CORAL: Similar Outcomes With Intervention, Medical Therapy in Renal Stenosis

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Revascularization with stenting added to optimal medical therapy (OMT) did not prevent clinical events in patients with atherosclerotic renal artery stenosis (ARAS) in the prospective, randomized, open-label, international, multicenter Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study [Cooper CJ et al. *N Engl J Med*. 2014].

The most common justifications to intervene in ARAS are resistant hypertension, declining or impaired renal function to prevent progression to end-stage renal disease, and recurrent congestive heart failure (CHF). However, there is little evidence that revascularization and stenting improve outcomes, stated Lance D. Dworkin, MD, Rhode Island Hospital, Providence, Rhode Island, USA. CORAL was conducted to evaluate OMT plus stent revascularization vs OMT alone in a study that was designed to address concerns regarding prior trials in ARAS, including possible selection bias, imprecise definition of renal artery stenosis (RAS), inadequate or unspecified medical regimen, surrogate end points, and crossovers between treatment groups.

In CORAL, patients with hypertension requiring ≥2 antihypertensive medications or ≥stage 3 chronic kidney disease (CKD) plus ARAS were randomized to OMT (n=472) or OMT plus stent revascularization (stent group; n=459). OMT consisted of candesartan (16 to 32 mg daily) ± hydrochlorothiazide (12.5 to 50 mg daily), a fixed-dose tablet of atorvastatin plus amlodipine (10-80/2.5-10 mg daily), and antiplatelet therapy. The only crossovers were from OMT to stenting, and the primary reason was experiencing a primary outcome event.

In most patients, stenosis (≥60% and ≤100%) was defined angiographically but with prior approval was defined noninvasively by duplex ultrasonography (systolic velocity >300 cm/s), magnetic resonance angiography, or computed tomographic angiography. The baseline angiographic and clinical characteristics were similar in both groups (Table 1).

The composite primary outcome was cardiovascular or renal death, stroke, myocardial infarction, heart failure hospitalization, progressive renal insufficiency, and permanent renal replacement therapy and was adjudicated by a blinded clinical events committee. At 3 years, 35.8% and 35.1% of the OMT and stent groups, respectively, had a primary outcome event (HR, 0.94; 95% CI, 0.76 to 1.17; $P=.58$). No differences were seen between groups for any of the components of the primary outcome or among the subgroups.

A significant reduction in the degree of stenosis was achieved with stenting, from a mean 67.94% to 16.25% ($P<.001$), with a mean 1.04 stents per vessel. An embolic protection device was used in 124 of 543 (22.8%) patients. A small (2.3 mm Hg) but significant reduction in systolic blood pressure (SBP) was found with stenting vs OMT ($P=.03$).

The small decline in the estimated glomerular filtration rate (eGFR) over time was not different between groups. A CKD event occurred in 175 (19%) participants. The baseline predictors of eGFR and CKD events were age, SBP, log albumin/creatinine ratio, and lower levels of total and high-density lipoprotein cholesterol; stenting and bilateral RAS were not predictive.

TREATMENT OF ARAS AFTER CORAL

Medical therapy is the preferred treatment of ARAS in patients with hypertension taking antihypertensive agents or with stage 3 CKD, based on the CORAL results, including patients with a creatinine ≥ or <1.6 mg/dL, with or without global cardiac ischemia, SBP ≥ or <160 mm Hg, or stenosis ≥ or <80%, stated Christopher J. Cooper, MD, University of Toledo College of Medicine, Toledo, Ohio, USA. When the need for revascularization is uncertain, medical therapy is preferred, based on the ASTRAL results [The ASTRAL Investigators. *N Engl J Med*. 2009].

Further, he stated that the data, including the CORAL results, do not support the recommendations for the appropriate use of renal artery stenting in the expert consensus statement by the Society for Cardiac Angiography and Interventions (SCAI) [Parikh SA et al. *Catheter Cardiovasc Interv*. 2014].

The CORAL study employed a rigorous vetting of the study sites that included an evaluation of the quality of renal artery stenting during the roll-in phase to ensure quality. Of the 115 sites evaluated, 12 (10%) did not qualify for the randomization phase, and 15 of the 239 cases were not interpretable [Murphy TP et al. *J Vasc Interv Radiol.* 2014]. The roll-in phase and feedback to the study sites resulted in better-quality procedures during the study, with a lower rate of complications (Table 2). Revascularization was clinically safe, with no patient requiring dialysis within 30 days of randomization and only 1 patient in the stent group needing dialysis between days 30 and 90 [Cooper CJ et al. *N Engl J Med*. 2014]. There was 1 stroke leading to death

Table 1. Baseline Characteristics in the CORAL Study

Characteristic	Stenting Plus Medical (n = 459)	Medical (n = 472)
Age, y	69.3 ± 9.4	69.0 ± 9.0
Men	51.0	48.9
White race	93.0	93.0
Black race	7.0	7.0
Body mass index, kg/m^2	28.2 ± 5.3	28.7 ± 5.7
Systolic blood pressure, mm Hg	149.9 ± 23.2	150.4 ± 23.0
Estimated glomerular filtration rate, mL/min/1.73 m^2	58.0 ± 23.4	57.4 ± 21.7
Medical history and risk factors		
Diabetes	32.4	34.3
Prior myocardial infarction	26.5	30.2
History of heart failure	12.0	15.1
Smoking in past year	28.0	32.2
Angiographic findings		
Percentage stenosis: core laboratory	67.3 ± 11.4	66.9 ± 11.9
Percentage stenosis: core investigator	72.5 ± 14.6	74.3 ± 13.1
Global ischemia	20.0	16.2
Bilateral disease	22.0	18.1

Values are given in percentages or means ± SD. There were no significant differences in clinical and angiography characteristics. There was approximately 20% global ischemia. Stenosis severity was similar to Food and Drug Administration approval trials.

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Table 2. Angiographic Complications During the Roll-in and Randomized Phases

	Roll-in	Randomized
Dissection	4.5	2.2
Embolism	3.7	1.2
Branch occlusion	1.2	3.7
Vessel rupture	0.8	0.2
Pseudoaneurysm	0.4	0.2
Wire perforation	0.8	0.2

Values are given in percentages.

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in the OMT group. Although the risk was low with this procedure, Dr Cooper noted that it was not without risk.

Patient selection did not affect the CORAL results. Neither the initial subgroup analysis nor a more in-depth retrospective subgroup analysis by quartiles of degree of stenosis, baseline SBP, and translesional pressure gradients identified a group of patients who would benefit from revascularization. CORAL included a representative sample of stenosis severity, similar to that in the Food and Drug Administration (FDA) approval studies (ranging from 62% to 68%).

The reduction in SBP in CORAL did not translate into a difference in clinical events. Although the FDA approval study for a new renal stent found a reduction in SBP, it was similar to the reduction obtained with OMT in CORAL. Thus, stenting to reduce SBP in patients with ARAS is not supported.

In contrast to the SCAI recommendations for revascularization and based on the CORAL results, OMT is preferred in patients with resistant hypertension, ischemic nephropathy, and CHF. The SCAI recommendation for revascularization in CHF was based on observational studies with a small number of patients, and Dr Cooper and colleagues are preparing to publish data showing that these patients have similar outcomes with OMT. Revascularization should not be performed in patients with unilateral stenosis and an eGFR < 45 until OMT has clearly failed or in patients with anatomically challenging or high-risk lesions.

Renal artery revascularization is rarely indicated in ARAS. Although it may have a role in patients with stage 4 to 5 CKD, Dr Cooper stressed that this is based only on expert opinion, not evidence.

OMT and risk factor management as practiced in the CORAL study provide decisive support of medical management as the initial approach for patients with ARAS, reinforced Kenneth A. Jamerson, MD, University of Michigan Health System, Ann Arbor, Michigan, USA.

A number of features of the study design—including vetting of the study sites, a survey to determine the willingness of investigators to randomize patients with ARAS to revascularization, monitoring of risk factor management via report cards to investigators, and targeting an SBP < 140 mm Hg—contributed to the outcomes achieved in CORAL and likely do not reflect medical management in usual clinical practice.

Notably, the study patients did not have refractory hypertension at baseline, and more likely were undertreated. Regardless of the baseline SBP levels, there was an early reduction in SBP in both groups, and patients benefited from treatment and achieved target SBP levels.

Contemporary studies have lower event rates because of the improvements in medical care over the decades that have led to optimal treatment of patients within the studies, making it difficult to show incremental improvements with additional treatment strategies, explained Dr Jamerson. Yet, the primary strategy to treat patients with ARAS is optimizing medical therapy and risk factor management.