Does Renal Artery Stenting Prevent Clinical Events?

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Atherosclerotic renovascular disease (ARVD) continues to pose a thorny challenge for clinicians. ARVD remains the most prevalent cause of renal artery stenosis in Western countries and regularly accompanies disease in other vascular beds, including coronary, cerebral, aortic, and peripheral vessels. Not surprisingly, ARVD is associated with high risk for clinical events, including resistant hypertension, renal insufficiency, pulmonary edema, and other adverse cardiovascular outcomes. It is commonly associated with cardiovascular risk factors, including hypertension, diabetes, dyslipidemias, and tobacco use.

For >80 years, reduction in perfusion pressure to the kidney beyond a stenotic lesion has been known to produce hypertension. Much of the initial impetus to revascularize the kidney derived from the failure of early antihypertensive drug therapy to treat renovascular hypertension, classically an angiotensin-dependent model of disease (1,2). Surgical renal revascularization developed as a life-saving maneuver for some malignant forms of hypertension, despite well recognized risks of the procedure itself (3). Remarkably, the recognition that renovascular occlusive disease could produce a reversible loss of kidney function was broadly appreciated only in the 1980s (4,5). Ischemic nephropathy became recognized as an underdiagnosed form of reversible renal failure, supported by reports of occasional stunning recovery of renal function after revascularization (6). Successful intervention sometimes led to discontinuation of dialytic support. More recently, episodes of circulatory congestion described as flash pulmonary edema have been recognized as a complication of bilateral ARVD that dramatically resolves after successful renal revascularization (7). For these patients, there is no question that renal revascularization prevents major clinical events.

Widespread application of more effective antihypertensive drug therapy in the recent era, including agents that block the renin-angiotensin-aldosterone system, has made achieving BP goals possible for most patients with ARVD, often for many years. With successful hypertension treatment more often possible, the goal of preserving renal function became a primary motivation for renal revascularization for many clinicians. Wider availability of sophisticated vascular and renal imaging tools and the introduction of endovascular stent procedures expanded the population of patients with ARVD who were considered potential candidates for both medical and interventional treatments, which we have reviewed (2). Application of renal artery stenting expanded rapidly between 1996 and 2005, even for candidates with mild, sometimes incidental, disease (8). However, these procedures introduced substantial costs, and sometimes, they were associated with complications. Some of these were catastrophic, including atheroembolic events, which could worsen kidney function irreversibly.

One result of the expanded use of vascular intervention for ARVD has been the performance of several prospective, randomized clinical trials (RCTs) to elucidate precisely what benefits endovascular stenting add to medical management. Remarkably, nearly all of these trials have failed to identify much added clinical benefit from renal revascularization, which we and others have reviewed (9,10). Recruitment of patients with clinically significant ARVD to participate in randomized trials has been difficult, however, partly because of the established success of revascularization in patients with extreme cases. This inevitably has resulted in a significant selection bias. The most recent and largest RCT to date was the Cardiovascular Outcomes with Renal Atherosclerotic Lesions (CORAL) Trial in the United States (11). Results from this trial indicated that stent revascularization did not improve cardiovascular outcomes when added to protocol–driven antihypertensive drug therapy, including an angiotensin receptor blocker (or angiotensin-converting enzyme inhibitor), to target levels combined with statin therapy and appropriate glucose control in patients with diabetes.

In this issue of the *Clinical Journal of the American Society of Nephrology*, Tuttle *et al.* (12) further report the effects of stenting on eGFR and predictors of clinical events for 931 participants in the CORAL Trial. Entry in this trial depended primarily on showing >60% lumen occlusion of one or more renal arteries. Over the course of enrollment, entry criteria were loosened to allow moderate hypertension (systolic hypertension on two or more drugs, although >25% were at goal BP on entry) and/or mild reductions in eGFR (entry allowed for eGFR<60 ml/min per 1.73 m^2), with mean levels of 59±24 ml/min per 1.73 m^2 at baseline that fell slightly to 55±23 ml/min per 1.73 m^2 over 3 years for the entire cohort. CKD events were defined as a 30% reduction in eGFR, need for dialysis, renal transplant, or death caused by uremia. Only 8% of subjects had stage 4 CKD (eGFR<30 ml/min per 1.73 m^2). Rates of change in eGFR were −1.5±7 versus −2.3±6.3 ml/min per 1.73 m^2 per year in the stented versus

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medical therapy groups ($P=0.18$). Levels of eGFR were lower in the medical therapy only group at 3 and 6 months but did not differ thereafter. Predictors of eGFR change over a mean follow-up of 1.84 years included age (−2.99 per decade), men (2.89), systolic BP (−0.57 per 10 mmHg), total cholesterol (0.31 per 10 mg/dl), HDL cholesterol (0.93 per 10 mg/dl), log urine albumin-to-creatinine ratio (−2.03 per SD), and diabetes (−2.01). Some form of CKD event occurred in 19% of CORAL Trial participants. Cardiovascular disease events (stroke, myocardial infarction, hospitalization for congestive heart failure, or death) occurred in 22%. Importantly, the rates of actual death (4.2%) or advanced renal failure (renal replacement <1%) were quite low in this cohort as previously reported (11). Tuttle *et al.* (12) argue that stent therapy, when added to optimal medical therapy, neither mitigated nor worsened eGFR for these participants during the follow-up period. From their perspective, "CORAL data support the effectiveness of risk factor treatment and blood pressure control with RAS inhibition as standard of care" in ARVD (12).

Does this report establish that renal artery stenting actually has no effect on clinical events or outcomes in ARVD? Reports continue to appear indicating reversal of advanced renal failure and/or accelerated hypertension resistant to medical therapy with successful revascularization (13–16). Clinicians managing complex disease recognize that some patients fail optimal medical therapy and can respond dramatically to restoration of renal perfusion. At some level, the RCT results have limited face validity—discordant with the obvious fact that completely depriving the kidney of blood flow ultimately leads to loss of kidney function.

Is it possible that the CORAL Trial data apply only to low-risk patients with ARVD who clinicians were willing to randomize? Registry data from the United Kingdom suggest that mortality risks are often far higher with complex ARVD than reported in the CORAL Trial (14). Data from the Angioplasty and Stenting for Renal Atherosclerotic Lesions Trial conducted over nearly the same time interval indicate that mortality was in excess of 25% in the cohort (compared with 4.2% in the CORAL Trial), and ESRD developed in 8% (17). A review of US Medicare data published in 2005 for individuals ages 65–67 years old indicated a mortality risk of 16.6% for those with incident ARVD compared with 6.3% in the general population (18). Taken together, these data suggest that the recruited CORAL Trial population had extremely low overall mortality and/or progressive renal disease risk. In such a low-risk population, the argument for depending primarily on medical management seems solid.

Do reports from negative trials inappropriately delay or deny patients the benefits of avoiding adverse outcomes by undergoing stent revascularization? This is the question at the heart of ongoing debates between internists and nephrologists and interventional colleagues (19,20) who offer renal revascularization. Failure to identify a therapeutic benefit in any trial is generally applicable only to the specific patients studied under the specific conditions of the trial. The fact that no benefit could be found for the overall group sampled in the CORAL Trial does not exclude a benefit for a subset of patients with ARVD not represented in that trial. (Recall the negative results identified in the Multiple Risk Factor Intervention Trial that failed to identify a benefit for reducing smoking, BP, or lipids in the prevention of cardiovascular disease during the trial period [21] as an example.) It is a reminder that generalizability and interpretation of any clinical trial must be put in the context of the individual patient being considered.

Recent mechanistic studies underscore the remarkable tolerance of the kidney to moderate reductions in blood flow. Despite reduced kidney size and perfusion, oxygenation and structural features remain intact for many patients during treatment of systemic hypertension (22). A valuable lesson from the CORAL Trial and other treatment trials remains that antihypertensive drug therapy combined with lipid and glucose control can achieve excellent BP control for patients with moderate disease for many years. There are obvious limits, however, and ultimately, severe ARVD activates injury pathways that threaten the viability of the kidney (23). The decision to move forward with renal revascularization for some patients, we argue, derives from failure to achieve these goals and/or demonstration of high-risk features, including progressive loss of renal function, intractable hypertension, or episodes of circulatory congestion. These features are consistent with a consensus document recently published by interventional groups (24). Results from prospective trials provide a general result for the populations included but few specific results for a particular subject. More than ever, therapeutic decisions for an individual patient regarding renal artery stenting demand thoughtful consideration by clinicians able to integrate trial results with vast observational experience.

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None.

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