

# Perspectives on Contemporary Studies on the Treatment of Renal Artery Stenosis and the Role of the CORAL Trial

Michael R. Jaff, DO, FACP, FACC, and Timothy Murphy, MD, discuss the impact of previous studies on the current state of renal artery stenosis therapy and the goals and progress of the landmark CORAL trial.

---

## How would you describe the clinical and political climates currently surrounding renal artery intervention?

**Dr. Jaff:** There has been a very negative pall cast over the entire field of renal artery revascularization, which largely began in 2000 with the publication of the DRASTIC trial. Since then, every major study that has come out has suggested that medical therapy is just as effective as renal artery intervention but without the risk. As a result, the Centers for Medicare & Medicaid Services (CMS) took a hard look at renal artery revascularization as a reimbursable procedure a few years ago, and I actually thought they might place restrictions on it. That didn't happen, because they are waiting for the CORAL trial to be completed. On top of that, CMS has to address an expanding array of therapies with a limited budget. With the push toward comparative effectiveness as a model to dictate how we treat patients, renal artery intervention is certainly a prime target for restricted use.

**Dr. Murphy:** As Dr. Jaff said, there is currently a lack of interest in evaluating patients for renal vascular disease. This is in large part the result of the outcomes of the three European studies that began a decade ago—one from France, one from the Netherlands, and another from the United Kingdom. These studies looked at angioplasty and some medical therapies that

would now be seen as somewhat dated. Also, two recent studies, ASTRAL and STAR, compared conventional, guideline-driven therapies versus stenting. STAR has been published, whereas ASTRAL has not, but its data are now increasingly well known because the study has been presented many times. The word is beginning to spread that ASTRAL and STAR were both negative studies for renal artery stenting.

## What are some of the specific issues you have seen in the recent trial data being reported?

**Dr. Murphy:** As we mentioned, a number of studies were published in 1999 and 2000 regarding the treatment of renal vascular disease, including the Scottish-Newcastle series, the EMMA study from France, and the DRASTIC study from the Netherlands, with the latter being published in the *New England Journal of Medicine* in 2000 by van Jaarsveld et al. Those studies used surrogate endpoints and restricted medical therapy in the intervention arm, which included mostly angioplasty alone, and they allowed patients to cross over if they had “inadequate blood pressure control,” but they did not define what exactly that was. As such, these studies were very subjective and susceptible to investigator bias. As it turns out, 44% of patients in DRASTIC's medical management arm did cross over, and yet they concluded that angioplasty offered little benefit in the management of people with renal artery stenosis. There

was an accompanying editorial in that issue of the *New England Journal of Medicine* by Ritz, a German nephrologist, who questioned whether patients with this disease should even be worked up anymore in the context of the negative trials.

**Dr. Jaff:** The ASTRAL trial, which was presented at the 2008 American College of Cardiology meeting, was a European study that randomized patients with chronic kidney disease and renal artery stenosis (RAS) to angioplasty and stenting versus medical therapy alone. The primary endpoint was improvement in renal function. However, its results did not show a difference between the patients who were treated medically and those who were treated with stents. There were a number of methodological flaws in that study, which I believe invalidates any conclusions that came about. The ASTRAL trial still has not been published in a peer-reviewed journal almost 16 months after its public presentation.

The STAR trial was recently published in the *Annals of Internal Medicine*. It had a very similar trial design to ASTRAL, including patients with chronic kidney disease and RAS with head-to-head randomization between stenting and best medical therapy. Like the ASTRAL trial, STAR suggested that there was no real advantage of stents. Again, I believe a number of very serious methodological flaws invalidate this study as well. However, because it has been published in the *Annals of Internal Medicine*, it goes to a huge audience of internal medicine physicians who evaluate these patients and then consider referral for specialty opinion. Overall, I think the data have been quite negative and potentially misleading.

### What are the specific limitations in evaluating and applying the data from these trials?

**Dr. Jaff:** In ASTRAL, the real problem is that we cannot accurately define the population that was eligible for the trial. In other words, a study is more useful if you can apply it to your own patient population, the “real-world” patients. In this study, however, the physicians enrolled patients only if they themselves did not know which treatment to recommend. That was really the deciding point. So, if a doctor saw a patient with hypertension, renal dysfunction, and RAS, and told the patient that he definitely needed a stent, that patient would not have been eligible for ASTRAL. If that same patient walked one door down and saw a second doctor, with the same presentation, and that doctor said that he should not get a stent, again, that patient would not be eligible for the ASTRAL trial. However, this would be the perfect patient to put in a randomized trial. In my view, that was the most serious methodological flaw in the trial design.

**Dr. Murphy:** I agree. In ASTRAL, the eligibility criteria were nebulous and hard to define, as well as difficult or impossible to reproduce from one site to the next. Whereas I view this to be an illogical study design, the authors have said they conducted it this way for ethical reasons. I believe their study design represents a significant difference of opinion regarding the ethics of randomization for studies involving diseases for which the best treatment is not yet known.

Also, STAR showed an absolute treatment-effect difference of approximately 8% and a relative difference of about 25%, with 31% of patients assigned to medical therapy achieving a 20% decline in kidney function compared to 23% in the stent group. However, the randomized groups were only powered for a 50% difference, and we think that represents a smaller difference than what is clinically meaningful. In order to detect that difference, you need many more patients than they were able to include, probably due to funding limitations. Additionally, because they did not use core labs, about 20% of their patients were found not to have significant RAS.

Interestingly, if you read between the lines in both ASTRAL and DRASTIC, there are actually some elements that point to the benefits of renal stenting. In addition to STAR's treatment-effect difference (despite its being insufficiently powered), in the DRASTIC study, the investigators found that the angioplasty group required fewer medications, and they were significantly more likely to have improvement in blood pressure control and were significantly more likely to be cured of hypertension. These patients were less likely to have worsening of their blood pressure control at 12 months—even despite 44% of patients being crossed over from the medical group to the angioplasty group. The benefits of stenting are not clear in these studies due to the aforementioned design and powering issues.

**Dr. Jaff:** I believe that any data derived from these trials are severely limited. To show that revascularization of a renal artery will improve kidney function, you have to be sure that the kidney dysfunction is due to RAS. I think that makes sense. You would not put a stent into someone's renal artery if the patient had diabetic nephropathy, for instance, with nephrotic range proteinuria, in order to improve their renal function. So, to say that RAS caused kidney disease, RAS would have to be present in both kidneys or in one kidney that was already occluded, with the other having high-grade stenosis. In the ASTRAL study, more than 80% of the patients had unilateral RAS alone. Therefore, I don't see how the trial could have possibly shown a kidney function benefit.

There are a number of other issues with these trials as well. They were supposed to include patients who had RAS, yet there were patients who only had 20% stenosis, which is not anywhere near hemodynamically important. It is unwise to place a stent in a 20% stenosis, and therefore, it doesn't compare to clinical applicability. I think the challenge has been what to do with the patients who are true conundrums: the person whose blood pressure is not well controlled on maximal doses of three hypertensive medications, or the person who has bilateral RAS or stenosis to a solitary functioning kidney and a creatinine level of 2.2 mg/dL. Those are the patients for whom we need some evidence to suggest whether revascularization makes a difference. However, those patients were not randomized in either ASTRAL or STAR.

## What types of difficulties are inherent in all renal stenting procedures and trials, which are not necessarily as significant a factor in other vascular beds?

**Dr. Jaff:** The first challenge is that many patients who have incidentally discovered RAS may not have a good clinical reason to do an intervention, and you are then faced with a disconnect between a high-grade RAS and someone whose kidney function is normal and blood pressure is well controlled on one medication. So, is there any advantage at all to revascularizing that renal artery? The second challenge is that these are not necessarily easy cases. For instance, in the STAR trial, there were two deaths in the stenting arm that resulted solely from the procedure. Clearly, there are some serious adverse events that can occur from a renal artery intervention.

I think the biggest challenge overall, however, is knowing who stands to gain the most from having this procedure done. Unfortunately, before we get the results from the CORAL trial, it's going to be very hard to know who those patients are.

## Moving on to CORAL, how was the concept for the trial conceived?

**Dr. Murphy:** A number of interventionists who have had the experience of seeing profound clinical responses to stenting procedures were motivated to determine whether a well-designed study would show a benefit. We knew that stenting provided clinical benefit on a carefully selected, patient-by-patient basis—that some patients did certainly benefit from intervention. However, none of us were sure whether the number of patients who benefited was the same, less, or more than the number who worsened when they were objectively studied in a controlled trial. A number of interventionists and nephrologists got together and began to talk about conducting a study with

a hard clinical endpoint, meaning cardiovascular events (rather than looking at kidney function or blood pressure) to determine if people lived longer with fewer events.

The National Institutes of Health put us in touch with a group of interventional cardiologists and nephrologists, led by Dr. Chris Cooper, who had submitted a grant proposal for a renal artery stent study with a blood pressure endpoint. Our two consortia sat down together in a massive multidisciplinary effort to try to address the problem, and collaboration has been a key to determining the ideal design for this study. In general, save for a few exceptions at our sites, the specialties have all pulled together to try to address this important problem. Without that multidisciplinary collaboration, this would not have been possible.

## Would you outline CORAL's study design and goals?

**Dr. Murphy:** The CORAL study is a prospective, randomized, unblinded, multicenter clinical trial powered to enroll 1,080 patients. Its primary endpoint is a composite of heart attack, heart failure, kidney failure, stroke, and death—all hard clinical events. The secondary endpoints include the usual evaluations of kidney function, blood pressure, medication usage, and interactions of various subgroups such as people with diabetes or those with bilateral disease.

Approximately 800 patients have been randomized as of press time, and we are hoping to complete recruitment by the first or second quarter of 2010. With three more years of follow-up planned, we are anticipating being able to share the first set of results in approximately 2013.

## How has CORAL been affected by the release of the data from previous studies?

**Dr. Murphy:** Despite significant flaws in the design of previous studies, the results of which are not definitive, they have affected enrollment in CORAL. We are hearing from our investigators that many of their referring physicians have stopped working patients up for renal artery disease, and are reluctant to refer them in for CORAL. Our investigators believe this is due to the publications and presentations of the other studies. However, as we've discussed, there are great differences between CORAL and these studies.

**Dr. Jaff:** Enrollment in CORAL has always been difficult because some physicians believe that there is no reason to randomize if they believe they know the right treatment, whether it is to stent or not to stent. Others believe that it is not "real world" enough; for instance, when the study started, embolic protection was mandated to be in that study, yet there wasn't a distal embolic protection device specifically designed for the renal artery. Some physicians

believed that it would be difficult to randomize using a device that was not specifically designed to be safely used in the renal artery. Despite these challenges and the recent negative press regarding renal artery intervention, I can tell you that the steering committee has been working tirelessly to continue to push forward on this trial.

## What are some of the most significant differences between CORAL and previous studies?

**Dr. Murphy:** In the CORAL study, we believe we have addressed many of the design issues from the previous trials. We have a very well-funded study, including more than \$36 million from the National Institutes of Health. We have core labs to ascertain eligibility in every patient and very clear criteria for determining that eligibility. It is a broad population that should reflect the general renal artery stenosis population at large. CORAL has hard clinical endpoints instead of the surrogate or intermediate endpoints that have been used in all of the other studies. We have state-of-the-art medical management, which is working well. For example, 95% of patients with normal kidney function, without diabetes, are normotensive on follow-up after receiving treatment as part of the study. Also, the study has a very strict crossover policy, and very few patients have crossed over.

If there was ever a study that had a chance to be positive for stenting, it's CORAL. This required significant funding and duration, but we felt it necessary to move away from using surrogate endpoints and shorter durations of follow up. The paradox is that the studies that are less thorough and comprehensive are able to be completed more quickly, and their data hit the podiums and publications first—sometimes changing the practice of medicine while the more robust studies are still ongoing, possibly changing the course of those studies as well.

One of the bigger philosophical differences is the design of CORAL's randomization, which is based on the concept that if we do not know what the best treatment is, we believe it is ethical to randomize patients between two reasonable options without expecting our investigators to use their biases to select patients for the study or not.

We hope that people will recognize the methodological rigor of CORAL compared to previous studies, and continue to recruit and refer patients to the CORAL study, because we believe that it is the definitive study on renal vascular disease.

## What, if any, precautions have been taken to ensure that the CORAL's design and conduct stay in line with evolving trends in therapy?

**Dr. Murphy:** With any study powered for a long duration of enrollment and follow-up, there comes the possi-

bility of being outpaced by the progress of technology. The CORAL study has committees in place on both the medical and interventional sides designed to monitor the current trends. Since the start of the study, however, there have not been dramatic changes in these therapies such that we would alter the design. We have observed some changes in the interventional technologies being used to treat renal artery stenosis since the start of CORAL, although none so considerable as to nullify the trial design, and in the last 10 years, we have seen refinement of medical management, including aggressive statin use, lowering of LDL cholesterol levels, antiplatelet therapy, and the use of ACE inhibitors.

We believe the therapies used in the study are currently relevant and will be relevant when its data are presented and published.

## What do you think will happen with renal artery intervention over the next 5 years?

**Dr. Jaff:** We will get the answer from the CORAL trial, but I don't know what that answer will be. I think if the outcome is flatly negative—in other words, if medication is just as effective as stenting—I would not be surprised if reimbursement was seriously curtailed to only cover certain clinical scenarios that would have to be demonstrated before reimbursement would be offered. If that were the case, the number of procedures would drastically decrease. My fear, of course, is that it would be completely restricted, because there are definitely patients, as I've mentioned, who would clinically benefit from a renal artery intervention. My hope is that the CORAL trial will come out with an endpoint that teaches us something so that we can do the right thing for our patients. Whatever the results tell us about the best treatment for renal artery stenosis, I'd certainly like to know. ■

*Michael R. Jaff, DO, FACP, FACC, is Associate Professor of Medicine, Harvard Medical School, and Medical Director, Vascular Center, Massachusetts General Hospital in Boston. Dr. Jaff is the Medical Director of the Vascular Ultrasound Core Laboratory for the CORAL trial. He has disclosed that he is a paid consultant to Abbott Vascular, Nexeon Medical, and Harvard Clinical Research Institute, and that he holds equity in Square One, Inc., and Hotspur, Inc. He has also disclosed that he is a board member of VIVA Physicians, a not-for-profit physician organization ([www.vivapvd.com](http://www.vivapvd.com)). Dr. Jaff may be reached at (617) 726-3784; [mjaff@partners.org](mailto:mjaff@partners.org).*

*Timothy Murphy, MD, is an interventional radiologist at Rhode Island Hospital and Brown University Medical School in Providence, Rhode Island. He is the Coprincipal Investigator for the CORAL trial. Dr. Murphy may be reached at [tmurphy@lifespan.org](mailto:tmurphy@lifespan.org).*