

The Renal Stenting Downturn

Why are we stenting less?

BY GEORGE V. MOUKARBEL, MD, AND MARK W. BURKET, MD

Renal artery stenosis (RAS) is a widely recognized cause of secondary hypertension, renal dysfunction, and flash pulmonary edema. Treatment is typically aimed at reducing or obviating the need for antihypertensive drugs and/or improvement in kidney function. Surgical revascularization has been largely replaced by percutaneous techniques, with stenting accounting for the vast majority of renal interventions. Following an enthusiastic initial rise in the number of procedures performed, randomized clinical trials that were conducted failed to show a clear-cut benefit of stenting over medical therapy alone. These results came at a time when the medical environment became more insistent upon evidence-based therapies.

Concern has grown that reimbursement may be limited to procedures performed with devices holding US Food and Drug Administration indications for renal artery stenting, supported by improved outcomes proven in randomized trials. Appropriate or not, this has led to a reduction in the number of stenting procedures being performed. Ongoing clinical trials will address some of the issues encountered in earlier trials, shed more light on the role of stenting in renal artery stenosis, and hopefully define the patient population that will derive the most benefit from the procedure.

RENAL ARTERY STENOSIS: MANIFESTATIONS AND PREVALENCE

RAS is commonly clinically silent and is detected on screening ultrasound studies or during vascular angiographic procedures. It can manifest clinically as hypertension, renal dysfunction, and flash pulmonary edema.¹ The prevalence of RAS varies depending on the population studied. It is more commonly found in hypertensive patients, patients with coronary or peripheral vascular

disease, or chronic kidney disease. The prevalence and significance of RAS increases when multiple risk factors coexist. Autopsy studies show that atherosclerotic changes in the renal arteries are present in various age groups but occur more commonly with advancing age.²

In hypertensive patients undergoing angiography, approximately 15% had evidence of RAS, and one-fifth of those had significant (> 60%) stenosis.³ In another angiographic study of patients with peripheral artery disease,⁴ about one-third of patients had evidence of atherosclerotic disease in the renal arteries, and significant (\geq 60%) stenosis was present in one out of 10 patients. In both studies, advanced age and the presence of disease in other vascular beds were risk factors for significant RAS. A recently published study of a cohort of 1,298 patients undergoing nonemergent cardiac catheterization found a relatively low (5.4%) occurrence of significant (defined as \geq 50%) RAS.⁵ This study identified clinical predictors of significant stenosis to be the presence of peripheral vascular disease, reduced renal function, age > 66 years, dyslipidemia, severity of coronary artery disease, and increased pulse pressure.

IDENTIFYING APPROPRIATE CANDIDATES FOR REVASCUARIZATION

It is rather difficult to differentiate whether the potential clinical manifestations of RAS, namely hypertension and renal dysfunction, are due to the stenosis alone or are also the result of the coexisting risk factors. This makes the a priori identification of the patient who will benefit from an intervention difficult. Also, patients with advanced tubulointerstitial fibrosis and atrophy⁶ may not show significant improvement after revascularization, even if the stenosis was in fact contributing to their kidney disease. The use of ultrasound-derived resistive

index was suggested as an indicator of the degree of parenchymal disease and therefore could potentially predict the response to intervention.^{7,8} However, its value has been questioned by other studies, and its use as a predictive tool has been largely abandoned.⁹ Captopril scintigraphy can be inaccurate in the presence of renal impairment, and likewise has been largely abandoned.¹⁰

These factors complicate the identification of patients who are appropriate for revascularization and make it difficult to design clinical trials on renal interventions. Whereas elevated blood pressure at baseline could be associated with the greatest improvement in blood pressure after renal artery stenting, it is difficult to identify predictors of improved renal function following the procedure.¹¹ Such findings are confirmed in a large meta-analysis of several, mostly nonrandomized studies.¹²

RENAL ARTERY REVASCULARIZATION

Despite being available for more than 30 years, endovascular revascularization of RAS, initially with balloon angioplasty and subsequently with stenting, has long been the subject of controversy in the medical community. Several reports indicated significant improvement with endovascular intervention,¹³ but early pooled analyses failed to show consistent improvement in blood pressure¹⁴ and kidney function. As stenting provided a better technical outcome than angioplasty alone,¹⁵ a sharp rise in the use of this procedure coupled with a drop in surgical revascularization was noted during the last decade.¹⁶ However, several analyses of published studies failed to show a clear-cut benefit of percutaneous renal artery intervention when compared to medical therapy alone. Trials comparing balloon angioplasty to medical therapy¹⁷⁻¹⁹ and their meta-analysis²⁰ showed only a modest effect on blood pressure reduction and no clear beneficial effect on renal function. Similar results were found in studies that compared stenting to medical therapy.

STAR (Stent Placement and Blood Pressure and Lipid-Lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery)²¹ and ASTRAL (Angioplasty and Stenting for Renal Artery Lesions)²² are the major published randomized trials of stenting in RAS, with 140 and 806 patients enrolled in each trial, respectively. Both trials showed no evidence of benefit in renal function or blood pressure reduction. In fact, percutaneous intervention was associated with a significant risk of procedure-related complications. A recent meta-analysis of all randomized trials in percutaneous interventions,²³ including balloon angioplasty and stenting, found no improvement in kidney function and clinical outcomes. There was sug-

gestion of a reduced requirement for antihypertensive medications with renal intervention.

Surgical revascularization is considered effective in relieving the stenosis²⁴ but is currently mostly offered to patients who are unsuitable for percutaneous revascularization or those undergoing surgical repair of the aorta. An analysis of selected nonrandomized studies of surgical and endovascular treatment of RAS showed similar technical success rates but greater improvement in hypertension control and kidney function in surgical patients.²⁵ There were several issues that question the validity of these findings. The majority of the surgical studies included in the analysis were retrospective, whereas endovascular studies were prospective. Selection bias is a major issue with these retrospective, nonrandomized studies; for example, surgical patients were younger than endovascular patients.

WHERE DID STENTING TRIALS GO WRONG?

In contrast to randomized trials with negative results, multiple large multicenter registries showed improved outcomes with stenting, leading to a reduction in blood pressure and improvement in kidney function, especially in patients with moderate degrees of renal impairment.^{26,27} This raises the possibility that patients with more clinically significant RAS were included in nonrandomized registries, whereas patients with less-severe disease were enrolled in randomized trials. If true, this would have major implications for the interpretation of trial results.

Several experts in the field agree that the randomized trials of renal stenting had major problems with their enrollment criteria. This led to the inclusion of patients in the stenting arms who were unlikely to benefit from intervention. STAR enrolled patients with renal dysfunction ($< 80 \text{ mL/min/1.73 m}^2$) and $\geq 50\%$ RAS based on noninvasive studies. The use of noninvasive studies to assess for RAS increased the chance of enrollment of patients with insignificant disease; in fact, the angiographic arm revealed a 19% false-positive rate in noninvasive criteria. One-third of the patients had 50% to 70% stenosis, and more than half of them had only unilateral disease. The study was weakened by the absence of core lab assessment of stenosis. It follows that a large proportion of patients enrolled in STAR did not have hemodynamically significant RAS; therefore, it is expected that any intervention will not lead to clinical improvement.

Furthermore, 18 out of 64 patients in the stenting arm did not receive assigned therapy for various reasons (notably, 12 of them were found to have $< 50\%$ stenosis on angiography). However, they were included in the intention-to-treat analysis as if they had received a stent.

Stenting was associated with a higher rate of technical failure and complications than typically seen in registries conducted by experienced operators. Of note, physician experience in the study was measured in years of renal interventions rather than in number of cases previously completed. Together with the knowledge that “the study was underpowered to provide a definitive estimate of efficacy”²¹ for the primary endpoint of renal function improvement, it is difficult to make any worthwhile conclusions from the results.

The large number of patients enrolled in ASTRAL did overcome the sample size limitations of previous trials. However, patient selection criteria suffered from major problems. Patients were enrolled when there was “uncertainty” about the benefit of revascularization. This created a glaring loophole, allowing exclusion of patients with the most critical disease and, presumably, those most likely to benefit from stent placement. The inclusion criteria were not clear on the required degree of stenosis, as patients had to have “substantial” stenosis in at least one of the renal arteries by imaging, and there was no angiographic core laboratory confirmation.

In fact, about 40% of trial participants had 50% to 70% stenosis. Only 163 patients (20%) had severe anatomical disease defined as bilateral stenosis > 70%, or stenosis > 70% in a single functioning kidney. Therefore, it is not surprising to find no significant effect of renal artery stenting on patients who have lesions that are not hemodynamically significant. Also, 25% of the patients had preserved renal function at enrollment (glomerular filtration rate [GFR] > 50 mL/min). Even though a post hoc subgroup analysis showed no significant difference in the patients with severe disease,²² the small number of patients excludes the ability to draw meaningful conclusions. As was the case with STAR, ASTRAL operators had a rate of technical success that was lower than expected.

There was an increased rate of complications found in both STAR and ASTRAL compared to other published experiences.^{11,28,29} This might have been related to the enrollment from centers with less-than-adequate experience in the procedure. There was a paucity of use of embolic protection devices during the procedure.³⁰

CURRENT GUIDELINES

The American College of Cardiology/American Heart Association 2005 guidelines²⁴ endorse (class I) renal revascularization in patients with significant stenosis and recurrent pulmonary edema. They favor (class IIa) revascularization in the presence of accelerated or resistant hypertension, unstable angina, and renal insufficiency with bilateral stenosis or stenosis of a solitary functioning kidney. In patients with asymptomatic disease and renal insufficiency

with unilateral stenosis, revascularization is unlikely to benefit (class IIb). It was recognized in the 2011 guideline updates that findings from recently published trials, such as ASTRAL, did not provide sufficient grounds to change the prior recommendations, given the issues with patient selection criteria.³¹ The recommendations are somewhat similar to those of the European Society of Cardiology.³²

CMS REIMBURSEMENT

An analysis of Medicare claims showed a sharp rise in the number of renal revascularization procedures between 1996 and 2000, amounting to approximately 22,000 procedures. With a near 50% reduction in the volume of surgical revascularization, this overall increase was due to a substantial expansion of the number of percutaneous revascularization procedures performed.¹⁶ A more recent analysis reported a decline in the rate of revascularization from 2001 to 2004, with a return to pre-1997 levels. This was thought to parallel the publication of early angioplasty studies showing no added effect on kidney function and blood pressure control.³³

The Centers for Medicare & Medicaid Services' policy for renal interventions limits the indication to “patients in whom there is an inadequate response to a thorough medical management of symptoms and for whom surgery is the likely alternative. Percutaneous transluminal angioplasty for this group of patients is an alternative to surgery, not simply an addition to medical management.” Given the uncertainty about the recent studies in renal interventions, it was decided to make no change to the current policy.³⁴

ONGOING TRIALS

In an effort to overcome the limitations of other studies, several studies were designed to investigate the effects of renal artery stenting on kidney function, blood pressure control, and cardiovascular outcomes.

CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions)³⁵ is the largest ongoing trial on renal artery stenting, with 1,080 patients randomly allocated to stenting with medical therapy versus medical therapy alone. The enrollment criteria addressed some of the weaknesses faced in STAR and ASTRAL: patients had to have at least 80% stenosis, or at least 60% in the presence of a significant pressure gradient, in addition to hypertension or renal dysfunction. The primary endpoint is a composite of cardiovascular and renal outcomes. This will test the hypothesis that neurohormonal activation plays a central role in morbidity in patients with RAS.

METRAS (Medical and Endovascular Treatment of Atherosclerotic Renal Artery Stenosis)³⁶ is a multicenter randomized trial with an estimated enrollment of 60 patients, testing the hypothesis that renal angioplasty

and stenting is superior or equivalent to optimal medical treatment for preserving GFR in the ischemic kidney as assessed by 99mTc-DTPA sequential renal scintiscan. It is also looking at effects on blood pressure, overall kidney function, cardiovascular outcomes, and quality of life.

RASCAD (Renal Artery Stenosis in Coronary Artery Disease)³⁷ is a single-center study that is randomly allocating patients who are discovered to have RAS (> 50% and ≤ 80%) at the time of cardiac catheterization to stenting plus medical therapy versus medical therapy alone. Left ventricular hypertrophy is the primary end-point of the trial, with cardiovascular morbidity and mortality being secondary endpoints. The estimated number of patients enrolled is 168.

The RADAR trial³⁸ was designed to determine the impact of stenting on renal function at 1-year follow-up in 300 patients with significant RAS by duplex ultrasound. The STRETCH (Study of Percutaneous Renal Artery Intervention for Patient With Heart Failure) trial³⁹ is planned to enroll 200 patients with heart failure and significant RAS to test the benefit of renal stenting in a randomized design.

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CONCLUSION

In summary, renal artery stenting has experienced a recent decline in popularity, which may be unjustified. Angioplasty without stent placement, as first reported in 1978, was fraught with limited technical success and high rates of restenosis. With the addition of stent therapy, initial results became predictably superior, and restenosis rates plummeted. Multiple prospective series accomplished by experienced operators demonstrated high rates of success, acceptably low complication rates, and an improvement in blood pressure. STAR and ASTRAL, two recently reported randomized trials, cast doubt on the procedure's efficacy, when in fact they may have more accurately depicted poor trial design and execution. Nevertheless, although the randomized trials were not well designed or well executed, their results appear to have influenced clinical practice.

CORAL, which addressed many of these design flaws, has not yet produced outcomes data, adding to an atmosphere of uncertainty about the role of stent placement. In this setting, there is a general atmosphere encouraging evidence-based therapies that have been supported by randomized trials and a concomitant skepticism of treatment options without such support. There is also growing pressure to link reimbursement for procedures with outcomes data and with the use of devices that bear US Food and Drug Administration indications for those specific procedures. All of these forces have combined to deflate enthusiasm for renal artery stenting while the debate about its proper role lingers on. ■

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