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REVIEW

The Management of Renal Artery Stenosis: An Alternative Interpretation of ASTRAL and CORAL

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WHAT THIS PAPER ADDS

This paper reviews renal physiology and highlights the methodological challenges and limitations for studies of renal artery stenosis.

Objectives: To assess the literature on intervention for renal artery stenosis (RAS), with special emphasis on the last two and largest randomized trials, the ASTRAL and CORAL trials.

Design: A review of renal physiology, pathology, and pathophysiology of RAS and a critical analysis of the randomized trials.

Materials: Published literature for renal physiology and RAS were assessed.

Methods: Renal physiology, renal intervention, and the limitations and challenges of both ASTRAL and CORAL are analysed.

Results: The last two reported, and largest randomized trials of percutaneous renal artery intervention for RAS were the ASTRAL and the CORAL trials; both generated much debate and much controversy, however both trials had methodological shortcomings, and assumed a simplistic approach to renal physiology. Both trials were hampered by slow recruitment, and there were protocol changes to accommodate, and CORAL was not powered for subgroup analysis. The primary outcome measure for ASTRAL was the reciprocal of serum creatinine levels and CORAL a complex composite endpoint of cardiovascular or renal events. In ASTRAL, 25% of patients had normal renal function and 40% almost normal renal function; and in CORAL, 50% of the cohort had either no renal failure, or were Stage I or Stage II CKD, (i.e. eGFR of $>$60 mls/min/1.73 m^2). In ASTRAL, 41% of patients had a stenosis of $<$70%; and an interim analysis of 611 patients (of 947 enrolled) in CORAL revealed that 55% had $<$70% renal artery stenosis.

Conclusions: Best evidence still supports intervention for patients with RAS of $>$80% with a significant trans-lesional pressure gradient; difficult to control blood pressure with more than three antihypertensives, especially in younger patients; and those with truncal rather than ostial stenosis; patient with a rapid deterioration of renal function; flash pulmonary oedema; and post-transplant RAS.

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INTRODUCTION

Renal artery stenosis (RAS) is associated with compromised renal perfusion, hypertension, ischaemic nephropathy, and end-stage renal failure, and also some other long-term complications of atherosclerotic disease. The majority of cases are due to atherosclerotic renal artery (RA) disease, and fibromuscular dysplasia (FMD) in about 10% of cases, and other less common pathology, and the disease may be bilateral in up to one-third of cases. The management options for RAS include conservative therapy, medical therapy, angioplasty or angioplasty and stent, or bypass surgery. The last two reported, and largest, randomized trials of percutaneous renal artery intervention for stenotic renal artery disease were the ASTRAL and the CORAL trials; both generated much debate and much controversy.[1,2] However, as discussed in this paper, both trials had methodological shortcomings, and assumed a simplistic approach to renal

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physiology, and concluded that renal artery intervention offered no advantage to patients with RAS.

Much modern thinking about renovascular disease is still deeply influenced by Henry Goldblatt's experiment.[3] A similar clinical situation in humans is seen when stenosis affects the RA with a relatively undamaged vascular tree (e.g. FMD, non-ostial or truncal stenosis, and transplanted kidney arterial stenosis).[3] Blood vessels to the kidney deliver more oxygenated blood than needed for basal metabolic demands and the metabolic requirements of the kidney are achieved with around 10% of normal blood flow.[4,5] A "critical stenosis" causes a reduction in renal perfusion pressure and occurs when the RA is narrowed by over 70—80%.[6,7] Deterioration of renal function (RF) with RAS may be the result of sustained hemodynamic insults, or other fibrogenic processes independent of hemodynamic changes.[8] Ostial stenosis reflects generalized atherosclerosis causing kidney damage, that is hypertensive damage, spontaneous cholesterol atheroembolism, and may account for low rate of RF recovery after revascularization. RAS of greater than 70—80% is also necessary to activate the intrarenal renin—angiotensin system (IRAS) and this degree of stenosis correlates with a translesional peak systolic pressure gradient (PG) of 15—25 mmHg.[6,7] Relative underperfusion in the presence of RAS may result in a medullary oxygen deficiency and may further stimulate the activation of IRAS that may then activate ischaemia and renal damage, in a progressively negative cycle.[8] Activation of IRAS also induces renal inflammation, cytokine activation, and oxidative stress and renal damage, including intrarenal fibrosis and scarring.[9—11]

Evaluating renal injury related to RAS, must consider that kidneys are bilateral in most patients, and vascular disease rarely affects both kidneys and all renal arteries to the same extent. In the presence of unilateral RA disease the contralateral kidney is capable of compensatory change, and contralateral renal hypertrophy may obscure change in the functional result of both kidneys and may cancel out changes induced by the stenotic kidney.[11]

RA disease is linked to the increasing systemic atherosclerosis in the ageing population.[12,13] Increased prevalence of ostial lesions is associated with aortic atherosclerotic disease and thrombus formation that may have already injured end-organs from progressive atheroembolization.[12] An inverse relationship exists between age of patients and cure of hypertension after revascularization, and also a positive correlation between age and the rate of worsening of RF after revascularization.[13—15]

Patients with more renal tissue at risk are more likely to have a response or improvement with primary renal intervention for RAS, including those with severe bilateral disease and with a solitary kidney. Patients with small kidneys ($<$7 cm) and those with significant proteinuria are less likely to benefit. But there is significant support for intervention and revascularization of unilateral RAS to improve RF but successful revascularization is dependent on the adequacy of relief of the RAS, the remaining viable functional renal tissue, and the safety of the revascularization procedure.[13,14]

Recovery of RF after revascularization is different with ostial stenosis compared with "true" RAS (non-ostial or truncal lesions); significant improvement of RF in 44.5—77% of cases with truncal stenosis, FMD, and post-transplant stenosis. However with well-documented ostial stenosis, improvement was seen in only about 20% of patients.[13,14] Improvement in RF after successful stent placement for RAS is only seen in around 25%, with RF remaining stable in 50%, and deteriorating in 25%.[13,14] The reason for this may be due to clinically evident acute atheroembolic renal disease, which is associated with a dramatically negative effect on prognosis. Although the majority of atheroembolic renal disease is subclinical the reported frequency of visible atherosclerotic debris recovered in protection devices is well above 50%, and perhaps this atheroembolization associated with the 25% of successfully revascularized kidneys showing a decline in RF.[15—17]

Evidence from randomized trials

Older renal artery trials, for example STAR (Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function) trial and the DRASTIC (Dutch Renal Artery Stenosis Intervention Cooperative) trial, were underpowered and seriously flawed.[18] And the RADAR trial, (A randomised, multi-centre, prospective study comparing best medical treatment versus best medical treatment plus renal artery stenting in patients with haemodynamically relevant atherosclerotic renal artery stenosis), was terminated prematurely.[19]

The last two reported and largest randomized trials of percutaneous RA intervention for stenotic RA disease were the ASTRAL (Angioplasty and Stenting for Renal Artery Lesions) trial in the UK, and CORAL (Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis) trial that was based in the United States.[1,2] Both trials generated much debate and much controversy, but no finality. A summary of the main outcome measures for the ASTRAL and CORAL trial is shown in Table 1.

Neither of these trials demonstrated a benefit of RA intervention over medical therapy, in contrast to the findings of large interventional cohort studies and meta-analyses. In the ASTRAL study, data were presented for the more affected kidney for which a surgical plan was provided at the time of randomization; in CORAL global ischaemia was defined as stenosis of 60% or more of the diameter of all arteries supplying both kidneys or stenosis of 60% or more of the diameter of all arteries supplying a single functioning kidney, and was present in only 20% of patients in the stenting group and 16.2% of the medical group; bilateral disease was present in 22% of the stenting group and 18.1% of the medical arm.

ASTRAL

The starting point for ASTRAL was that the treating physician had to be guided by an "uncertainty principle", which said that the physician had to be undecided or have "clinical equipoise" that the patient would have a worthwhile