

Life After ASTRAL

Strengths and limitations of renal artery stenting trials
and a look at what's next in this arena.

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Despite clear associations of atherosclerotic renal artery stenosis (RAS) with renovascular hypertension, ischemic nephropathy, and cardiac disturbance syndromes (unstable angina and volume overload states), renal artery stenting has not been proven to be superior to medical therapy with currently available published, randomized data.^{1,2} A recent meta-analysis compiling data from 1,208 patients concluded that renal stenting offered no benefits in terms of blood pressure control, renal function preservation, or all-cause mortality.³ Fortunately, this pessimism for renal artery revascularization rests on inferences from trials with significant design flaws and inherent selection bias.⁴ Given this background, if renal artery revascularization is to remain a viable therapy for patients with RAS, future trials are needed that optimally select patients, rigorously test the efficacy of new technologies, and identify relevant clinical endpoints that connote patient benefits long-term. Here we discuss the limitations of the available randomized data on renal artery stenting and review what is anticipated in the future with regard to renal intervention trials.

MODERN, RANDOMIZED TRIALS OF RENAL STENTING

STAR

STAR was a multicenter, randomized study of 140 patients comparing renal artery stenting with medical therapy to medical therapy alone. Relevant entry criteria included the presence of RAS > 50% without any confirmation of hemodynamic significance, renal impairment defined as a glomerular filtration rate (GFR) < 80 mL/min, and stable blood pressure defined as < 140/90 mm Hg. The primary endpoint was progression of renal disease

defined as an increase in serum creatinine level > 20% from baseline during 2 years of follow-up.

Of the 64 patients assigned to stenting, only 46 (72%) actually received a stent. The most common reason for not receiving a stent related to findings of insignificant RAS at angiography (stenosis < 50%). Overall, 16% of the stent group and 22% of the medical therapy arm reached the primary endpoint (HR, 0.73; 95% CI, 0.33–1.61) using an intention-to-treat analysis. There were no differences in blood pressure control or overall mortality between the groups. Complication rates in the stent group were high and included two deaths (3%) and 11 hematomas (17%), both of which are excessive in comparison to contemporary practice. The investigators concluded that there was no apparent benefit with renal stenting, though it did cause harm.¹

ASTRAL

ASTRAL was a multicenter, prospective randomized study comparing renal stenting with medical therapy to medical therapy alone. In contrast to other studies, in addition to having RAS of > 50%, treating clinicians had to be uncertain as to whether the potential subjects would benefit from revascularization. Similarly, any individual who was believed to need revascularization within 6 months was excluded. A total of 806 patients were enrolled. Only 83% of those randomized to stenting actually underwent the procedure; 6% of the medical arm received renal artery revascularization. The primary endpoint, change in renal function as assessed by the slope of the reciprocal of serum creatinine, showed a trend in favor of the stenting group compared to medical therapy during a mean follow-up of 34 months (95% CI, –0.002–0.13;

TABLE 1. LIMITATIONS OF PUBLISHED, RANDOMIZED TRIALS FOR RENAL ARTERY STENTING

	STAR	ASTRAL
Inclusion/exclusion criteria	<ul style="list-style-type: none"> • 50%–70% stenosis allowed without evidence of hemodynamic significance • Stable blood pressure (< 140/90) necessary for inclusion • Renal impairment defined as GFR < 80 mL/min 	<ul style="list-style-type: none"> • 50%–70% stenosis allowed without evidence of hemodynamic significance • Clinician must be uncertain as to whether or not stenting would be beneficial (patients certain to benefit not included) • 25% had normal renal function at baseline in trial aimed to examine change in renal function
Crossover	<ul style="list-style-type: none"> • Only 72% in stent group received intervention • Analyzed in stent group due to intention-to-treat design 	<ul style="list-style-type: none"> • 83% in stent group underwent procedure • 5% in medical arm received revascularization
Procedural complications	<ul style="list-style-type: none"> • Death 3% • Hematoma 17% 	<ul style="list-style-type: none"> • 9% overall complication rate: five occlusions, four perforations, five embolizations
Power considerations	<ul style="list-style-type: none"> • 22% actual vs 50% anticipated event rate in medical arm • Authors acknowledge “results are inconclusive with regard to efficacy” due to lack of power 	<ul style="list-style-type: none"> • N/A

$P = .06$). There were no significant differences in blood pressure or adverse renal or cardiovascular events between groups. Five (1.2%) serious complications including death or amputation occurred in the stenting group. The investigators concluded that there was risk of harm, but no clinical benefit with stenting for RAS.²

Although it is true that the available data from published randomized trials do not support routine percutaneous revascularization for all patients with RAS, it is equally valid to state that these data were derived from trials with significant flaws.⁴ In addition, due to entry criteria in these trials, the patients most likely to benefit from revascularization were either not allowed to participate, or they were mixed with other RAS patients in whom revascularization was of dubious benefit from the onset. Some of these relevant limitations are shown in Table 1.

ONGOING TRIALS AND RECENTLY PUBLISHED RESULTS

CORAL

CORAL (NCT00081731) is a National Heart, Lung, and Blood Institute–sponsored, multicenter, randomized trial comparing renal stenting with medical therapy to medical therapy alone. Importantly, to be eligible for inclusion, a stenosis of 60% or greater must be present, and intermediate lesions of 60% to 80% must have documentation of a significant pressure gradient of > 20 mm Hg. Furthermore,

in contrast to previous studies, CORAL utilizes a clinical primary endpoint consisting of “hard” cardiovascular and renal events including death, stroke, myocardial infarction, heart failure, and renal deterioration or need for dialysis. Enrollment is complete, and results are anticipated in the future.

CORAL should add substantially to the current knowledge regarding clinical efficacy of renal revascularization.⁵ It should be noted that multiple protocol modifications were made throughout the trial, and excessively slow enrollment necessitated a reduction in the planned sample size. If and how these changes influence the results remains to be determined.

STRETCH

The STRETCH trial (NCT0143714) began in mid-2011 and aims to examine the clinical impact of renal artery stenting on heart failure outcomes. Patients presenting with heart failure and with hemodynamically significant RAS (> 50% stenosis, pressure wire assessment performed if needed for intermediate lesions) will be randomized to medical therapy or renal stenting. Alternative explanations of heart failure exacerbations such as ischemia and valvular disease are relevant exclusion criteria. The primary endpoint is cardiac mortality or heart failure admission at 1 year.⁶ While small cases series have been reported, STRETCH represents the first randomized attempt to

specifically examine RAS treatment outcomes in a heart failure population.

OTHER ONGOING TRIALS

Several trials are currently ongoing that are examining the impact of renal stenting on renal function long-term. RADAR (NCT00640406) is a multicenter, international trial randomizing 300 hypertensive patients with RAS to medical therapy or medical therapy plus stenting. The primary endpoint is change in GFR at 1 year. One of the important distinctions of this trial is that only patients with > 70% stenosis are eligible for inclusion. This should eliminate the majority of intermediate lesions that are hemodynamically insignificant. In addition, this trial includes some novel secondary endpoints including quality-of-life assessments and symptom classification, which will be an important contribution given the lack of consistent reporting of these features previously.⁷

METRAS (NCT01208714) is another similarly designed, randomized trial comparing stenting to medical therapy. The primary endpoint is change in GFR at 2 years as assessed quantitatively by renal scintigraphy. Patients with stenotic lesions > 70% and those < 70% but with poststenotic dilatation are eligible for inclusion assuming that resistive indices on duplex ultrasonography do not demonstrate the presence of severe parenchymal disease.⁸

**Further investigations are needed
to identify markers of clinical
response with renal stenting.**

The frequency of cardiac structural abnormalities including left ventricular hypertrophy in patients with RAS is significantly increased.⁹ Previous nonrandomized studies have demonstrated significant left ventricular mass regression in RAS patients treated with stenting.^{10,11} RASCAD (NCT01173666) is an ongoing, randomized trial attempting to confirm earlier, observational results. In this study, approximately 160 patients will be randomized to medical therapy alone or medical therapy plus stenting. The primary endpoint is change in left ventricular mass assessed by echocardiography at 1 year. Extended follow-up out to 5 years will be completed to assess for cardiovascular morbidity and mortality.¹² Given the known significant risk that ventricular hypertrophy poses on all-cause mortality,¹³ and because previ-



(Courtesy of T. Carlton, Altimed Medical Corporation.)

Figure 1. Renal covered stent.

ous trials have had difficulty demonstrating consistent benefits in blood pressure reduction and renal preservation, this trial has the potential to provide novel information.

To date, studies investigating sirolimus-coated stents in the renal vasculature have been disappointing.¹⁴ Paclitaxel is an alternative antiproliferative agent that has been used in most vascular beds,¹⁵ and renewed interest in its use has developed given the recently reported results of the ZILVER-PTX trial, which showed substantial reductions in restenosis when treating femoropopliteal disease with a polymer-free, paclitaxel-coated stent.¹⁶

Cook Medical (Bloomington, IN) is now examining the use of paclitaxel in renal arteries after recently reporting the encouraging 2-year results of the REFORM trial. REFORM was a single-arm, 100-patient study assessing the safety and efficacy of the Formula bare-metal stent, designed to treat RAS. Primary patency at 9 months was 92%, and adverse events occurred in only 2.2% of patients. At 24 months, 55% of patients had a > 10 mm Hg reduction in blood pressure, and 20% had a significant improvement in renal function, (defined as > 25% increase in GFR or 0.5 mg/dL decrease in serum creatinine).¹⁷ Cook Medical has now initiated a randomized trial comparing its uncoated Formula stent to a paclitaxel-coated Formula stent in renal arteries (NCT01057316). In addition to having a control arm and assessing restenosis rates at 9 months, there are also three experimental arms testing different doses of paclitaxel.¹⁸

The results of HERCULES, a multicenter single-arm study investigating the Herculink stent (Abbott Vascular, Santa Clara, CA), were recently reported. This stent met pre-defined safety and efficacy standards and demonstrated significant reductions in systolic blood pressure. Restenosis at 9 months was 10.5%, significantly lower than the objective performance goal of 28.6%. A secondary analysis that examined preprocedural B-type natriuretic peptide as a predictor of blood pressure response to renal stenting was

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also performed. Unfortunately, no association was identified.¹⁹ This was in contrast to a previously published study that suggested a B-type natriuretic peptide level > 50 pg/mL may identify patients in whom stenting will reduce blood pressure.²⁰ Reasons for the discrepant results are likely multifactorial and may be related to the different populations studied, both in terms of patient and lesion characteristics. Further investigations are needed to identify markers of clinical response with renal stenting. Indeed, a readily available marker predictive of clinical response to renal artery stenting would greatly aid patient selection.

Laird et al recently published the results from FORTRESS, a study that was examining the safety and feasibility of the FiberNet embolic protection system (Medtronic, Inc., Minneapolis, MN) used during renal interventions. Of 20 patients enrolled, procedural success was 100%, embolic material was retrieved in all cases, and no significant renal deterioration was identified during the follow-up period.²¹ Although randomized data are needed to determine if embolic protection can improve outcomes in renal intervention, these results are consistent with previous retrospective data showing favorable outcomes on renal preservation.

Atrium Medical Corporation (Hudson, NH) will soon initiate a single-arm trial testing the performance of a covered stent specifically designed for use in the renal arteries (Figure 1, personal communication, T. Carlton, Atrium Medical Corporation, December 19, 2011). Deployment of a covered stent within a renal artery has the theoretical potential to limit the risk of embolic debris entering the renal microvasculature. Further prospective, randomized data are needed to determine if either of these embolic protection strategies can improve renal stenting outcomes.

CONCLUSION

Clinical investigation must prove that renal stenting has a well-defined role for patients with RAS. Fortunately, many trials are underway that are examining methods to improve patient outcomes after renal stenting, and many are using better patient selection methods to avoid some of the pitfalls of earlier, randomized studies. While await-

ing the results of these trials, it is reassuring to know that the vascular community has not let the setbacks afforded by STAR and ASTRAL limit scientific inquiry. Indeed, brighter days may be ahead. ■

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