CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will adopt a more selective approach to intervention for renal artery stenosis

JAMES F. SIMON, MD
Department of Nephrology and Hypertension,
Glickman Urological and Kidney Institute,
Cleveland Clinic

Stenting atherosclerotic renal arteries: Time to be less aggressive

ABSTRACT

Percutaneous intervention has become very popular for treating atherosclerotic renal artery stenosis, as the use of stents has boosted the rate of technical success and as more cases are being discovered incidentally during angiography of the coronary or other arteries. Yet randomized trials indicate that the procedure does little in terms of controlling blood pressure and may actually harm as many patients as it helps in terms of renal function. Needed are better ways to predict which patients will benefit and better ways to prevent adverse effects such as atheroembolism.

KEY POINTS

Two large randomized trials of intervention vs medical therapy showed negative results for intervention. A third trial is under way.

Intervention is not recommended if renal function has remained stable over the past 6 to 12 months and if hypertension can be controlled medically.

The best evidence supporting intervention is for bilateral stenosis with "flash" pulmonary edema, but the evidence is from retrospective studies.

Stenosis by itself, even if bilateral, is not an indication for renal artery stenting.

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Author's note: Atherosclerosis accounts for about 90% of cases of renal artery stenosis in people over age 40.[1] Fibromuscular dysplasia, the other major cause, is a separate topic; in this paper "renal artery stenosis" refers to atherosclerotic disease only.

Renal artery stenosis is very common, and the number of angioplasty-stenting procedures performed every year is on the rise. Yet there is no overwhelming evidence that intervention yields clinical benefits—ie, better blood pressure control or renal function—than does medical therapy.

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Earlier randomized controlled trials comparing angioplasty without stents and medical management showed no impressive difference in blood pressure.[2,3] The data on renal function were even more questionable, with some studies suggesting that, with stenting, the chance of worsening renal function is equal to that of improvement.[4]

Two large randomized trials comparing renal intervention with medical therapy failed to show any benefit of intervention.[5–7] A third study is under way.[8]

It is time to strongly reconsider the current aggressive approach to revascularization of stenotic renal arteries and take a more coordinated, critical approach.

RENAL INTERVENTIONS ON THE RISE

Renal angioplasty began replacing surgical revascularization in the 1990s, as this less-invasive procedure became more readily available and was shown to have similar

clinical outcomes.[9] In the last decade, stent placement during angioplasty has become standard, improving the rates of technical success.

As these procedures have become easier to perform and their radiographic outcomes have become more consistent, interventionalists have become more likely, if they see stenosis in a renal artery, to intervene and insert a stent, regardless of proven benefit. In addition, interventionalists from at least three different specialties now compete for these procedures, often by looking at the renal arteries during angiography of other vascular beds (the "drive-by").

As a result, the number of renal interventions has been rising. Medicare received 21,660 claims for renal artery interventions (surgery or angioplasty) in 2000, compared with 13,380 in 1996—an increase of 62%. However, the number of surgeries actually decreased by 45% during this time, while the number of percutaneous procedures increased by 240%. The number of endovascular claims for renal artery stenosis by cardiologists alone rose 390%.[10] Since then, the reports on intervention have been mixed, with one report citing a continued increase in 2005 to 35,000 claims,[11] and another suggesting a decrease back to 1997 levels.[12]

HOW COMMON IS RENAL ARTERY STENOSIS?

The prevalence of renal artery stenosis depends on the definition used and the population screened. It is more common in older patients who have risk factors for other vascular diseases than in the general population.

Renal Doppler ultrasonography can detect stenosis only if the artery is narrowed by more than 60%. Hansen et al[13] used ultrasonography to screen 870 people over age 65 and found a lesion (a narrowing of more than 60%) in 6.8%.

Angiography (direct, computed tomographic, or magnetic resonance) can detect less-severe stenosis. Thus, most angiographic studies define renal artery stenosis as a narrowing of more than 50%, and severe disease as a narrowing of more than 70%. Many experts believe that unilateral stenosis needs to be more than 70% to pose a risk to the kidney.[14,15]

Angiographic prevalence studies have been performed only in patients who were undergoing angiography for another reason such as coronary or peripheral arterial disease that inherently places them at higher risk of renal artery stenosis. For instance, renal artery stenosis is found in 11% to 28% of patients undergoing diagnostic cardiac catheterization.[16]

No studies of the prevalence of renal artery stenosis have been performed in the general population. Medicare data indicate that from 1999 to 2001 the incidence of diagnosed renal artery stenosis was 3.7 per 1,000 patient-years.[17] Holley et al,[18] in an autopsy series, found renal artery stenosis of greater than 50% in 27% of patients over age 50 and in 56.4% of hypertensive patients. The prevalence was 10% in normotensive patients.

WHO IS AT RISK?

Factors associated with a higher risk of finding renal artery stenosis on a radiographic study include[14]:

- Older age
- Female sex
- Hypertension
- Three-vessel coronary artery disease
- Peripheral artery disease
- Chronic kidney disease
- Diabetes
- Tobacco use
- A low level of high-density lipoprotein cholesterol
- The use of at least two cardiovascular drugs.

The prevalence of renal artery stenosis in at-risk populations ranges from 3% to 75% (**TABLE 1**).[2,4,6,19,20]

It is time to strongly reconsider the current aggressive approach to revascularization of stenotic renal arteries

HOW OFTEN DOES STENOSIS PROGRESS?

The reported rates of progression of atherosclerotic renal artery lesions vary depending on the type of imaging test used and the reason for doing it.

In studies that used duplex ultrasonography, roughly half of lesions smaller than 60%

TABLE 1

Prevalence of renal artery stenosis in at-risk populations

POPULATION	PREVALENCE (%)
Undergoing coronary angiography without indication for renal angiography[11]	
With unilateral stenosis > 50%	6.3–11
With unilateral stenosis > 75%	1.8–4.8
With bilateral stenosis	0.8–4.0
With chronic kidney disease	15%[4]
Starting dialysis	12%[16] 40.8%[19]
With abdominal aortic aneurysm	33.1%[19]
With peripheral artery disease	25%[19]
With diabetes plus hypertension	20%[19]
With refractory hypertension, undergoing angiography	3.2%[20]

Renal artery interventions increased 240% from 1996 to 2000

grew to greater than 60% over 3 years.[21,22] The risk of total occlusion of an artery was relatively low and depended on the severity of stenosis: 0.7% if the baseline stenosis was less than 60% and 2.3% to 7% if it was greater.[21,22]

In a seminal study in 1984, Schreiber and colleagues[23] compared serial angiograms obtained a mean of 52 months apart in 85 patients who did not undergo intervention. Stenosis had progressed in 37 (44%), and to the point of total occlusion in 14 (16%). In contrast, a 1998 study found progression in 11.1% over 2.6 years, with older patients, women, and those with baseline coronary artery disease at higher risk.[24]

The the rates of progression differed in these two studies probably because the indications for screening were different (clinical suspicion[23] vs routine screening during coronary angiography[24]), as was the severity of stenosis at the time of diagnosis. Also, when these studies were done, fewer people were taking statins. Thus, similar studies, if repeated, might show even lower rates of progression.

Finally, progression of renal artery stenosis has not been correlated with worsening renal function.

FOUR CLINICAL PRESENTATIONS OF RENAL ARTERY STENOSIS

Renal artery stenosis can present in one of four ways:

Clinically silent stenosis. Because renal artery stenosis is most often found in older patients, who are more likely to have essential hypertension and chronic kidney disease due to other causes, it can be an incidental finding that is completely clinically silent.[16,25]

Renovascular hypertension is defined as high blood pressure due to up-regulation of neurohormonal activity in response to decreased perfusion from renal artery stenosis. Renal artery stenosis is estimated to be the cause of hypertension in only 0.5% to 4.0% of hypertensive patients, or in 26% of patients with secondary hypertension.[3]

Ischemic nephropathy is more difficult to define because ischemia alone rarely explains the damage done to the kidneys. Activation of neurohormonal pathways and microvascular injury are thought to contribute to oxidative stress and fibrosis.[26] These phenomena may explain why similar degrees of stenosis lead to varying degrees of kidney damage in different patients and why the severity of stenosis does not correlate with the degree of renal dysfunction.[27]

Furthermore, stenosis may lead to irreversible but stable kidney damage. It is therefore not surprising that, in studies in unselected populations (ie, studies that included patients with all presentations of renal artery stenosis, not just those more likely to benefit), up to two-thirds of renal interventions yielded no clinical benefit.[25]

As a result, if we define ischemic nephropathy as renal artery stenosis with renal dysfunction not attributable to another cause, we probably will overestimate the prevalence of ischemic nephropathy, leading to overly optimistic expectations about the response to revascularization.

Recurrent "flash" pulmonary edema is a less common presentation, usually occurring in patients with critical bilateral renal artery stenosis or unilateral stenosis in an artery supplying a solitary functioning kidney. Most have severe hypertension (average systolic blood pressure 174–207 mm Hg) and poor renal function.[28–30]

TABLE 2

Commonly cited indications for intervention in renal artery stenosis

INDICATION	SUPPORT IN THE LITERATURE
Hypertension resistant to three drugs, including a diuretic	Subgroup analysis of a randomized controlled trial[38]
Recurrent flash pulmonary edema	Retrospective[28–31]
Acute kidney injury after introduction of a renin-angiotensin system inhibitor	Retrospective
Rapidly declining renal function	Not supported by subgroup analysis from randomized controlled trials[7]
New onset or worsening control of hypertension in older patients	Retrospective
Resistive index < 0.8	Conflicting data[42–44]

The association between pulmonary edema and bilateral renal artery stenosis was first noted in 1998 by Pickering et al,[31] who in several case series showed that 82% to 92% of patients with recurrent pulmonary edema and renal artery stenosis had bilateral stenosis, compared with 20% to 65% of those with other presentations. Later case series corroborated this finding: 85% to 100% of patients with renal artery stenosis and pulmonary edema had bilateral stenosis.[28–30]

STENTING IS NOW STANDARD

Stenting has become standard in the endovascular treatment of renal artery stenosis.

Most atherosclerotic renal artery lesions are located in the ostium (ie, where the artery branches off from the aorta), and many are extensions of calcified aortic plaque.[26,32] These hard lesions tend to rebound to their original shape more often with balloon angioplasty alone. Stenting provides the additional force needed to permanently disrupt the lesion, leading to a longer-lasting result.

Rates of technical success (dilating the artery during the intervention) are higher with stents than without them (98% vs 46%–77%).[33,34] If the lesion is ostial, this difference is even more impressive (75% vs 29%). In addition, restenosis rates at 6 months are lower with stents (14% vs 26%–48%).[34]

GOALS: LOWER THE BLOOD PRESSURE, SAVE THE KIDNEY

On autopsy, 1/4 of people over age 50 have renal artery stenosis

Because endovascular procedures pose some risk to the patient, it is critical to intervene only in patients most likely to respond clinically. The decision to intervene depends largely on the clinical goal, which should depend on the clinical presentation.

In renovascular hypertension, the goal should be to improve blood pressure control. In ischemic nephropathy, the goal should be to slow the decline in renal function or to improve it. Other indications for intervention include relatively rare but compelling events such as recurrent flash pulmonary edema,[31] which typically resolves after intervention, and acute kidney injury after starting a renin-angiotensin system inhibitor (TABLE 2). In the latter case, stopping the medications leads to resolution of the acute kidney injury, but intervening either prevents further problems or allows the medication to be restarted.

However, if renal artery stenosis is clinically silent, most of the evidence suggests that intervention has no benefit. Furthermore, although retrospective studies have indicat-

ed that intervention may improve survival rates,[35,36] prospective studies have not. Similarly, studies have not shown that intervention generally improves cardiovascular outcomes, even though renal artery stenosis is associated with cardiovascular risk.

Hypertension plus stenosis is not necessarily renovascular hypertension

Essential hypertension and clinically silent renal artery stenosis often coexist, which is why blood pressure control often does not improve after stenting. Also, essential hypertension often coexists with renovascular hypertension.[37] In this situation, stenting may not eliminate the need for antihypertensive drugs, although it may improve blood pressure control and decrease the drug burden.

Before stents came into use, several randomized controlled trials found that blood pressure was no better controlled after angioplasty,[2,3,38] except in cases of bilateral stenosis.[2] This may be because stenosis tended to recur after angioplasty without stents.

The severity of stenosis does not correlate with the degree of renal dysfunction

The 2000 Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study was the first randomized controlled trial to examine the effect of angioplasty on blood pressure control in renal artery stenosis.[38] It had significant design flaws. For example, many patients crossed over from the medical management group to the intervention group because their hypertension was resistant to medical therapy. Overall, intervention (balloon angioplasty without stents in 54 of 56 patients, with stents in the other 2) carried no benefit. However, in subgroup analysis, the patients who crossed over because of resistant hypertension (failure of a three-drug regimen) were more likely to benefit from angioplasty. This suggested that risk stratification should take place early on, before proceeding with revascularization.

With stents, Zeller,[39] in a prospective nonrandomized study, found that the mean arterial pressure decreased by 10 mm Hg. Randomized trials (see below) have failed to demonstrate such a benefit.

Stenting may not improve renal function

Coincidental renal artery stenosis in a patient with unrelated chronic kidney disease is very hard to differentiate from true ischemic nephropathy. Furthermore, most patients with ischemic nephropathy do not benefit from revascularization, making it challenging to identify those few whose renal function may respond.

Given that patients with chronic kidney disease tend to have a higher risk of cardiovascular disease, it is not surprising that 15% of them may have renal artery stenosis,[4] most often incidental.

Chábová[40] examined the outcomes of 68 patients who had chronic kidney disease and a renal artery lesion larger than 70% who did not undergo angioplasty. In only 10 (15%) of the patients did the glomerular filtration rate (GFR) decline by more than 50% of its baseline value during the study period of 3 years. Given the retrospective nature of the study, it cannot be determined (and is rather unlikely) that ischemic nephropathy was the cause of the decline in kidney function in all 10 patients.

When a patient with chronic kidney disease undergoes renal revascularization, renal function can respond in one of several ways (**FIGURE 1**). Positive responses include improvement in GFR, stabilization of declining GFR, and continued decline in GFR but at a slower rate (delaying the onset of end-stage renal disease). The worst result would be an accelerated decline in renal function, suggesting that harm was done to the kidneys. Acutely, this can be caused by contrast-related injury, atheroembolism, or reperfusion injury. Atheroembolism or stent thrombosis could cause a more lasting injury.[4] If renal function was stable before the intervention, any result other than an improved GFR should not be considered a success.

In a prospective cohort study in 304 patients with chronic kidney disease and renal artery stenosis who underwent surgical revascularization, Textor[4] reported that the serum creatinine level showed a meaningful improvement afterward in 28%, worsened in 19.7%, and remained unchanged in 160 52.6%. (A "meaningful" change was defined as > 1.0 mg/dL.) Findings were similar in a cohort that underwent stenting.[33]

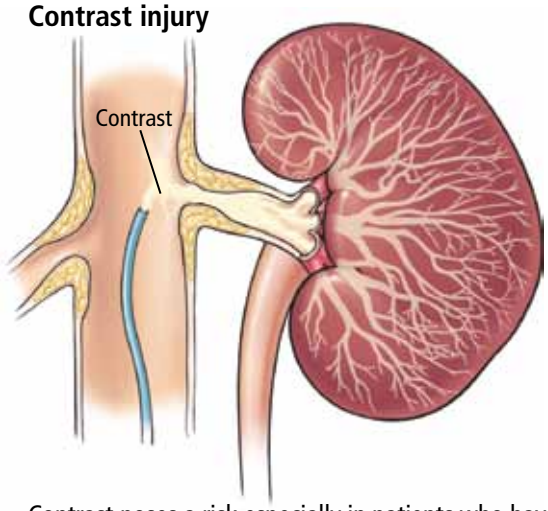
Davies et al[41] found that 20% of patients who underwent renal stenting had a persistent increase in serum creatinine of 0.5 mg/dL or

Percutaneous intervention: Some are helped, but some are harmed

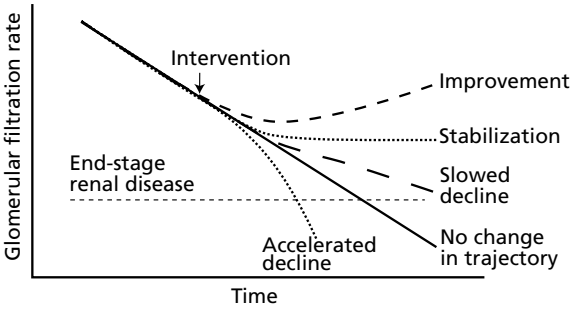
In studies of patients with chronic kidney disease, percutaneous intervention on atherosclerotic renal artery stenosis can have variable effects on renal function.

Possible causes of adverse outcomes

Contrast injury



Contrast poses a risk especially in patients who have preexisting renal impairment.

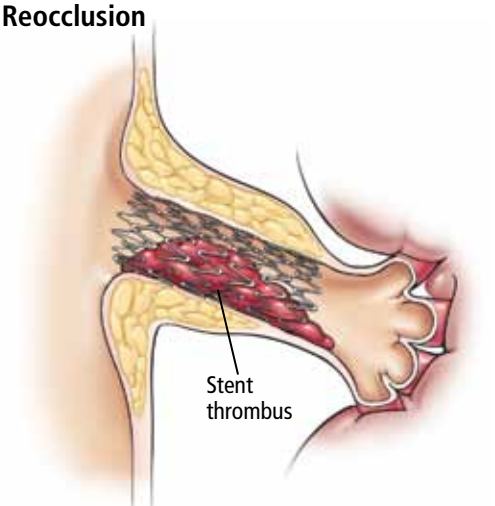


Stenting can improve renal function in some and worsen it in others, but in most cases the rate of decline in renal function does not change. Currently, there is no way to predict the outcome.

Atheroembolism

Atheroembolism can occur as the stent crushes the plaque against the vessel wall.

Reocclusion



The renal artery can sometimes reocclude, either due to restenosis or stent thrombosis.

CCF
Medical Illustrator: Joseph Pangrace ©2010

FIGURE 1

more. These patients were nearly three times more likely (19% vs 7%) to eventually require dialysis, and they had a lower 5-year survival rate (41% vs 71%).

Zeller et al[39] found that renal function improved slightly in 52% of patients who received stents. The mean decrease in serum creatinine in this group was 0.22 mg/dL. However, the other 48% had a mean increase in serum creatinine of 1.1 mg/dL.

From these data we can conclude that, in an unselected population with renal artery stenosis, stenting provides no benefit to renal function, and that the risk of a worsening of renal function after intervention is roughly equal to the likelihood of achieving any benefit.

Other predictors of improvement in renal function have been proposed, but the evidence supporting them has not been consistent. For example, although Radermacher et al[42] reported that a renal resistive index (which reflects arterial stiffness downstream of the stenosis) lower than 0.8 predicted a response in renal function, this finding has not been reliably reproduced.[43,44] Similarly, while several studies suggest that patients with milder renal dysfunction have a higher likelihood of a renal response,[45,46] other studies suggest either that the opposite is true[39] or that baseline renal function alone has no impact on outcome.[47]

If the stenosis is clinically silent, intervention may have no benefit

In addition, once significant renal atrophy occurs, revascularization may not help much, since irreversible sclerosis has developed. Thus, the goal is to identify kidneys being harmed by renal artery stenosis during the ischemic phase, when the tissue is still viable.

Unfortunately, we still lack a good renal stress test—eg, analogous to the cardiac stress test—to diagnose reversible ischemia in the kidney. The captopril renal scan has that capability but is not accurate in patients with bilateral stenosis or a GFR less than 50 mL/min, severely limiting its applicability.[26] Newer technologies such as blood-oxygen-level-dependent (BOLD) magnetic resonance imaging are being investigated for such a role.[48]

Cohort studies in patients with declining renal function

In several case series, patients whose renal function had been declining before intervention had impressive rates of better renal function afterward.[33,39,47,49–54] In a prospective cohort study by Muray et al,[47] a rise in serum creatinine of more than 0.1 mg/mL/month before intervention seemed to predict an improvement in renal function afterward.

One would expect that, for renal function to respond to intervention, severe bilateral stenosis or unilateral stenosis to a solitary functioning kidney would need to be present. However, this was an inconsistent finding in these case series.[33,39,47,52,53] The Angioplasty and Stent for Renal Artery Lesions (ASTRAL) trial,[6,7] discussed later, sheds a bit more light on this.

Stenting usually improves flash pulmonary edema

Acute pulmonary edema in the setting of bilateral renal artery stenosis seems to be a unique case in which improvement in clinical status can be expected in most patients after intervention. Blood pressure improves in 94% to 100% of patients,[28,31] renal function either improves or stabilizes in 77% to 91%,[28–31] and pulmonary edema resolves without recurrence in 77% to 100%.[28–30]

NEW RANDOMIZED TRIALS: STAR, ASTRAL, AND CORAL

Despite the lack of evidence supporting revascularization of renal artery stenosis, many interventionalists practice under the assumption that the radiographic finding of renal artery stenosis alone is an indication for renal revascularization. Only three randomized controlled trials in the modern era attempt to examine this hypothesis: STAR, ASTRAL, and CORAL.

STAR: No clear benefit

The Stent Placement and Blood Pressure and Lipid-lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery (STAR) trial[5] was a European multicenter trial that enrolled 140 patients with ostial renal artery stenosis greater than 50%, blood pressure controlled to less than 140/90 mm Hg, and creatinine clearance 15 to 80 mL/min.

Patients were randomized to undergo

stenting or medical therapy alone. High blood pressure was treated according to a protocol in which angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers were relegated to second-line use. All patients received a statin, regardless of lipid levels.

At 2 years, the primary end point (a decline in creatinine clearance of 20% or greater) had been reached in 10 (16%) of the 64 patients in the stent group and 16 (22%) of the 76 patients in the medication group; the difference was not statistically significant (hazard ratio 0.73, 95% confidence interval 0.33–1.61). No difference was seen in the secondary end points of the degree of blood pressure control or the rates of cardiovascular morbidity and death.[5]

TABLE 3

Recommendations for intervention in renal artery stenosis

Intervention is not recommended:
In patients whose renal function has remained stable over the past 6 to 12 months and whose hypertension can be controlled medically

Intervention should be considered:
In patients with recurrent episodes of congestive heart failure without an obvious cardiac cause and with bilateral renal artery stenosis or stenosis to a single functioning kidney

In patients whose renal function has been rapidly declining over the past 3 to 6 months with bilateral renal artery stenosis or stenosis to a single functioning kidney, without another obvious cause

In patients in whom it is impossible to control hypertension with intense medical management (at least three maximally dosed antihypertensive medications, one of which is a diuretic)

ASTRAL: Also no clear benefit

In the international, multicenter ASTRAL trial,[6,7] 806 patients with at least one stenotic renal artery considered suitable for balloon angioplasty, stenting, or both[7] were randomized to undergo intervention or medical management. Hypertension treatment was not specified by a protocol. The mean estimated GFR was 40 mL/min. Most patients (95%–96%) were on statin therapy. The primary outcome was the rate of decline of renal function over time. Secondary outcomes included blood pressure control, renal events, cardiovascular events, and death.

Results. At a mean follow-up of 33.6 months (range 1–4 years), no difference was noted between treatment groups in decline in renal function or blood pressure control at 1 year. Renal function worsened slightly in both groups.

The decline in renal function over time, calculated as the mean slope of the reciprocal of the serum creatinine level over time, was slightly slower in the revascularization group, but the difference was not statistically significant (-0.07×10^{-3} vs -0.13×10^{-3} L/µmol/year, $P = .06$). This difference did not appear until the last year of the study. There was no difference in the number of patients whose renal function improved or declined during the study.

There was no difference in the rate of any secondary outcome. The medical management group required a slightly higher number of antihypertensive drugs, reaching statistical but not clinical significance (2.97 vs 2.77 drugs, $P = .03$). More people in the revascularization group were taking ACE inhibitors or angiotensin receptor blockers. There was no difference in the number of patients on any antihypertensive therapy (97% vs 99%). Interestingly, amputations were more common in the revascularization group, occurring in 42 (12%) of the 386 patients in the revascularization group vs 29 (7%) of the 395 patients in the medical group ($P = .04$).

Randomized controlled trials leave us with fewer indications for placing renal stents

Seventeen percent of patients randomized to intervention did not have the procedure done. An as-treated analysis of the 317 (83%) patients randomized to revascularization who did receive it showed no differences in outcomes.

There were no differences in outcomes among specific, predefined subgroups based on severity of stenosis at baseline, renal length, baseline estimated GFR, baseline serum creatinine, and rate of progression of renal dysfunction before randomization.[7]

Comments. ASTRAL contradicts previous nonrandomized studies that suggested that rapidly declining renal function (loss of 20% in 1 year) predicts response to intervention. Considering the large number of patients with unilateral disease in the study, it would be in-

teresting to see what effect stenting had on patients with both severe disease and declining renal function.

ASTRAL has been criticized because it lacked a central laboratory to interpret the severity of stenosis, it did not use a standardized intervention technique (5% of patients underwent angioplasty without stents, although this did not affect outcomes[7]), and patients were enrolled only if the clinician involved in the case was uncertain of the appropriate management.

This last issue raises the concern for selection bias toward inclusion of more difficult cases that may not respond to intervention. But these shortcomings are not serious enough to negate the fact that preliminary results from the largest randomized controlled trial to date confirm conclusions of other randomized trials, ie, that intervention in renal artery stenosis yields no benefits over medical management in most patients.

Based on the results of STAR and ASTRAL, the practice of indiscriminately revascularizing stenosed renal arteries without strong evidence that the procedure will provide a clinical benefit is no longer tenable. The challenge is to identify those few patients who will respond, and to intervene only on them. Unfortunately, none of the subgroups from ASTRAL helped characterize this population.

CORAL: A large trial is ongoing

The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial,[8] an ongoing multicenter randomized controlled trial in the United States, may be of additional help.

Unlike ASTRAL, CORAL is studying patients who have difficult-to-control hypertension (systolic blood pressure ≥ 155 mm Hg on two or more drugs).[8] Chronic kidney disease is not an exclusion criterion unless the serum creatinine concentration is greater than 3.0 mg/dL.

CORAL is using a standardized medical protocol to control blood pressure. In addition, use of embolic protection devices during stenting is encouraged. Hopefully, the large size (a goal of 1,080 patients) and the inclusion of patients with more marked hypertension will address the utility of intervention in higher-risk populations with renal artery stenosis.

RECOMMENDED APPROACH TO INTERVENTION IN RENAL ARTERY STENOSIS

As we wait for CORAL to be completed, we have two modern-era randomized controlled trials that leave us with fewer indications for renal intervention. **TABLE 2** lists commonly cited indications for intervention in renal artery stenosis and the evidence to support them. As most of these are based on retrospective data or have conflicting support in the literature, their utility remains in question. At this point we can safely recommend:

- Patients with preserved or even decreased but stable renal function will not likely have a benefit in renal function after intervention.
- Patients with resistant hypertension may benefit.
- The best evidence supporting intervention is for bilateral stenosis with flash pulmonary edema, but the evidence is from retrospective studies.
- Stenting in bilateral disease without another indication has no apparent benefit.
- Declining renal function is not a guarantee of success.
- It is unclear if patients with severe bilateral stenosis or severe stenosis to a solitary functioning kidney with declining renal function will benefit. Anecdotally, they do respond more often, but as with many other indications for intervention that have gone by the wayside, this may not bear out when studied properly.

Based on the current evidence, imperfect as it is, recommendations for a basic approach to intervention in renal artery stenosis are presented in **TABLE 3**.

As the utility of intervention narrows, the scope of practice for such interventions should narrow accordingly. Attention should now be focusing on clinical, rather than radiographic, indications for intervening on renal artery stenosis.

Therefore, the decision to intervene must not be made solely by the interventionalist. A

multidisciplinary approach should be adopted that at the very least includes the input of a nephrologist well versed in renal artery stenosis. In this way, the clinical risks and benefits of renal intervention can be discussed with the patient by providers who are likely to be involved in their care should renal function or hypertension fail to improve afterward.

RISK OF ATHEROEMBOLISM

While renal stenting yields improved technical success in the treatment of renal artery stenosis, it carries with it an increasingly common risk to kidney function: atheroembolism as the stent crushes the plaque against the vessel wall. This may lead to obstruction of the renal microvasculature, increasing the risk of irreversible damage to renal function.

Atheroembolic kidney disease can manifest as progressive renal failure occurring over weeks to months, commonly misdiagnosed as permanent damage from contrast nephropathy.[55]

Embolic protection devices, inserted downstream of the lesion before stenting to catch any debris that may break loose, have been developed to help address this problem.

Holden et al [57] prospectively studied 63 patients with renal artery stenosis and deteriorating renal function (undefined) who underwent stenting with an embolic protection device. At 6 months after the intervention, renal function had either improved or stabilized in 97% of patients, suggesting that many of the deleterious effects of stenting on renal function are related to atheroembolism.

The Prospective Randomized Study Comparing Renal Artery Stenting With or Without Distal Protection (RESIST) trial, in which renal dysfunction was mild and the GFR was not declining (average estimated GFR 59.3 mL/min), found contrary results.[57] In a two-by-two factorial study, patients were randomized to undergo stenting alone, stenting with the antiplatelet agent abciximab (ReoPro), stenting with an embolic protection device, or stenting with both abciximab and an embolic protection device. Interestingly, renal function declined in the first three groups, but remained stable in the group that received both abciximab and an embolic protection device.

ANTIPLATELET THERAPY AFTER RENAL STENTING: HOW LONG?

We have no data on the optimal duration of antiplatelet therapy after renal stenting, and guidelines from professional societies do not comment on it.[58] As a result, practice patterns vary significantly among practitioners.

While in-stent restenosis rates are acceptably low after renal stenting, the risks and side effects of antiplatelet therapy often lead to arbitrary withdrawal of these drugs. The effect on stent patency is yet to be determined.

FUTURE DEVELOPMENTS

Results of STAR and ASTRAL confirm the growing suspicion that the surge seen in the last decade in renal artery stenting should be coming to an end. We await results either from CORAL or possibly a post hoc analysis of ASTRAL that might identify potential high-risk groups that will benefit from renal intervention. And as embolic protection devices become more agile and suitable to different renal lesions, there remains the possibility that, due to lower rates of unidentified atheroembolic kidney disease, CORAL may demonstrate improved renal outcomes after stenting. If not, the search for the best means to predict who should have renal intervention will continue.

We know through experience that stenting does provide great benefits for *some* patients with renal artery stenosis. Furthermore, the clinical problem is too intriguing, and too profitable, to die altogether.

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***ADDRESS**: James F. Simon, MD, Department of Nephrology and Hypertension, Glickman Urological and Kidney Institute, Q7, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail simonj2@ccf.org.*