Renal artery stenosis (RAS) occurs in up to 5% of people with hypertension and is associated with ischemic nephropathy and other complications. It has been hypothesized that RAS is a potentially reversible cause of hypertension and these other sequelae, and the practice of renal artery stenting has grown to meet this perceived need. However, data from randomized controlled trials is somewhat equivocal, demonstrating little response in blood pressure or kidney function following stenting. Such trials have led to a spirited debate as to the quality and robustness of the data.

In this issue of the Journal, Murphy et al. (1) discuss data from high-risk subsets of the CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial (2), which included 947 patients with RAS randomized to stent placement plus medical therapy or to medical therapy alone. These patient subsets had high-grade stenoses at baseline, higher intra-arterial pressure gradients, and higher baseline blood pressure. The authors found no difference or significant treatment effect from stenting. We commend the authors for bringing this data to the public sphere.

Many have criticized the CORAL trial. One criticism is that “severe” renal lesions were not enrolled and were stented outside the trial because of patient or physician preference; likewise “mild” renal lesions were not enrolled and were sent to medical therapy. Therefore many lesions included in the trial were actually nonobstructive and of intermediate severity. To the authors’ credit, the CORAL trial has listed reasons for screening failures in the appendix showing that a higher degree of stenosis severity was not a reason for patient exclusion. However, critics respond that the “selection” happened before a patient was even considered for the study, an assertion that is hard to prove or disprove. Another criticism is that 2-dimensional angiography was used to select functional severity, without hemodynamic assessment. White, in a recent editorial published in JACC: Cardiovascular Interventions after publication of the CORAL trial (3), poses 2 remaining questions: 1) Does renal revascularization with stenting plus medical therapy offer an effective treatment for RAS in patients whose blood pressure remains uncontrolled despite multifactorial medical therapy?; and 2) What is the benefit of renal artery stenting plus medical therapy for RAS that is confirmed hemodynamically and not just by angiography?

Murphy et al. (1) attempt to address those 2 questions, but there are even more basic issues of trial design to address. There was no period of repeated blood pressure measurements prior to enrollment. Although this was true for both groups, this nevertheless introduces more statistical “noise,” as this may have caused more patients with spuriously high blood pressure or “white-coat” hypertension to be included in the study. Furthermore, the number of medications increased in both groups (stenting + “OMT” [optimized medical therapy] vs. “OMT”) from 2.1 ± 1.6 at baseline to 3.3 ± 1.5 and 3.5 ± 1.4 medications, respectively. The increase in medications...
may make it difficult to determine what, if any differences were attributable to stenting.

Whether RAS is the cause of hypertension is a much larger question than finding out whether RAS is “significant.” If RAS is a reversible cause of a patient’s hypertension, then stenting may be helpful whether the blood pressure is uncontrolled. If RAS is not a reversible cause of a patient’s hypertension, then stenting even a severe lesion will not be helpful regarding blood pressure control. Stenting may be a better treatment option than taking life-long medications in cases where a stenosis is the cause of hypertension, because it is a 1-time intervention, unlike medications that have compliance and side effects issues that are relevant in clinical and especially in real-world settings.

As for the question of hemodynamic benefit: If we assume that stenosis severity is the main driver of the effect of RAS on hypertension, then the method by which the stenosis is measured is important. The CORAL trial required a ≥60% stenosis, which the authors argue was a common threshold in use at that time and would therefore reflect general practice. Anatomic stenosis is also variable, with angiographic stenosis often not matching actual stenosis. The majority of RAS is due to ostial stenosis, which is sometimes difficult to visualize in a standardized fashion on angiography. Pressure gradient assessment in the study required the on-site investigator’s assessment of stenosis severity as ≥60% or <80%, and was considered “positive” if the gradient was ≥20 mm Hg. Even in those patients, however, this was not always strictly followed. Figure 1 in Murphy et al. (1) shows 230 patients in the stent group and 208 in the medical therapy group with 60% to 80% stenosis, but pressure gradients were only measured in 121 patients in the stent group and 78 in the medical therapy group (53% and 34%, respectively). When mean gradients are used, the numbers are even worse (113 and 70 patients, or 49% and 34%, respectively). How reliable are the data when one-half or fewer of patients underwent the indicated additional gradient measurement? This lends credence to the concern that less severe stenoses were addressed by the trial, which is biased in favor of medical therapy. In addition, pressure gradients of at least 20 mm Hg alone may not be the best indicator for stenting. Should a higher gradient be used as the cutoff for enrollment? Why not 40 or 50 mm Hg? Murphy et al. (1) point out that higher gradients “seem” to be pushing toward medical therapy; however, patients with even higher gradients or stenoses were the ones most likely to be excluded from the study by physicians. In addition, other studies point to functional testing with dopamine as having an additional benefit and a greater area under the receiver-operating characteristic curve for these patients, and may therefore be the preferred test in questionable subsets (4–6). Renal fractional flow reserve is another potential functional study (7) that may be helpful.

From a statistical standpoint, there are issues with analyzing subgroups from a trial. The authors point out that subgroup tests are underpowered. Of note, only 18% of patients were originally randomized from the 5,322 patients deemed suitable—raising the question of validity of subgroup analysis from this cohort. The appendix from the original CORAL article goes through the reasons for not enrolling in 4,375 patients, including 34.5% where RAS was <60%, and 23% for whom study exclusion was for either patient or physician preference. The high number of exclusions for patient or physician preference reflects the fact that 1 of 5 patients were excluded because randomization was not preferred, a potential source of bias.

Murphy et al. (1) do not analyze the specific clinical situations where renal stenting may have been beneficial. Those include patients with severe hypertension, advanced chronic kidney disease, or more rapid decrease in renal function, as well as those with severe bilateral RAS or severe unilateral stenosis in a patient with solitary kidney. These clinical groups may benefit from stenting, but were not included in this trial. The door to renal stenting is not closed yet.

Meta-analyses including the CORAL trial have shown some benefit of renal artery stenting. These include the 7-study report by Caielli et al. (8), which showed a decrease in diastolic blood pressure and less need for antihypertensive drugs following stenting. This was also shown in the 8-study meta-analysis by Bavry et al. (9), demonstrating a reduction in the number of antihypertensive medications required at follow-up.

We commend the authors for publishing this paper and findings, which were part of the critique from the original CORAL trial publication. Although this paper explores some of the critical questions left over by publication of the CORAL trial, there are enough issues with the main CORAL trial enrollment and trial design to make the results of this paper susceptible to similar criticisms.

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