

ACC INTERVENTIONAL SCIENTIFIC COUNCIL: NEWS AND VIEWS

Renal Artery Stenting

Lessons From ASTRAL (Angioplasty and Stenting for Renal Artery Lesions)

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The investigators of the recently published ASTRAL (Angioplasty and Stenting for Renal Artery Lesions) trial concluded that there was “substantial risk without worthwhile clinical benefit from revascularization in patients with atherosclerotic renovascular disease” (1). We believe that the unconventional study design and significant methodologic flaws of this trial led to inaccurate, somewhat hysterical, conclusions (1,2).

ASTRAL was a multicenter, randomized, unblinded clinical trial conducted in Europe and Australia. Patients were eligible for inclusion if clinical findings (hypertension or unexplained renal dysfunction) suggested a diagnosis of renal artery stenosis (RAS), imaging studies confirmed stenosis in at least 1 renal artery, and if the physician was uncertain that the patient would benefit from revascularization. Patients were excluded if they required surgical revascularization or were considered to have a high likelihood of requiring revascularization within 6 months. This is a flawed enrollment strategy, excluding the very patients who should have been randomized in a clinical trial.

Very unconventional for a trial of this size was the lack of an objective “core” laboratory to adjudicate or validate the on-site visual estimates of RAS. The absence of objective oversight and reliance on visual estimation make it very likely that the degree of renal artery narrowing was overestimated (3). Overestimation of RAS creates a significant bias against revascularization because these mild lesions are not likely to be causing renal hypoperfusion that would benefit from percutaneous renal intervention (PRI). Overestimation of RAS stenosis also creates a bias in favor of the medical therapy (MT) group because the milder

lesion would be less likely to cause significant ischemia, progress in severity, or any harm to the patient.

The trial enrolled 806 patients (403 patients in the PRI group and 403 patients in the MT group) from 2000 to 2007 to be followed over a 5-year period. Patients were randomly assigned to undergo PRI with MT or to receive MT alone. Although the baseline characteristics appeared similar, 40% (nearly one-half) of the patients in both groups had RAS <70%, which is another source of significant bias against PRI. Not only were 40% of study patients not likely to benefit from revascularization of a mild stenosis, the risk of further loss of renal function with medical therapy is also unlikely. The ASTRAL investigators failed to recognize or acknowledge that there is no clinical equipoise in randomizing mild RAS lesions to revascularization.

Only 83% of patients randomized to revascularization actually underwent PRI. Of those randomized to revascularization, only 78.6% had a successful procedure. This success rate is far below the 96% to 98% success rate expected in clinical practice and another major source of bias against intervention programmed into this poorly constructed trial (4). Moreover, there was a serious complication rate of 9% in the PRI group, which is far higher than that reported in current clinical trials (4–8). Questionable operator renal intervention skills further weaken the conclusions reached in ASTRAL. During the 7 years of recruitment, 24 centers randomized between 1 and 5 patients (42% of all randomized patients) and 35 centers randomized ≤10 patients (65% of all randomized patients). This implies that 65% of all participating centers randomized <1 patient per year! The ASTRAL investigators would not qualify as high-volume interventionalists.

The end points are compromised by the trial’s poor study design. Change in renal function cannot serve as a legitimate outcome measure when 25%

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of the patients in each group had normal baseline renal function and an additional 15% had near-normal renal function. The secondary end point of blood pressure improvement is also questionable when the mean number of antihypertensive drugs per patient in each treatment group was only 2.8, which is less than the requirement of 3 antihypertensive medications recommended by the American College of Cardiology/American Heart Association practice guidelines before revascularization (9).

As stated earlier, the primary and secondary end points are poor outcome measures based on this study design randomizing patients with uncertain indications for revascularization. Despite multiple biases against intervention built into this trial, there was a significant decrease in mean systolic blood pressure at 3 months after revascularization ($p = 0.05$) and a lower average number of antihypertensive agents at 1 year ($p = 0.03$) in the PRI group.

Summary

The ASTRAL trial was a severely flawed study that inappropriately concluded that the risks of renal stenting were not justified by the benefits. The conclusion should have been that patients with mild RAS have little to benefit from renal stent placement. Perhaps future trials—such as CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions), RADAR (Randomised multi-centre prospective study comparing best medical treatment versus best medical treatment plus renal artery stenting in patients with hemodynamically relevant atherosclerotic renal artery stenosis), and NITER (Nephropathy Ischemic Therapy)—

designed to evaluate treatment strategies in hemodynamically significant RAS will shed light on the true outcomes of renal artery revascularization.

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