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EDITOR'S PAGE

The "Chicken Little" of Renal Stent Trials: The CORAL Trial in Perspective

The subject of renal artery stenting has received considerable attention with the release of the results of the CORAL Trial. I have asked Dr. Chris White, associate editor of this journal, to put these findings in perspective.

—Spencer B. King III, MD, MACC
Editor-in-Chief, *JACC: Cardiovascular Interventions*

Spencer B. King III, MD, MACC

Editor-in-Chief, *JACC: Cardiovascular Interventions*

Christopher J. White, MD

No, "the sky is not falling" after the release of the results of CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) (1). There is absolutely no justification for the "Chicken Little" hysteria portending the demise of renal artery stenting (2). The CORAL study did not support a preference for renal stenting as the initial treatment for presumed atherosclerotic renovascular hypertension, but neither do the current American College of Cardiology and American Heart Association guidelines (3). These guidelines recommend renal artery stenting as a reasonable option for patients with one of the following: an atherosclerotic severe renal artery stenosis (>70% angiographic diameter renal artery stenosis or 50% to 70% stenosis with hemodynamic confirmation of lesion severity) associated with 1) resistant or uncontrolled hypertension and the failure of 3 antihypertensive drugs, 1 of which is a diuretic agent, and 2) hypertension and intolerance to medication.

The CORAL study found that the primary composite end point (death from cardiovascular or renal causes, myocardial infarction, stroke, hospitalization for congestive heart failure, progressive renal insufficiency, or the need for renal replacement therapy) in patients with renal artery stenosis (>60% diameter stenosis) and poorly controlled hypertension, on 2 or more medications, did not differ between groups treated with multifactorial medical therapy alone compared with multifactorial medical therapy with renal stenting. In the CORAL study, multifactorial medical therapy consisted of an angiotensin receptor–blocking agent, a thiazide-type diuretic drug, amlodipine, atorvastatin, antiplatelet therapy, and diabetes managed according to clinical practice guidelines. The number of blood pressure medications in the group assigned to medical therapy alone increased from baseline at 2.1 ± 1.6 to 3.5 ± 1.4 (not different from the stent group, at 3.3 ± 1.5) at the completion of the trial. Interestingly, both groups had similar decreases in systolic blood pressure, 15.6 ± 25.8 mm Hg in the medical therapy group and 16.6 ± 21.2 mm Hg in the stent group, implying that the medical treatment group had not actually failed 3-drug antihypertensive medical therapy. The investigators reasonably concluded multifactorial medical therapy to be the initial treatment of choice for patients with uncontrolled hypertension taking 2 or more medications rather than renal stenting.

The CORAL trial was well planned and reasonably well run. As with many large, federally funded trials, the original plan had to be altered along the way because of slower than expected patient enrollment. A major issue impeding enrollment was a lack of equipoise between medical therapy and stent placement. Patients with severe renal artery lesions, who clinicians "knew" needed revascularization, were not likely to be enrolled in CORAL, as indicated by modest average renal artery stenosis of 67% found by the core laboratory. Patients with mild renal artery stenoses also were not likely to be enrolled in the trial, because clinicians "knew" they did not need revascularization. This leaves the middle ground—the uncertain lesions for which there is equipoise—for randomization in CORAL, and that is what they got. Because there was no opportunity to enroll into a registry those patients in whom clinicians "knew" the correct therapy,

Dr. White is a consultant for St. Jude and Neovasc; and performs research with Baxter.

the CORAL study group missed a huge opportunity to understand the impact of the 2 treatment strategies in patients who represent the majority of patients who are treated for renovascular hypertension.

The "Achilles' heel" of renal artery intervention is our dependence on invasive angiography to determine which renal artery stenoses cause renal ischemia. Angiography has been shown to poorly discriminate the hemodynamic severity of moderate renal artery stenoses (4). There is no relationship between moderate (50% to 70%) renal artery stenosis determined with quantitative angiography and the hemodynamic severity of a renal artery stenosis. The major limitation of the CORAL study (as was true of the Angioplasty and Stenting for Renal Artery Lesions and Stenting in Renal Dysfunction Caused by Atherosclerotic Renal Artery Stenosis trials) was the inability to select hemodynamically severe renal artery stenoses for treatment. This is particularly relevant for moderate lesions (mean 67% stenosis determined by the core laboratory) enrolled in the CORAL study. Without measuring the hemodynamic severity of the renal artery stenosis, one cannot hope to separate patients with true renovascular hypertension from those with atherosclerotic renal artery disease and essential hypertension (5–7).

Experienced interventionalists have repeatedly demonstrated in device trials sponsored by the US Food and Drug Administration the technical ability to successfully place renal artery stents ≥95% of the time (94.6% in the CORAL trial), which is out of proportion to the clinical benefit reported for hypertension control (about 70%) and improvement of renal function (about 75%), suggesting that either 1) we are stenting renal stenoses that are not causing renal ischemia, or 2) the clinical syndromes (hypertension and chronic kidney disease) we are treating are not related to the renal artery obstructive lesions. Both of these issues likely influenced the CORAL outcomes. The systolic blood pressure reduction and medical therapy to achieve that effect were very similar in both treatment groups. This implies that renal stenting had little to no effect in addition to the antihypertensive therapy. One wonders, with the inaccuracy of 2-dimensional angiography for renal artery stenosis assessment, how many of the renal stenoses included in this trial were not causing kidney hypoperfusion and what percent of the study patients' hypertension was "essential" and not related to renal ischemia. We will never know for sure, but it is likely that the CORAL study actually demonstrated that multifactorial medical therapy alone was equivalent to medical therapy plus stenting in patients with essential hypertension and nonobstructive atherosclerotic renal artery stenoses.

How should the results of the CORAL trial affect our clinical practice for patients suspected of having renovascular hypertension? Patients with presumed atherosclerotic renovascular hypertension should be given a trial of multifactorial medical therapy to lower their blood pressure, as suggested by the results of CORAL. However, for patients whose blood pressure is not controlled with medical therapy, I would follow the recommendation of the American College of Cardiology and American Heart Association guidelines document, which states that it is reasonable to offer renal artery stenting to patients with atherosclerotic severe renal artery stenoses (>70% angiographic diameter renal artery stenosis or 50% to 70% stenosis with hemodynamic confirmation of lesion severity) associated with resistant hypertension and failure of 3 drugs, 1 of which is a diuretic agent, or patients with hypertension and intolerance to medication (3).

Two major questions remain since the completion of the CORAL study: 1) Does renal revascularization with stenting plus medical therapy offer an effective treatment for renal artery stenosis in patients whose blood pressure remains uncontrolled despite multifactorial medical therapy? 2) What is the benefit of renal artery stenting plus medical therapy versus multifactorial medical therapy for renal artery stenoses that have been hemodynamically confirmed as a cause of renovascular ischemia? It is not likely that federal funding will be available any time soon for another major clinical trial in this patient population to satisfy the questions raised by CORAL. What is promising, however, is the concept of a randomized registry trial, as outlined by Lauer and D'Agostino (8), and the opportunity created by the expansion of the National Cardiovascular Database Registry's Carotid Artery Revascularization and Endarterectomy registry into the new Peripheral Vascular Interventions registry, a sister registry to the CathPCI Registry, which will eventually enroll a national sample of renal stent patients. This registry population of renal stent patients may lend itself to relatively low-cost, efficient, prospective queries that will help us move this very important field forward.

Address correspondence to:
Christopher J. White, MD
The Ochsner Clinical School and University of Queensland
Ochsner Medical Center
New Orleans, Louisiana 70121

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