trial's design weaknesses and strengths. We have provided our recommendations for contemporary treatment guidelines based on our interpretation of the available empirical data. (J Vasc Surg 2015;61:1613-23.)

Renal artery stenosis (RAS) is a recognized cause of secondary hypertension, renal dysfunction, and flash pulmonary edema (Pickering syndrome).[1] Atherosclerotic renal artery stenosis (ARAS) is the most common cause of RAS, accounting for more than 90% of cases[2]; about 16% of those patients currently undergo revascularization in the United States.[3] Other nonatherosclerotic causes include vasculitis, dissection, and fibromuscular dysplasia. Nonatherosclerotic RAS treatment paradigms vary from angioplasty for fibromuscular dysplasia to anti-inflammatory treatments for vasculitis and thus are beyond the scope of this review.

ARAS is associated with advanced systemic atherosclerosis and is present in 38%, 33%, and 39% of patients with abdominal aortic aneurysms, aortoiliac occlusive disease, and peripheral vascular disease, respectively.[4] Autopsy data suggest that the prevalence of ARAS increases with age, diabetes, peripheral arterial disease, coronary artery disease, hypertension, and dyslipidemia.[2] It is estimated that 15% of hypertensive patients will have evidence of ARAS, with one fifth of them having >60% RAS by angiography.[5] The prevalence among patients with coronary artery disease is estimated to be 5.4% to 38.8%,[6-8] although the incidence is slightly higher in women >60 years old who have ≥coronary artery disease involving two or more vessels.[9] Epidemiologic data suggest that ARAS appears to be a relatively common clinical finding and is present in 6.8% of patients older than 65 years.[2] In patients with peripheral artery disease, incidental RAS (diameter reduction >50%) predicts long-term mortality (65% vs 43%).[4]

The goals of therapy in patients with ARAS are to control blood pressure, to reduce fluid shifts that may cause sudden pulmonary congestion, and to improve or stabilize renal function. There have been significant advances in contemporary pharmaceutical antihypertensive discovery, including angiotensin-converting enzyme inhibitors, calcium channel blockers, angiotensin receptor blockers, and beta blockers; thus, blood pressure control has become less of a challenge. In addition, the evolution of statin and antiplatelet therapy may have improved medical outcomes, further narrowing the risk/benefit window.

When intervention was indicated, surgical revascularization was the "gold standard," with many acceptable techniques, including endarterectomy and aortorenal, splenorenal, or hepatorenal bypasses. However, during the last two decades, renal artery stenting (RASt) has become an attractive alternative to surgery because of the less invasive approach and low morbidity.[10,11] The initial enthusiasm for RASt was augmented by a refinement in technology and a decrease in the complication rates. This led to an exponential increase in patients undergoing RASt in the late 1990s, with 7500 patients undergoing RASt in 1996 compared with 18,500 in 2000.[12] However, recent conflicting data from multiple trials have added significant uncertainty as to whether RASt provides a clear-cut benefit over best medical therapy.[13-16] This invited review outlines current available data from retrospective, prospective, and randomized trials in an attempt to define the selected population that would gain the most benefit from renal revascularization. We believe that the best outcome can be achieved by selecting the appropriate patient with clear indications in a center with an experienced team.

ARTICLE SELECTION AND REVIEW METRICS

To perform a thorough literature search for trials addressing medical therapy or percutaneous intervention

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for ARAS, we selected trials with enough patients to have statistical validity and that followed contemporary outcome guidelines. Various studies were chosen on the basis of their design, including patient number and treatment arms. Studies were included that were recent (at least in the past decade), had a sample size of 50 or more, reported actual outcome measures such as hypertension or renal function, defined the type of treatment or intervention, or were recent prospective clinical trials. Baseline characteristics for each study population were collected when reported. Clinical outcomes included renal function, blood pressure response (systolic [SBP], diastolic [DBP], or both), number of antihypertensive medications, mortality, restenosis, and target vessel revascularization (TVR). Because of nonuniform presentation of data, we reported results as a statistically significant change from baseline ($P < .05$) or not ($P > .05$), according to the publication conclusions and data presented. In some cases, no statistical value was given for a clinical outcome, but it was reported as stabilized, improved, or worsened.

Study outcomes were captured during mean/median follow-up or at study end point as reported by the authors. Indications and exclusions varied by study and in some cases were not reported. In general, patients had to have either renal dysfunction or hypertension and imaging findings of ARAS to be included in the trials. Exclusion criteria generally included anatovious intervention, renal size on ultrasound, and severe renal dysfunction based on study definition. Renal improvement was recorded when a statistically significant change in renal function was reported. Some studies reported renal stabilization and were recorded as such. If no statistically significant change in renal function or stabilization was reported, then neither was recorded. Thus, no change was coded as 0, whereas 1 and 2 were used for improvement and stabilization, respectively. All other variables were coded as 0 (not occurring) or 1 (occurred or existence). A quasi–meta-analysis method was used to combine, collate, and compare all of the data elements that were extracted from the selected studies. The studies included in our overall analysis are detailed in Table I.

Many studies attempted to identify which patients are most likely to experience a change in their blood pressure after intervention. Although hypertension was rarely cured (no medication required to keep blood pressure <140/90 mm Hg), improvement from baseline was noted in the majority of studies, and fewer antihypertensive medications were generally required. Various stenting-only studies noted that patients with the greatest blood pressure benefit were those having the highest preintervention blood pressure.[17-20] Some studies also found that stenting enhanced blood pressure control with fewer required antihypertensive medications.[17,21-28] Bilateral stenting seemed to confer a minor advantage in blood pressure outcome in some studies[27,29-32] but not in others.[17,18,20,22,24,33] A poor blood pressure response was predicted by male sex,[18,23] poor renal function,[18,24] degree of stenosis,[24] and left ventricular hypertrophy.[24] The number of baseline antihypertensive medications was found to be a predictor of improved blood pressure control in one study[19] but the opposite in another.[24] In some studies, normal renal parenchymal thickness was found to be a good predictor of blood pressure response.[31,32]

Three recent clinical trials (Cardiovascular Outcome in Renal Atherosclerotic Lesions [CORAL],[14] Angioplasty and Stenting for Renal Artery Lesions [ASTRAL],[15] and Stent Placement in Patients with Atherosclerotic Renal Artery Stenosis and Impaired Renal Function [STAR][13]) reported an improved blood pressure outcome in both the stenting and medical therapy arms of their trials. CORAL noted that the stenting arm had a small but statistically significant lower SBP compared with the medical arm. The Stenting of Renal Artery Stenosis in Coronary Artery Disease (RAS-CAD)[16] reported improved blood pressure control with medical therapy but did not find a statistically significant improvement with percutaneous intervention. All four of these clinical trials employed statins, antiplatelet agents, and optimal blood pressure medications for use in their groups.

On the other hand, Pizzolo et al[30] found improvement in blood pressure in the percutaneous intervention group but not after medical management. Two older studies comparing percutaneous transluminal angioplasty (PTA) with medical therapy found no difference. However, PTA did allow blood pressure control with fewer antihypertensive drugs, although portions of the medical group crossed over to the angioplasty group during the study.[34,35] van de Ven et al[36] reported superior rates of primary patency and lower restenosis for stenting but no difference in clinical outcomes. One study demonstrated a significant improvement in blood pressure control for patients with bilateral RAS randomized to RASt.[29] Studies indicating blood pressure improvement are summarized in Table II.

An interesting prospective review by Kalra et al[3] has shown an improvement in renal function in the intervention group compared with medical treatment, particularly in the latter stages of chronic kidney disease (stage 4-5), with survival advantage by reducing risk of death by 45% in all patients combined (relative risk, 0.55; $P = .013$).

Attempts to identify patients who are most likely to benefit in renal function after intervention have been extensively studied. Various study results suggest that patients with baseline[17,26,37,38] or more severe[24,31,39] renal dysfunction are more likely to have improved or stabilized renal function after stenting. Others reported that patients with poor baseline renal function were less likely to improve after stenting[31] or had associated increased mortality.[22,40-42] Other studies have noted that patients with a recent decline in glomerular filtration rate (GFR) derive the greatest benefit.[25,37,42-44] Bilateral stenting was found to improve or to stabilize renal function in some studies[32,37] but not in others.[16,21,29,38,43-45] Bilateral disease was noted to adversely affect survival,[22,40] whereas baseline stenosis[32] and good left ventricular function[39] were found to be predictors for improved renal function. Bates et al[42] demonstrated that comorbid conditions,