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The Uncertain Value of Renal Artery Interventions

Where Are We Now?

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Improved technology for detection of and endovascular procedures for renal artery stenosis due to atherosclerosis has been associated with increases in renal artery intervention. Hypertension with accelerated target organ injury, reduced kidney function, and episodic circulatory congestion in patients with renovascular disease predict reduced patient survival. Recent studies indicate that activation of pressor mechanisms depends upon hemodynamic gradients that are often overrated by visual estimates. Although activation of the renin-angiotensin system initiates renovascular hypertension, additional mechanisms perpetuate vascular remodeling and kidney injury that may not depend upon large vessel occlusion. Major advances in medical therapy have led to initiation of at least 4 major prospective trials comparing optimal medical therapy with or without stenting. Up to now, outcome data fail to support broad application of renal revascularization, including results from a recent large, prospective trial from the United Kingdom, despite small groups of patients that experience major clinical benefit. The ambiguity of these results partly reflect poor characterization of the severity of vascular lesions and competing risks within the population related to aging and pre-existing disease. Many patients currently undergoing renal artery interventions derive little net benefit and some are exposed to significant complications, including atheroembolic disease. Determining the appropriate role for renal artery interventions will depend on developing better methods for judging the role of large vessel occlusive disease regarding tissue oxygenation, activation of profibrotic pathways, and irreversible injury in the post-stenotic kidney. (J Am Coll Cardiol Intv 2009;2:175–82) © 2009 by the American College of Cardiology Foundation

Technical advances in endovascular intervention for renal artery atherosclerosis have been stunning in recent years. Even complex atherosclerotic lesions are routinely treated with stents achieving lumen patency in more than 98% of cases. These developments allow more patients with extensive renovascular disease to be considered for revascularization than ever before. Why, then, does endovascular stenting for patients with renal artery disease remain controversial? Debates appear regularly at national meetings and in major journals, reflecting both skepticism and large gaps in persuasive outcome data (1,2).

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These debates underscore a major divergence between individual physicians and subspecialty groups such as internists, cardiologists, and nephrologists caring for patients with atherosclerotic renal artery stenosis (RAS). Clinicians recognize that renovascular occlusive disease accelerates hypertension, is associated with high cardiovascular mortality, and can lead to irreversible loss of kidney function (3). Up to now, however, prospective clinical trials—some small, and some recent larger trials from the United Kingdom and Europe—fail to demonstrate benefits

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of renal revascularization regarding cardiovascular or kidney outcomes as compared with intensive medical therapy alone (4,5). Occasionally, renal artery interventions lead to adverse outcomes, including catastrophic complications such as atheroembolic disease or aortic dissection. These results have been sufficiently ambiguous so that no fewer than 4 prospective, randomized trials have been undertaken specifically to examine whether stenting adds benefit as compared with optimized medical therapy alone (6).

Despite these concerns, renal artery interventions seem to have irresistible appeal, particularly in the U.S. Reviews of Medicare claims indicate the number of procedures between 1996 and 2005 rose more than 4-fold, from 8,000 to more than 35,000 (6,7). The increased rates of intervention appear to be driven mainly by cardiologists, rather than interventional radiologists or surgeons. The Center for Medicaid and Medicare Services convened a meeting of its medical advisory group in 2007 regarding treatment of atherosclerotic RAS. This meeting followed a formal review by the Agency for Healthcare Research and Quality that indicated that the available published data were insufficient to conclude substantial benefit regarding blood pressure control, kidney function, or mortality for atherosclerotic renal artery disease (4). Although no change in coverage has yet appeared, there remains a concern that these procedures are overused in the U.S. Reports that the U.S. per capita health care spending is nearly double that of other Western countries, notably Australia, Canada, Germany, the Netherlands, New Zealand, and the United Kingdom, are consistent with this concern. Despite higher costs, outcomes regarding "preventable deaths before the age of 75" are actually higher in the U.S. than in these countries (8).

Abbreviations and Acronyms

RAS = renal artery stenosis

Professional societies have offered "consensus" statements freely supporting peripheral arterial interventions, including renal artery stenting. Several of these offer the position that renal artery stenting procedures are "reasonable" or "usually effective," despite the lack of supporting evidence (9). Some endorse screening aortography to examine the renal arteries as part of coronary angiography for patients considered at risk for having renovascular disease (10). The nephrology community has viewed these developments with increasing skepticism (11). This review will explore the current status of renal artery interventions regarding complex hypertension and protecting kidney function. We hope to highlight areas where further information is needed to provide intervention for patients who would truly benefit.

Population at Risk

Some of the rising prevalence of systemic atherosclerotic disease relates directly to the aging population. In some respects, the problem of atherosclerotic renal artery disease is an outgrowth of success from reduced mortality from coronary artery disease and from other causes. The average age reported in interventional series rose from the mid-50s to the early 70s over the last 2 decades. Population-based studies indicate that among a free-living community, RAS above 60% (by ultrasound) can be detected in 6.8% of individuals above age 65 years. Screening for renal artery disease in subjects with coronary disease or atherosclerotic peripheral vascular disease and hypertension yields a prevalence of RAS between 18% and 40% (9). Hypertension and decreased glomerular filtration rate estimated by the MDRD (Modification of Diet in Renal Disease) study equation also are nearly ubiquitous in this population. Renewed emphasis on attaining optimal blood pressure control and the association of reduced kidney function with adverse cardiovascular risk understandably predisposes many clinicians to revascularize the kidney when the opportunity arises.

Clinical manifestations of RAS reflect complications of elevated arterial pressure and impaired kidney function. Studies of patients with presumed renovascular hypertension indicate that circadian pressure rhythms are frequently disturbed leading to "nondipper" status with accelerated target organ manifestations. Patients with limited cardiac reserve can develop worsening congestive heart failure (sometimes designated "flash" pulmonary edema) that can be managed more easily after renal revascularization. In the past, these features were refractory to most medical therapy. In recent years, however, the availability of effective, well-tolerated antihypertensive therapy including agents that block the renin-angiotensin-aldosterone system largely has overcome these problems. Series of patients successfully treated for "resistant hypertension" routinely include many with associated renovascular disease. Most of these patients now can be treated to "goal" levels with attention to drug selection and management of volume effects (12). The CORAL (Cardiovascular Outcomes of Renal Atherosclerotic Lesions) study (13) requires external monitoring to ensure that participants be treated to goal blood pressures consistent with Joint National Commission (JNC)-7 guidelines. Renin-angiotensin system blockade with candesartan is provided for all patients in this trial.

Mechanisms of Hypertension

The potential for reduced renal perfusion pressure to induce a systemic rise in blood pressure remains a seminal observation in hypertension. Renovascular hypertension induced by renal-artery clips, or more recently by progressive renal artery occlusion induced by a proinflammatory material such as a copper stent (14), remains among the most widely studied models of hypertension.

Reduced perfusion pressure beyond a stenotic kidney lesion releases renin and thereby activates angiotensin II.

Early studies using angiotensin-converting enzyme inhibition, and more recent studies with genetic knockout animals lacking the angiotensin I receptor, confirm that renovascular hypertension requires the angiotensin effect to develop. The sustained pressor role for the renin-angiotensin system depends greatly upon whether a normal "contralateral" kidney is present to excrete sodium (designated 2-kidney-1-clip hypertension) as we have reviewed elsewhere (3). The magnitude of renovascular occlusion required to activate the renin-angiotensin system in this disorder is underscored by recent studies in humans by De Bruyne et al. (15). These investigators demonstrate that renin release beyond an inflated occlusive balloon is proportional to the gradient developed across the lesion and requires at least a 10% gradient. These effects are illustrated in Figure 1. Early studies using cast models of vascular occlusion suggest that hemodynamic effects of pressure or flow reduction are detected only above 60% to 70% lumen occlusion (3) Some clinical trials employ a visually estimated threshold of "50%" stenosis (16). Recent experience (14) demonstrates that such estimates commonly overstate the degree of occlusion. These studies are hampered by the lack of standardized methods to assess the status of the intrarenal microcirculation and renal hemodynamic and functional reserve (17). The fact that many renal artery stenoses fail to produce hemodynamic gradients may partly account for the limited benefit observed in previous trials of renal revascularization.

To complicate matters, activation of the renin-angiotensin system is often transient. Recent studies indicate that additional pressor systems become activated with time, including a production of reactive oxygen species leading to "oxidative stress" (18). Sympathetic nerve activation and recruitment of endothelium-based pressor systems are commonly identified, only some of which are reversible upon restoring renal perfusion (19). Vascular responses within the kidney are modified by early atherogenic changes related to high cholesterol levels (20). Inflammatory and profibrogenic pathways become activated during sustained renal artery occlusion and perpetuate irreversible renal damage. These factors lead to scarring and loss of glomerular filtration with time. At some point, restoring renal artery perfusion no longer produces meaningful recovery of function.

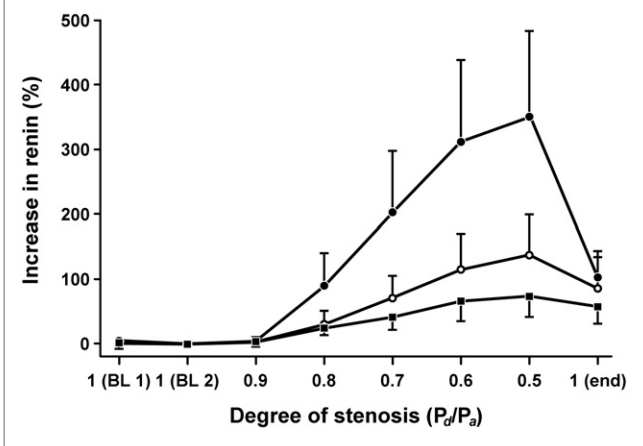

Figure 1. Trans-Stenotic Gradient Required for Renin Release

Balloon-induced, controlled, graded stenosis in human subjects followed by measurement of the plasma renin concentration in the vein of the stenotic kidney **(solid circles)**, in the vein of the nonstenotic kidney **(open circles)**, and in the aorta **(squares)**. These studies underscore the hemodynamic requirements for activation of the renin-angiotensin system in subjects with renal artery stenosis. Such effects require development of a pressure gradient across the lesion. Reproduced, with permission, from De Bruyne et al. (15). BL = baseline.

It is important to recognize that the principles and success of vascular intervention in the coronary and peripheral arteries may not extend to renal circulation. Unlike blood vessels supplying the heart or brain, the vessels to the kidney deliver an excess of oxygenated blood, far more than needed for basal metabolic demands (21). Much of the oxygen consumption beyond basal levels is related to solute transport, which can vary widely and can increase efficiency under stress. Moreover, functional units of the kidney can "hibernate" and can regenerate after an ischemic insult. Hence, the kidney can be less susceptible to moderate changes in blood flow than either heart or neural tissue in the absence of pre-existing renal disease. Deterioration of renal function beyond a stenotic lesion then may reflect late effects of sustained hemodynamic injury or result from other fibrogenic processes that do not primarily reflect hemodynamic changes (22).

Technical Issues Related to Renal Artery Stenting

Tools used for percutaneous renal artery intervention have improved over recent years with pre-mounted, ultra-low-profile stent/balloon combinations on 0.014- or 0.018-inch wire platforms designed specifically for renal artery use. Gone are the days of manually shaping stents over 5- or 7-F balloon catheters designed for 0.035-inch guidewires. The use of steerable guiding catheters is now routine and allows for gentle engagement of renal artery ostia. More precise imaging tools allow stent placement to ensure lesion coverage and targeted stent extension into the abdominal aorta. These tools undoubtedly allow management of more complex cases safely without adding much procedural risk.

Atheroembolic disease remains a major concern with manipulation of the abdominal aorta. Renal artery manipulation is a predictor of serious embolic events (23), and small embolic showers are often undetected. Distal embolic protection devices designed originally for coronary and cerebrovascular applications have been employed in the renal arteries in an effort to mitigate renal injury. These devices include either filter wires or balloon occlusion and

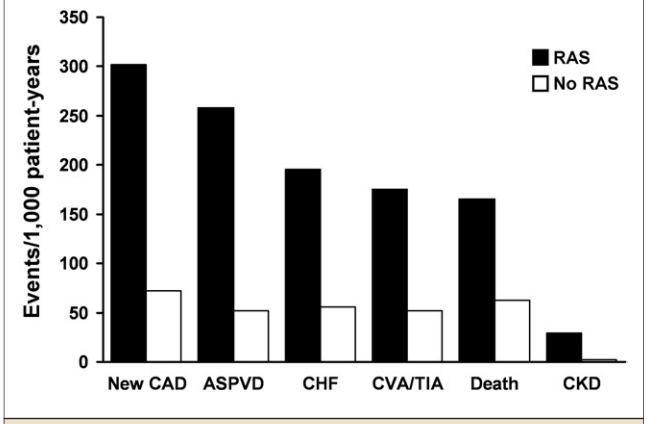

Figure 2. Clinical Events in Patients With RAS

New clinical events reflected as Medicare claims in the 2 years after identification of new atherosclerotic renal artery stenosis (RAS), based on a review of 1,085,250 claims between 1997 and 2001. These observations confirm the increased rate of new cardiovascular events, including death, in patients with identified renovascular disease in the population above age 65 years in the U.S. Cardiovascular events were far more frequent than further loss of kidney function (CKD). Data taken, with permission, from Kalra et al. (27). ASPVD = atherosclerotic peripheral vascular disease; CAD = coronary artery disease; CHF = congestive heart failure; CVA = cerebrovascular accident; Dx = diagnosis; TIA = transient ischemic attack.

aspiration designs. Embolic protection appears logical and has been used successfully in several series (24,25).

However, the true benefits of embolic protection devices for the renal circulation remain unproven in general use. Cooper et al. (26) published a randomized, prospective trial that showed a decline in estimated glomerular filtration rate in patients treated with no protective device, in patients treated with a distal embolic protection device (Angiogard, Cordis Endovascular, Miami Lakes, Florida), and in patients treated with a platelet glycoprotein IIb/IIIa inhibitor (abciximab) as an antithrombotic agent. The only group with no loss of glomerular filtration rate was treated with both the embolic protection device and abciximab. A treatment interaction was observed between the use of the Angiogard and abciximab in this trial. This raises the question of whether use of the device pre-disposed the patient to have intravascular thrombosis. Regardless of the reason, the company producing the Angiogard has ceased its development, and its use has been discontinued in the CORAL trial. Other devices are sometimes employed and require considerable operator experience for optimal use. Early bifurcation of the renal artery with insufficient length for the device deployment sometimes presents anatomic limitations and may render up to 50% of the renal parenchyma vulnerable to embolization even with a device in place. As a practical matter, development of renal embolic events can occur over days and weeks after vessel manipulation, making temporary protection have only limited value.

Competing Risk and Results of Revascularization for RAS

A major confounder related to treatment of renal artery atherosclerotic disease is "competing risk" from other manifestations of atherosclerosis. Nearly all of these patients have pre-existing hypertension and/or other risk factors, such as smoking, advanced age, dyslipidemia, diabetes. A review of Medicare claims data for newly identified subjects with claims attributable to renal artery disease indicates that claims over the following 2 years vastly exceed those of a control population without renal artery disease. These claims mainly relate to new cardiovascular disease including acute coronary syndromes, congestive heart failure, stroke, and similar conditions (Fig. 2) (27). The risks of these events were numerically far greater than complications related to renal failure. Some argue that renal artery disease primarily reflects the burden of atherosclerotic disease elsewhere, but does not itself determine the outcome of this disease, at least over the near term. This conclusion is consistent with follow-up data over periods up to 8 years comparing surgical renal revascularization with intensive medical therapy for renal artery atherosclerotic lesions in a randomized, prospective trial (28) (Fig. 3). Several small trials of percutaneous angioplasty nearly a decade ago failed to identify clinical benefits in terms of blood pressure

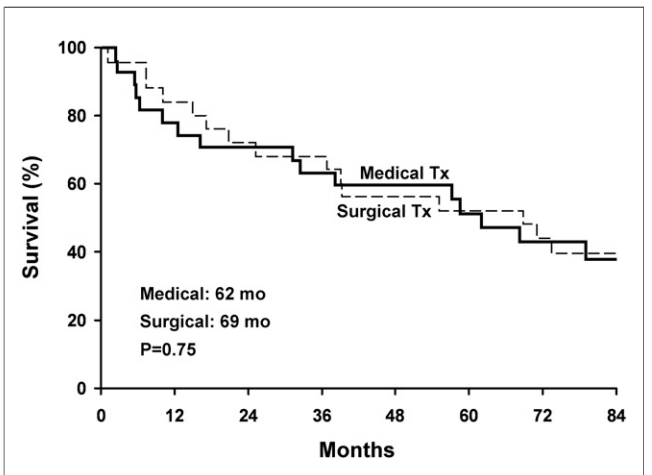

Figure 3. Survival After Medical Therapy or Renal Artery Revascularization

Follow-up data regarding survival after intensive medical therapy as compared with surgical revascularization of patients with atherosclerotic renovascular disease affecting the entire renal mass. Despite excellent vascular patency, no survival differences for the groups were apparent during follow-up for more than 7 years. The cumulative mortality exceeded 50% over 5 years, which is consistent with widespread atherosclerotic vascular disease that was not affected by renal artery reconstruction. Initial results from the ASTRAL (Angioplasty and Stenting for Renal Artery Lesions) trial including 806 patients are similar, identifying no detectable difference in either progressive renal dysfunction or mortality (see text). Data taken, with permission, from Uzzo et al. (28). Tx = treatment.

Table 1. Reasons for Uncertainty Regarding Renal Artery Revascularization

1. Imprecise definition of "severity" regarding occlusive disease
Inclusion of subcritical lesions in clinical trials
Failure to define causal role in disease syndromes:
a. Hypertension
b. Declining kidney function
c. Congestive heart failure (circulatory congestion)
2. Failure to revascularize kidneys with potential for recovery
3. Lack of standard methods to assess renal hemodynamic/functional reserve
4. Compensatory actions of the nonstenotic kidney
5. Complications of the procedure, for example,
a. Atheroembolic disease
b. Vessel dissection/occlusion
c. Contrast nephrotoxicity
d. Ischemia/reperfusion injury
6. Advances in medical therapy for hypertension and atherosclerosis
a. Blockade of the renin-angiotensin system
b. Effective, well-tolerated antihypertensive drugs
c. Statins and other lipid-lowering drugs
d. Antiplatelet agents: aspirin, clopidogrel
e. Smoking cessation
7. Competing risks of comorbid disease
a. Aging population
b. Pre-existing coronary and cerebrovascular disease
c. Renovascular disease as an incidental finding
8. Negative outcomes data from randomized trials
a. PTRA trials
b. Surgical revascularization
c. ASTRAL (preliminary)
d. STAR (preliminary)

ASTRAL = Angioplasty and Stenting for Renal Artery Lesions trial; PTRA = percutaneous transluminal renal angioplasty; STAR = STent placement and BP and lipid lowering for progression of renal dysfunction caused by Atherosclerotic ostial stenosis of the Renal artery.

control, renal function, or mortality during the short term, as we have reviewed elsewhere (3). Many patients with severe disease were not included in these trials, and analysis was complicated by high rates of treatment crossover between medical and revascularization therapy.

Taken together, current data related to renal artery interventions do not support a major benefit for most patients with atherosclerotic disease. Table 1 summarizes some of the reasons for continued uncertainty regarding the benefits of renal revascularization.

Large Trials in Progress

Blockade of the renin-angiotensin system, statins, and antiplatelet therapy are now bedrocks for the clinical management of atherosclerotic disease, including RAS (29). Although the benefits of restoring blood flow to the kidney may appear to be obvious, vascular stenting carries well-recognized risks of atheroembolic disease, restenosis, and local complications (e.g., vessel dissection and thrombosis) that remain problematic. Hence, whether endovascular stenting provides additional benefits beyond meticulous management of blood pressure, blockade of neurohumoral activation, and management other risk factors is controversial. This is the basic question underlying current prospective treatment trials such as the CORAL trial in the U.S. and the ASTRAL (Angioplasty and Stenting for Renal Artery Lesions) trial in the United Kingdom.

Enrollment in the ASTRAL trial used somewhat ambiguous criteria to recruit patients "in whom clinicians were substantially uncertain whether to recommend revascularization" (5). Lesion severity exceeded 70% lumen occlusion by most criteria. The mean serum creatinine in this trial was 2.02 mg/dl. More than 90% of patients in both treatment arms were treated with statins and aspirin. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were used in 38% to 47% of patients. Initial results from 806 subjects in the ASTRAL trial with a median follow-up of more than 2 years demonstrated no important differences between stenting and medical therapy (5). No differences were observed in mortality (7.4% vs. 8.2%) hospitalization for congestive heart failure, serum creatinine changes, systolic blood pressure, or time to first renal event in this trial. Complete reports regarding the patient population and outcome data have not yet been published.

The CORAL trial seeks to examine long-term outcome differences (5 years) using observed cardiovascular events, rather than blood pressure levels or renal function alone, in more than 1,000 patients. More than 600 subjects have been already enrolled. Enrollment and randomization criteria require more stringent definition of lesions exceeding 60% lumen occlusion and there are few exclusions, beyond advanced renal failure (creatinine above 4.0 mg/dl) and reduced left ventricular ejection fraction (below 30%). The fact that the National Institutes of Health is funding this study reinforces the level of "equipoise" that remains between the risks and benefits of renal artery interventions. Acceptable candidates may have high-grade stenosis to a solitary functioning kidney and/or episodes of congestive heart failure. The investigators argue essentially that no credible data establish a positive net benefit of renal revascularization for any condition (1). Remarkably, initial results confirm that excellent risk factor improvement can be achieved for the entire group of patients (30). Oversight committees review blood pressure and lipid and glucose levels for CORAL participants to ensure achievement of "goal" levels in both treatment arms. All subjects are treated with angiotensin receptor blockers and intensive management of atherosclerotic disease using statins, smoking cessation, and glucose control. There have been few crossovers in the first 600 subjects enrolled.

Where Do We Go From Here?

As a result of the negative results noted, nephrologists have moved toward a more conservative clinical stance in recent years, perhaps as a pragmatic counterweight to enthusiastic interventional cardiologists and radiologists (11). Despite the difficulty in demonstrating benefits in large groups, some patients do experience major improvements in kidney function and cardiovascular stability after successful renal revascularization.

The challenge facing thoughtful clinicians in this arena is to prevent conservatism from interfering with the best interests of patients who might benefit from renal artery revascularization to a major degree. A recognized drawback of clinical treatment trials is the intermixture of high-risk and low-risk subjects into the "average" of the entire cohort (31). Those actively managing patients with atherosclerotic disease recognize that some individuals should be treated with revascularization.

Many criteria have been proposed to better define patients likely to benefit from renal artery intervention, including measurement of renal vein renin levels, circulating brain natriuretic peptide, changes in renographic appearance after angiotensin-converting enzyme inhibition, and others. In some instances, these maneuvers can be helpful, but most have proven to have low positive predictive value when applied to general populations. The most consistent predictor of benefit regarding both blood pressure response and recovery of kidney function has been the rate of change up to the point of diagnosis and revascularization (32). Those individuals detected soon after a major change in clinical status are most likely to respond to revascularization. Figure 4 is an angiogram obtained from a patient in whom recently advancing renal insufficiency associated with bilateral renal arterial stenosis could be reversed after renal artery revascularization. This example highlights the clinical observation that restoring renal perfusion to ischemic kidneys sometimes does prevent progressive renal failure.

How does one identify such patients? Atherosclerotic RAS has a poorly defined relationship between the presence of large vessel occlusive disease and target injury in the kidney. Unlike fibromuscular disease, the degree of severity of vascular occlusion in atherosclerosis bears little relationship to measured blood flow, kidney volume, degree of fibrosis, or glomerular filtration rate (3). These observations provide the basis for experimental studies of interactions between vascular occlusion and other vectors of kidney injury, including endothelial dysfunction, tissue oxidative stress (18), and the atherosclerotic milieu produced by dyslipidemia (20). It is not clear whether high-grade vascular occlusion induces repeated episodes of transient kidney ischemia that activate profibrotic pathways similar to other acute models. How to identify regional ischemia in human kidneys is not yet certain. Recent studies using blood oxygen level–dependent magnetic resonance indicate that poststenotic kidneys have a range of metabolic activity and oxygen consumption linked to active solute transport (33). Our initial studies suggest that total vascular occlusion and loss of filtration is associated with reduced levels of deoxyhemoglobin and minimal change during furosemide administration (34). By contrast, viable, functioning kidneys beyond an atherosclerotic lesion have relatively high levels of accumulated deoxyhemoglobin, particularly in the medulla. Such kidneys can respond briskly to reduce deoxyhemoglobin levels after intravenous administration of furosemide to reduce solute transport. Whether elevations of deoxyhemoglobin and furosemide-suppressible oxygen con-

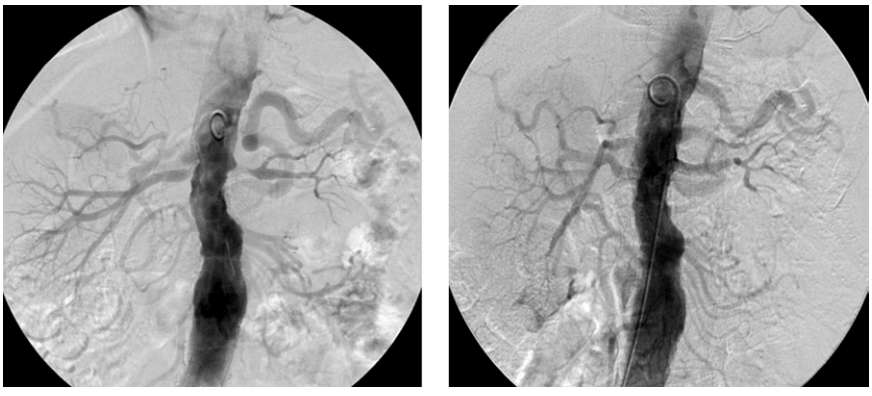

Figure 4. Stent Placement for High-Grade Bilateral RAS

Aortogram **(left)** demonstrating high-grade bilateral RAS near the origins. The **right panel** illustrates improved flow to both kidneys on the aortogram after bilateral endovascular stent placement. This individual recently had developed a rise in serum creatinine from 1.7 to 3.8 mg/dl over the previous 6 months. After stent placement, serum creatinine fell to 1.6 mg/dl. A recent change in kidney function remains the best predictor of clinical recovery (see text). Abbreviation as in Figure 2.

Table 2. Issues Central to Determining Role for Renal Revascularization in Atherosclerotic RAS

Questions	Tools for Evaluation
1. Severity of vascular occlusion?	Quantitative angiography, translesional gradients, intravascular ultrasound, Doppler
2. Treatable?	Vessel location, associated disease, accessory vessels, aneurysm, occlusion
3. Responsible for disease?	Evident activation of pressor systems, for example, renin
	Duration of change, such as blood pressure, renal function, other measures of tissue ischemia (e.g., BOLD MRI, PET energy consumption), activation of fibrogenic, inflammatory, or oxidative pathways
4. Benefit from revascularization?	Rapidity of evolution, pre-existing injury (e.g., hypertension, diabetes, other kidney disease), comorbid disease risk, associated procedural risk to kidney (e.g., atheroembolic potential), response to other medical therapy
	Risk of disease progression, salvagability of kidney function (resistive index, BOLD MRI)

BOLD MRI = blood oxygen level–dependent magnetic resonance imaging; PET = positron emission tomography; RAS = renal artery stenosis.

sumption induce cytokine release or toxic oxidative stress warrants further study.

It is almost certain that many, if not most, patients now being subjected to endovascular stenting of the renal arteries show only limited benefits, either regarding blood pressure response or improvement in kidney function (11). Equally important to recognize is that a subset of patients with "critical" RAS stands to have a major clinical benefit from restoring kidney perfusion and major adverse outcomes if not detected and treated (6). Table 2 summarizes several clinical issues that address whether patients are likely to warrant renal revascularization. Most imaging procedures focus specifically upon the anatomic severity and approachability of renal vascular lesions. Although these characteristics are important, they are clearly not sufficient to predict the outcome of renal revascularization. Further work is needed to examine the third and fourth items, specifically diagnostic tools to establish the role of vascular occlusive lesions in generating disease and the likelihood of clinical benefit after restoration of vessel patency. Further studies in the renal vasculature should be aimed at defining these characteristics more fully. Clinicians remain in sore need of better tools to identify renal parenchyma at true risk of "ischemic injury" and to identify when kidney function can be (or can no longer be) improved with renal revascularization.

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