MITCHELL D. WEINBERG, MD
The Zena and Michael A. Wiener Cardiovascular Institute and The Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai School of Medicine, New York, NY

JEFFREY W. OLIN, DO
Professor of Medicine, Director, Vascular Medicine, The Zena and Michael A. Wiener Cardiovascular Institute and The Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai School of Medicine, New York, NY

Stenting for atherosclerotic renal artery stenosis: One poorly designed trial after another

THE ROLE OF STENTING for atherosclerotic renal artery stenosis is hotly debated among different specialties.[1,2] If we may generalize a bit, interventionalists (cardiologists, interventional radiologists, vascular surgeons, and vascular medicine specialists) have been in favor of liberal use of stenting, and nephrologists often favor medical therapy alone. And as with all controversial issues, each group feels rather strongly about its position.

Because few prospective randomized trials have been completed, the management of atherosclerotic renal artery stenosis has been guided by retrospective studies and case series.[3]

We contend that the three randomized trials published so far were seriously flawed

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In this issue of the *Cleveland Clinic Journal of Medicine*, Dr. James Simon[4] provides an excellent overview of the prevalence, natural history, and clinical presentation of atherosclerotic renal artery stenosis. In addition, he does an admirable job of reviewing the available prospective randomized trials and providing editorial commentary about the role of the various specialists in the management of renal artery disease. And while the title of his paper says that it is "time to be less aggressive," Dr. Simon ultimately comes to the same conclusions that we do[5] on the indications for renal artery stenting (see **TABLE 3** of Dr. Simon's article), which are those of the multidisciplinary 2006 American College of Cardiology/American Heart Association guidelines on the management of peripheral artery disease.[3]

So what then is all the controversy about? We all agree that prospective randomized trials that provide class I, level A evidence impart the only unbiased scientific information on the best treatment strategy for patients with renal artery disease. The basic controversial issue is the *interpretation* of these trials. We contend that the three randomized trials of stenting vs medical therapy published so far[6–8] (see below) are so seriously flawed that it is impossible to make treatment decisions based on their results.

Since these trials were published in well-respected journals, their results are often taken as gospel. However, careful review of each of these will reveal the flaws in study design and implementation.

THE DRASTIC TRIAL

In the Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) trial,[6] 106 patients with renal artery stenosis and hypertension (diastolic blood pressure > 95 mm Hg) despite treatment with two antihypertensive medications were randomly assigned to either renal angioplasty (n = 56) or drug therapy (n = 50).

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Authors' conclusions

"In the treatment of patients with hypertension and renal-artery stenosis, angioplasty has little advantage over antihypertensive-drug therapy."[6]

Four serious problems

As we discussed in a letter to the editor of the *New England Journal of Medicine* on August 10, 2000, this study had four serious problems that invalidate its authors' conclusions.[9]

The sample size was insufficient to detect a significant difference between treatment groups. In other words, the chance of a type 2 statistical error is high.

Balloon angioplasty without stenting was used as the method of revascularization. Experts now recognize that stenting is required for renal artery intervention to have a durable result.[3,5]

Renal artery stenosis was defined as greater than 50% stenosis. This allowed a large number of patients to enter the trial who had hemodynamically and clinically insignificant lesions. Most clinicians believe that stenosis of less than 70% is not hemodynamically important.[5,10,11]

Twenty-two of the 50 patients randomized to medical therapy crossed over to the angioplasty group because their blood pressure became difficult to control. In other words, 44% of the patients in the medical group underwent angioplasty, an astounding percentage in an intention-to-treat analysis comparing one therapy with another.

Despite these serious flaws, the results of DRASTIC influenced therapy for years after its publication.

THE STAR TRIAL

In the Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function (STAR) trial,[7] 140 patients with a creatinine clearance of less than 80 mL/min/1.73m^2, renal artery stenosis greater than 50%, and well-controlled blood pressure were randomized to either renal artery stenting plus medical therapy (n = 64) or medical therapy alone (n = 76). The primary end point was a 20% or greater decrease in creatinine clearance. Secondary end points included measures of safety and cardiovascular morbidity and mortality.

Authors' conclusions

"Stent placement with medical treatment had no clear effect on progression of impaired renal function but led to a small number of significant procedure-related complications. The study findings favor a conservative approach to patients with [atherosclerotic renal artery stenosis], focused on cardiovascular risk factor management and avoiding stenting."[7]

Serious flaws

A number of serious flaws render this study uninterpretable.

Mild renal artery stenosis. At least 33% of the patients in the study had mild renal artery stenosis (50%–70%), and 12 (19%) of the 64 patients in the group randomized to stenting actually had stenosis of less than 50%. How can one expect there to be a benefit to stenting in patients with mild (and hemodynamically insignificant) renal artery stenosis? This is especially true when the primary end point is a change in renal function.

More than half of the patients had unilateral disease. It seems intuitive that if one were to plan a trial with a primary end point of a change in renal function, only patients with bilateral renal artery stenosis of greater than 70% or with stenosis of greater than 70% to a solitary functioning kidney would be included. One would not expect that patients with unilateral disease and a stenosis of less than 70% would derive any benefit from revascularization.

In DRASTIC, 44% of the patients randomized to the medical group underwent angioplasty

Not all "stent" patients received stents. All of the patients in the medical group received medication and there were no crossovers. However, only 46 (72%) of the 64 patients randomized to stenting actually received a stent, while 18 (28%) did not. There were two technical failures, and 12 patients should not have been randomized because they had less than 50% stenosis on angiography and thus were not stented. Yet all 64 patients were analyzed (by intention to treat) in the stent group. With these numbers, one could predict that the results would be negative.

Like DRASTIC, this trial was underpowered, meaning that the chance of a type

2 statistical error is high. In fact, the editors of the *Annals of Internal Medicine*, in a note accompanying the article, cautioned that the study "was underpowered to provide a definitive estimate of efficacy."[7] If the study was underpowered to answer the question at hand, why was it deemed worthy of publication?

High complication rates. The periprocedural complication and death rates were much higher than in many other reports on renal artery stenting (see details below).[5]

THE ASTRAL TRIAL

In the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial,[8] the primary outcome measure was the change in renal function over time as assessed by the mean slope of the reciprocal of the serum creatinine. In this trial, 806 patients with atherosclerotic renal artery stenosis were randomized to either stent-based revascularization combined with medical therapy or medical therapy alone.

Authors' conclusions

"We found substantial risks but no evidence of a worthwhile clinical benefit from revascularization in patients with atherosclerotic renovascular disease."[8]

Despite size, flaws remain

Unlike the other trials, ASTRAL had a sample size large enough to provide an answer. However, numerous flaws in study design and implementation invalidate its results for the overall population of patients with renal artery stenosis. The major flaws in ASTRAL were:

Selection bias. For a patient to be enrolled, the treating physician had to be undecided on whether the patient should undergo revascularization or medical management alone. However, the treatment of atherosclerotic renal artery stenosis is so controversial that physicians of different specialties cannot agree on the most effective treatment strategy for most patients.[1,2] Therefore, to exclude patients when their physicians were sure they needed or did not need renal artery revascularization is incomprehensible and introduces considerable selection bias into the trial design.

Normal renal function at baseline. The primary outcome was a change in renal function over time. Yet 25% of patients had normal renal function at the outset of the trial. In addition, a significant number had unilateral disease, and 41% had a stenosis less than 70%. What made the investigators think that stent implantation could possibly be shown to be beneficial if they entered patients into a renal function study who had near-normal renal function, unilateral disease, and mild renal artery stenosis? These are patients whose condition would not be expected to worsen with medical therapy nor to improve with stenting. Most clinicians would not consider stenting a patient to preserve renal function if the patient has unilateral mild renal artery stenosis.

There was no core laboratory to adjudicate the interpretation of the imaging studies. To determine the degree of stenosis of an artery in an accurate and unbiased fashion, a core laboratory must be used.

The reason this is so important is that visual assessment of the degree of stenosis on angiography is not accurate and almost always overestimates the degree of stenosis.[12,13] In a study assessing the physiologic importance of renal artery lesions, the lesion severity by visual estimation was 74.9% ± 11.5% (range 50%–90%), which exceeded the quantitative vascular angiographic lesion severity of 56.6% ± 10.8% (range 45%–76%).[13]

The STAR trial lacked power to provide a definitive estimate of efficacy

Therefore, in ASTRAL, some patients in the 50%–70% stenosis group (about 40% of patients entered) actually had a stenosis of less than 50%. And some patients in the group with stenosis greater than 70% had stenosis of less than 70%. This further illustrates that, for the most part, the patients in ASTRAL had mild to moderate renal artery stenosis.

A high adverse event rate. The major adverse event rate in the first 24 hours was 9%, whereas the usual rate is 2% or less.[14–18] Of the 280 patients in the revascularization group for whom data on adverse events were available at 1 month, 55 (20%) suffered a serious adverse event (including two patients who died) between 24 hours and 1 month after the procedure. This is in contrast to a major complication rate of 1.99% in five reports involving 727 patients.[5]

The trial centers were not high-volume centers. During the 7 years of recruitment,

24 centers (42% of all participating centers) randomized between one and five patients, and 32 centers (61% of all participating centers) randomized nine patients or fewer. This means that many participating centers randomized, on average, less than one patient per year! This was not a group of high-volume operators.

WILL CORAL GIVE US THE ANSWER?

The CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial is under way.[19] Enrollment was to have ended on January 31, 2010, and it will be several years before the data are available for analysis.

CORAL, a multicenter study funded in 2004 by the National Institutes of Health, will have randomized more than 900 patients with greater than 60% stenosis to optimal medical therapy alone or optimal medical therapy plus renal artery stenting. Inclusion criteria are a documented history of hypertension on two or more antihypertensive drugs or renal dysfunction, defined as stage 3 or greater chronic kidney disease based on the National Kidney Foundation classification (estimated glomerular filtration rate < 60 mL/min/1.73 m^2 calculated by the modified Modification of Diet in Renal Disease [MDRD] formula) and stenosis of 60% or greater but less than 100%, as assessed by a core laboratory. The primary end point is survival free of cardiovascular and renal adverse events, defined as a composite of cardiovascular or renal death, stroke, myocardial infarction, hospitalization for congestive heart failure, progressive renal insufficiency, or need for permanent renal replacement therapy.

We hope this trial will give us a clear answer to the question of whether renal artery stenting is beneficial in the patient population studied. One note of caution: recruitment for this trial was difficult and slow. Thus, there were a number of protocol amendments throughout the trial in order to make recruitment easier. Hopefully, this will not be a problem when analyzing the results.

The many serious flaws in the design of ASTRAL essentially render the trial insubstantial

WE ALL AGREE ON THE INDICATIONS FOR STENTING

So, are we really so far apart in our thinking? And is it really "time to be less aggressive" if we follow the precepts below?

***All* renal arteries with stenosis do not need to be (and should not be) stented.**

There must be a good clinical indication *and* hemodynamically significant stenosis. This means the degree of stenosis should be more than 70% on angiography or intravascular ultrasonography.

Indications for stenting. Until more data from compelling randomized trials become available, adherence to the American College of Cardiology/American Heart Association guidelines on indications for renal artery stenting is advised[3]:

- Hypertension: class IIa, level of evidence B. Percutaneous revascularization is reasonable for patients with hemodynamically significant renal artery stenosis and accelerated hypertension, resistant hypertension, and malignant hypertension.
- Preservation of renal function: class IIa, level of evidence B. Percutaneous revascularization is reasonable for patients with renal artery stenosis and progressive chronic kidney disease with bilateral renal artery stenosis or a stenosis to a solitary functioning kidney.
- Congestive heart failure: class I, level of evidence B. Percutaneous revascularization is indicated for patients with hemodynamically significant renal artery stenosis (ie, > 70% stenosis on angiography or intravascular ultrasonography) and recurrent, unexplained congestive heart failure or sudden, unexplained pulmonary edema.

REFERENCES

1. **Cooper CJ, Murphy TP**. Is renal artery stenting the correct treatment of renal artery stenosis? The case for renal artery stenting for treatment of renal artery stenosis. Circulation 2007; 115:263–269.
2. **Dworkin LD, Jamerson KA**. Is renal artery stenting the correct treatment of renal artery stenosis? Case against angioplasty and stenting of atherosclerotic renal artery stenosis. Circulation 2007; 115:271–276.
3. **Hirsch AT, Haskal ZJ, Hertzer NR, et al**. ACC/AHA Guidelines for the Management of Patients with Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic): A Collaborative Report from the American Association of Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Interventional Radiology, Society for Vascular Medicine and Biology and the American College of Cardiology/American Heart Associa-

tion Task Force on Practice Guidelines. Circulation 2006; 113:e463–e654.
4. **Simon JF**. Stenting atherosclerotic renal arteries: time to be less aggressive. Cleve Clin J Med 2010; 77:178–189.
5. **White CJ, Olin JW**. Diagnosis and management of atherosclerotic renal artery stenosis: improving patient selection and outcomes. Nat Clin Pract Cardiovasc Med 2009; 6:176–190.
6. **van Jaarsveld BC, Krijnen P, Pieterman H, et al**. The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. Dutch Renal Artery Stenosis Intervention Cooperative Study Group. N Engl J Med 2000; 342:1007–1014.
7. **Bax L, Woittiez AJ, Kouwenberg HJ, et al**. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. Ann Intern Med 2009; 150:840–841.
8. **Wheatley K, Ives N, Gray R, et al**. Revascularization versus medical therapy for renal-artery stenosis. N Engl J Med 2009; 361:1953–1962.
9. **Tan WA, Wholey MH, Olin JW**. The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis [letter]. N Engl J Med 2000; 343:438.
10. **Rocha-Singh KJ, Eisenhauer AC, Textor SC, et al**. Atherosclerotic Peripheral Vascular Disease Symposium II: intervention for renal artery disease. Circulation 2008; 118:2873–2878.
11. **Textor SC, Lerman L, McKusick M**. The uncertain value of renal artery interventions: where are we now? JACC Cardiovasc Intervent 2009; 2:175–182.
12. **Topol EJ, Nissen SE**. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. Circulation 1995; 92:2333–2342.
13. **Subramanian R, White CJ, Rosenfield K, et al**. Renal fractional flow reserve: a hemodynamic evaluation of moderate renal artery stenoses. Catheter Cardiovasc Interv 2005; 64:480–486.
14. **Burket MW, Cooper CJ, Kennedy DJ, et al**. Renal artery angioplasty and stent placement: predictors of a favorable outcome. Am Heart J 2000; 139:64–71.
15. **Dorros G, Jaff M, Mathiak L, et al**. Four-year follow-up of Palmaz-Schatz stent revascularization as treatment for atherosclerotic renal artery stenosis. Circulation 1998; 98:642–647.
16. **Rocha-Singh K, Jaff MR, Rosenfield K**. Evaluation of the safety and effectiveness of renal artery stenting after unsuccessful balloon angioplasty: the ASPIRE-2 study. J Am Coll Cardiol 2005; 46:776–783.
17. **Tuttle KR, Chouinard RF, Webber JT, et al**. Treatment of atherosclerotic ostial renal artery stenosis with the intravascular stent. Am J Kidney Dis 1998; 32:611–622.
18. **White CJ, Ramee SR, Collins TJ, Jenkins JS, Escobar A, Shaw D**. Renal artery stent placement: utility in lesions difficult to treat with balloon angioplasty. J Am Coll Cardiol 1997; 30:1445–1450.
19. **Cooper CJ, Murphy TP, Matsumoto A, et al**. Stent revascularization for the prevention of cardiovascular and renal events among patients with renal artery stenosis and systolic hypertension: rationale and design of the CORAL trial. Am Heart J 2006; 152:59–66.

***ADDRESS**: Jeffrey W. Olin, DO, The Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, Mt. Sinai Medical Center, One Gustave L. Levy Place, Box 1033, New York, NY 10029; e-mail: jeffrey.olin@mssm.edu.*