The Need for Randomized Trials to Prove the Safety and Efficacy of Parachutes, Bulletproof Vests, and Percutaneous Renal Intervention

In this issue of Mayo Clinic Proceedings, the informative review on atherosclerotic renal artery stenosis (ARAS) by Lao et al.1 reminds us of the uncertainty and confusion regarding treatment with percutaneous renal intervention (PRI). Before we can consider treatment outcomes, however, it is necessary to appreciate the complexity of ARAS. It is not a single entity but manifests as 3 clinical conditions that may overlap: (1) renovascular hypertension, (2) ischemic nephropathy, and (3) the cardiac destabilization syndromes of flash pulmonary edema, refractory heart failure, and unstable angina.

The debate over the effectiveness of PRI has been confused by a paradigm shift in treatment techniques. In the past, small randomized trials of balloon angioplasty for ARAS and renovascular hypertension had slightly positive outcomes favoring angioplasty;2,4 as did a cohort-controlled study5 and 2 meta-analyses.6,7 During the past 15 years, treatment of ARAS has evolved from simple balloon angioplasty, which was marginally effective, to the current strategy of balloon-expandable stent placement, which reliably (>95%) yields patent renal arteries. Renal stent placement has been proven superior to balloon angioplasty in a randomized trial8 and a meta-analysis.9 Multiple clinical series and meta-analyses have demonstrated the safety and efficacy of renal stents for lowering blood pressure,9 and multiple convincing nonrandomized studies and case series have shown the safety and efficacy of renal stenting for ischemic nephropathy.10 Such an investigational history will lead many to wonder whether more prospective, randomized trials are needed.

Contemporary medicine’s indiscriminate desire for randomized controlled trials to assess treatment efficacy needs to be more carefully considered. No reasonable person would argue that randomized trials are needed to prove the efficacy of parachutes, bicycle helmets, or bulletproof vests,11 ie, situations in which ethical and other reasons would hinder participation in a control vs a treatment group. But, what if—in these highly divergent situations—we specified that treatment results would be analyzed only in “borderline situations”? What if we wanted to understand the benefit of a parachute when jumping from a footstool, from a second story window, or from an airplane at 10,000 feet? At some point, we reach a situation of uncertainty (second story window) between the certainty that the parachute is not helpful (footstool) and the certainty that the parachute is helpful (10,000 feet from an airplane).

The same argument can be made for renal stents. There are conditions for which reasonable persons would agree that renal stents are not useful (eg, <50% stenosis without a translesional pressure gradient). Conversely, there are ARAS conditions for which most would agree that renal stents are useful (eg, bilateral 90% ARAS and flash pulmonary edema).12 Finally, there are borderline ARAS conditions, eg, mild to moderate lesions with mild to moderate translesional pressure gradients, for which most of us are uncertain regarding the efficacy of PRI. These borderline conditions will, by definition, meet criteria for clinical equipoise, which is necessary for ethical randomization.

Two recently published randomized trials, Angioplasty and Stenting for Renal Artery Lesions (ASTRAL)13 and 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 (STAR),14 showed no benefit for renal stenting in mild to moderate ARAS. However, there is good reason to doubt the validity of the studies’ conclusions. Major problems included the involvement of renal interventionists whose experience was minimal and who generated unacceptably high procedure complication rates and the indiscriminate enrollment of patients with mild ARAS who would not have benefitted from PRI.15 The reliance on visual angiographic assessment of severity of ARAS lesions and failure to ensure competence of renal interventionists are important flaws that corrupted the results of ASTRAL13 and STAR.14

The efficacy of renal artery stenting depends on our ability to identify which patients with ARAS are likely to respond to revascularization.16 A meta-analysis suggests that only 60% to 70% of hypertensive patients with ARAS will clinically improve after renal stenting.3 Why would a procedure with such a high technical success rate (>95%) result in such a modest clinical response? The answer is that we are likely treating some patients who do not have obstructive ARAS. The visual estimation of mild to moderate ARAS is an inadequate method to select patients for PRI.
When determining the efficacy of any treatment, it is critically important to carefully define the population being studied. It is becoming clear that the “Achilles heel” of renal artery stenting is the inaccuracy of the traditional criterion standard of diagnosis, angiographic determination of ARAS severity. The visual estimation of lesion severity by angiography, the so-called oculostenotic reflex, has been shown repeatedly to overestimate the severity of arterial stenoses. Even with quantitative measurement, angiography is unable to discriminate between nonobstructive and significant ARAS (Figure). One solution that would improve patient selection for PRI is hemodynamic assessment of ARAS. Hemodynamic confirmation of severity of angiographic lesions can be accomplished by placing a small nonobstructive catheter (≤3 F) or a micromanometer-tipped pressure measuring guidewire (0.014-in) across the renal artery stenosis to measure a simultaneous translesional pressure gradient.

Unfortunately, the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial, which has recently completed enrollment, is unlikely to settle this dispute or help to clarify which patients, lesions, and clinical conditions will benefit from renal stent placement. Once again, the investigators relied on angiographic criteria to select ARAS lesions for treatment. The inability of angiography to differentiate the severity of lesions will be problematic for the final analysis, particularly for intermediate ARAS lesions.

Percutaneous renal intervention with renal artery stenting has benefitted many patients. It is important that we not throw the renal artery stent “baby” out with the bath water. Emotions run high on both sides of this argument, polarizing practitioners along specialty lines. Clearly, we need a better understanding of the value of PRI for “borderline conditions.” Angiographers and interventionists need to accept the fact that using hemodynamic criteria (translesional pressure gradient), not angiography, is the best way to determine the severity of ARAS. Because PRI clinical data have relied on angiographic selection criteria, we currently lack the evidence required to resolve these questions. What is needed, going forward, is less debate and more rational investigation.

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