despite, or perhaps because of, medical and technological advances in endovascular therapy, the impact and the appropriate treatment of renal artery stenosis has become increasingly controversial. Renal artery stenosis, depending on its severity and whether it is bilateral or unilateral, can be wholly asymptomatic, or it can produce high blood pressure and/or diminished kidney function. Generally, if only one renal artery is affected, only high blood pressure will result. However, if both renal arteries are involved, or if one or both of the kidneys has been damaged either by high blood pressure or by other parenchymal causes such as diabetes, both hypertension and renal dysfunction can result.

The enthusiastic overtreatment by stenting of nonsymptomatic patients and of easily controlled hypertensives with less than 50% stenoses by some operators, as well as the somewhat nihilistic underreferral for stent treatment of ischemic nephropathy advocated by others are two sides of the controversy. These arguments spark the whole debate as to whether renal artery stenting is overused or underused. My answer to this question is emphatically “Yes!”

IS AGGRESSIVE PROPHYLACTIC TREATMENT OF NONSIGNIFICANT STENOSES JUSTIFIED?

The issue of whether to prophylactically treat asymptomatic, especially incidentally discovered, renal artery stenosis (“drive-by stenting”) has become a fairly controversial topic. Generally speaking, asymptomatic renal artery stenoses are those that are <50% of the artery diameter, and certainly <50% of the cross sectional area. It is generally acknowledged that for renal artery narrowing to be physiologically significant, it must produce approximately 80% reduction of the cross sectional area.

Because a high percentage of patients who have coronary disease also have renal artery narrowing, some interventionists choose to perform aortography of the renal arteries at the time of the coronary angiogram. If they find a narrowing, whether the patient is symptomatic or not, they place a stent. The reasoning in most instances has been that these procedures prevent the progression of disease; however, this does not take into consideration the potential complications related to stenting in an asymptomatic patient and/or the likelihood of the stent itself developing a stenosis (as it does in approximately 15% to 20% of cases). The outcome may be worse than the original asymptomatic stenosis that the patient had.

Many interventionists who would stent any renal artery narrowing, regardless of severity, support this course of action, citing data from an authoritative study on the progression of renal artery disease. These studies were completed prior to the new treatment paradigm of vascular disease (ie, before the introduction of lipid-lowering drugs and the broad application of lifestyle alterations). As a result, the progression of disease measured was probably exaggerated.
or otherwise not representative of today's clinical reality. The investigators concluded that although renal artery disease progression is a frequent occurrence, progression to total renal artery occlusion is not. The risk of renal artery disease progression was highest among individuals with pre-existing high-grade stenosis in either renal artery, elevated systolic blood pressure, and diabetes mellitus. A recent paper by Axelrod et al, based on hypothetical calculations compared prophylactic stenting to therapeutic stenting (stenting only if and when clinically indicated) in hypothetical cohorts of 50% unilateral renal artery stenosis followed age 61 to death. Prophylactic stenting as compared to therapeutic stenting results in more quality adjusted life years (QALYs)/patient (10.9 vs 10.3) at higher lifetime costs ($23,664 vs $16,558). Prophylactic stenting was not cost effective ($>50,000/QALY) if the modeled incidence of restenosis exceeded 15%/y and the incidence of progression in the contralateral renal artery was <2%/y. This could clearly be the case with effective current medical therapy. The authors recommended that prophylactic stenting should be undertaken judiciously until it was proven effective in a prospective randomized study.

Recent advocacy of very aggressive statin therapy to lower lipids should shift the renal stenosis treatment paradigm. Studies in the coronary and carotid arteries have shown that the progression of existing plaque can essentially be halted by the aggressive administration of these drugs in addition to lifestyle changes (eg, smoking cessation and diet and exercise modification). These studies have not been conducted in the renal arteries, but one can extrapolate from the carotid and coronary data that the same would be true in all the vascular beds in the body. As such, lipid-lowering therapy and lifestyle modifications may be sufficient prophylactically to prevent a nonsignificant and asymptomatic renal artery stenosis from progressing to cause high blood pressure or renal failure. Statins may well end the debate whether prophylactic stenting of such stenoses with all attendant risks of the intervention is justified.

STENTING FOR CONTROL OF BLOOD PRESSURE

Similarly, there is disagreement over the use of stenting in the relatively gray area of blood pressure control. There is debate as to how effectively high blood pressure that is produced by a renal artery stenosis >70% in diameter can be reversed. Almost all of the data in the literature indicate that no more than 15% to 20% of patients who have high blood pressure will be cured if their renal artery narrowing is treated. An additional 50% to 60% will experience improved blood pressure control, and the remainder would fail to have any response to stenting. There are multiple reasons for these disparate results. One is that most hypertension in the elderly population is not due to a renal artery stenosis mediated by the renin angiotensin aldosterone system, but rather is due to essential hypertension, the etiology of which is not entirely clear and is probably multifactorial. Certainly, treating a renal artery stenosis that is not causing a patient's hypertension is not going to alter that condition.

BLOOD PRESSURE, A SOFT ENDPOINT

Control of blood pressure is actually a very soft endpoint. This is primarily because it is most often measured by a combination of the decrease in blood pressure and an alteration in the number of drugs used to control the high blood pressure. This means of evaluation is insufficient because physicians will often exchange three or four less-effective drugs for one or two more powerful or appropriate drugs, and suddenly the blood pressure will be more effectively controlled, but simultaneously a renal artery stent had been used, or the change in drugs might occur after the stent had been placed. The result is that it would appear as if the stent were responsible for the improved blood pressure control, when in fact the change might be due in part or in toto to the altered drug regimen. Almost none of the articles that summarize the results of renal artery stenting for high blood pressure specify changes in the type of drugs, only their number. If the regimen is said to have been altered, especially when the number of drugs is reduced, it is taken as a sign of success, but without investigating the types of drugs that had been substituted and whether those drugs are responsible for the decrease in blood pressure. The situation has unfortunately been further muddied by the often-cited DRASTIC study. van Jaarsveld et al compared medical therapy for hypertension to renal artery angioplasty without stenting. They concluded that there were no significant differences between the two. Unfortunately, their methodology was seriously flawed: many in the medical group were crossed over to angioplasty after they failed medical therapy, yet these patients, in many of whom angioplasty successfully controlled hypertension, continued to be included in the medical group. For these reasons, with some justification, many experts advocate reserving renal artery stenting only for hypertension, which is difficult to control by medication.

STENTING FOR RENAL DYSFUNCTION

Unfortunately, the effect of the debate about stenting asymptomatic stenoses and that of treating hypertension only has spilled over to negatively influence even stent treatment for ischemic nephropathy, one of the few potentially reversible causes of renal failure.

In my opinion, renal artery stenting is overused in asymptomatic patients and in patients who have easily controlled hypertension, especially in cases without confirmation that the renal artery narrowing is responsible for the high blood
pressure. It is, however, likely underused by referring clinicians who have observed overuse of stenting in inappropriate cases and have been influenced by negative papers such as the DRASTIC study, and in turn conclude that the procedure should not be performed even in patients who have renal artery narrowing that is likely causing renal failure. According to most renal artery stenting advocates, such patients are exactly those in whom stenting would be most appropriate. Meta-analyses of renal artery stenting indicate that after stenting, depending on the level of serum creatinine and how long the kidney function has been abnormal, approximately 25% to 30% of patients have a decrease in renal failure, and another 40% have stabilization of their kidney function. These two groups are generally classified together as having benefited. Unfortunately, in every series, there are 25% to 35% of patients who have decreasing kidney function after the procedure.

**NOT-QUIET-Ideal SOLUTIONS FOR INTRAPROCEDURAL CHOLESTEROL EMBOLIZATION**

The explanations investigators have given for this worsening have ranged from the natural history of the disease, to contrast nephrotoxicity, to microcholesterol embolization. There are investigators who believe that it is possible to eliminate microcholesterol embolization using distal protection devices similar to those used in the carotid arteries. The problems inherent in this solution stem from the fact that these protection devices were not designed for the renal arteries, which means that they are inappropriate in length, they often cannot protect all the branches, and they may be very difficult to deploy. Additionally, the current filter type devices have a pore size of approximately 100 µm, yet most microcholesterol crystal emboli are only approximately 10 µm to 20 µm. If an embolic protection device is to be used in this setting, it should be an occlusion balloon type, which totally occludes flow, and the debris can be aspirated out from behind the balloon. The occlusion balloon would provide complete protection if it could be deployed in an appropriate location in the renal artery.

The second issue related to cholesterol embolization is that much of it likely occurs during the “scraping around” in the abdominal aorta. Because the abdominal aorta is usually very diseased in these patients, depending on the type of anatomy and the experience of the operator, there can be much manipulation in the abdominal aorta while trying to cannulate the renal artery. That activity alone can produce considerable cholesterol embolization, and even the best filter will not eliminate that occurrence.

A paper by Holden et al., often cited to illustrate the usefulness of filters in the renal arteries, used a controversial procedural technique. Their data show that with filter use, renal function has basically not deteriorated in any of the patients. The number of patients studied is relatively small (approximately 20 or 30), and they are compared to a group of their own patients in whom no filter was used and there was a very high incidence of cholesterol emboli. The reason these data are controversial is that the technique involves crossing the renal artery with an 8-F sheath before the filter is placed. An 8-F sheath being pushed across the renal artery is likely to cause as much cholesterol embolization as most techniques used while performing the entire stenting procedure.

“Unfortunately, in every series, there are 25% to 35% of patients who have decreasing kidney function after the procedure.”

Henry, another early advocate of renal artery protection devices, recently reported that after stenting without filters the incidence of renal function deterioration has been reduced to almost 0% in 56 patients from 20% to 40% without filters; however, in a larger previous study of 210 patients treated without protection devices, Henry reported the incidence of renal functional deterioration to be only 4%. These are clearly conflicting and controversial data; the final word is yet to be written. An effective, simple protection device would be desirable, but until it is available, using meticulous technique and as little iodinated contrast material as possible are the best ways to salvage renal function.

**BREAKING DOWN THE DEBATE**

In my opinion, there is a certain group of patients who have serum creatinine of >25 to 3 mg/dL, severe bilateral disease, or documented significant diminution in the length of the kidneys who exhibit rapidly progressing renal dysfunction due to a renal artery stenosis that has a gradient across it that should be stented. These are the patients most likely to benefit, but unfortunately they are also the ones most likely to have a complication such as cholesterol emboli. However, we know that if not treated, a very substantial number of them will go on to progressive renal failure and dialysis. Physicians who oppose the decision to stent these patients believe that if the procedure is performed and cholesterol embolization or a mechanical complication occurs, not only has the procedure not helped the patient, it has worsened his or her condition and hastened the onset of dialysis. Overall, they believe the results would be similar to, if not better than stenting—just at a much lower expense.
Our group believes that it is a reasonable decision to stent appropriate patients for ischemic nephropathy. Careful technique and experience using catheters and guidewires, a comprehensive understanding the ideal applications for all treatment alternatives, and using as little iodinated contrast material as possible comprise the best means of ensuring that renal function is preserved and cholesterol embolization is minimized.

COMPOUNDING THE DEBATE

The currently ongoing CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) study was designed to compare the efficacy of ideal medical therapy versus stenting for treatment of ischemic nephropathy and thus to answer and resolve these issues.11 There are significant controversies regarding the design of the CORAL study.

Because of the way the CORAL study is designed, randomization does not occur after the MRA prior to any invasive procedures; instead, patients have an MRA, and those eligible based on the MRA and clinical findings undergo an aortogram and often a selective catheterization of the renal artery to measure a pressure gradient. The aortogram, and especially the selective catheterization, carry a considerable risk. The risk involves both nephrotoxicity due to the iodinated contrast material and the physical manipulation that is involved when catheterizing the aorta and in crossing the renal artery, which potentially causes cholesterol embolization and other mechanical complications. Thus, all patients with a severe narrowing, including the entire medical group, will have been exposed to many of the risks of the invasive group by undergoing an aortogram and having the narrowing crossed. Therefore, due to the study design, a significant number of patients may be excluded simply because many clinicians already have their own prejudices that will prevail over randomization in cases that seem clear for them (ie, either that intervention in a certain group of such patients is detrimental, or conversely, they have had very good experience in a certain group of patients and they believe that a patient who is clearly a candidate should not be randomized).

Many critics believe that randomization should have been based on the MRA, which could have been validated in the patients who were randomized to intervention by an aortogram and having the narrowing crossed. Therefore, due to the study design, a significant number of patients may be excluded simply because many clinicians already have their own prejudices that will prevail over randomization in cases that seem clear for them (ie, either that intervention in a certain group of such patients is detrimental, or conversely, they have had very good experience in a certain group of patients and they believe that a patient who is clearly a candidate should not be randomized).

My concerns are not only the questions of the timing of the randomization and the safety of the patient, but also, and just as importantly, the validity of the data, which will likely influence many physicians’ decisions regarding renal artery stenting for many years to come.

CONCLUSION

The debate on whether and when to stent renal artery stenoses cuts across specialties, but essentially, one side would intervene in any patient who has at least a 50% stenosis, whether or not the patient has clinical symptoms. The other side would not intervene in any renal artery stenosis, regardless of the presence and severity of the symptoms, which range from hypertension to severe renal dysfunction. The physicians who would take the middle ground would try to find some reasonable criteria for intervention. The problem is that by being overly aggressive in minimal indications, some operators have driven otherwise rational clinicians to the extreme of supporting those who would not intervene under most circumstances, and those who would severely restrict intervention even in renal dysfunction.

Due to the unresolved issues related to complications and the relative lack of data supporting stenting in the renal arteries in real-life patient cohorts, the question regarding the appropriateness of renal artery stenting has yet to be sufficiently resolved. The best hope so far is CORAL, but I fear, if completed, its results may not yield the clarity we all seek.

Thomas A. Sos, MD, is Professor and Vice Chair of Radiology at the New York Presbyterian Weill Cornell Center in New York. Dr. Sos may be reached at (212) 746-2601; tas2003@med.cornell.edu.