A remarkable drama unfolded in 2007 regarding renovascular disease. The Center for Medicaid and Medicare Services (CMS) convened a meeting of its medical advisory group regarding treatment of renovascular disease, specifically atherosclerotic renal artery stenosis (RAS). The introductory statement read as follows: “In view of the uncertainty regarding optimal strategies for evaluation and management of atherosclerotic RAS, as well as the controversy about the risks and benefits of treatment, the CMS internally generated in February 2007 a national coverage analysis to examine the best treatment of RAS.”

That CMS is reviewing its payment coverage for atherosclerotic RAS undoubtedly reflects the increase in endovascular stent procedures for Medicare beneficiaries, rising from 7660 in 1996 to 18,520 in 2000. Estimates at the meeting suggested this increased further to more than 35,000 in 2005. The largest portion of this increase derives from procedures undertaken by cardiologists. Recent guidelines from professional organizations based on admittedly weak data lend support to the application of interventional vascular procedures into the renal arteries and inclusion of renal arteriography as part of coronary angiographic procedures. As part of their review, CMS commissioned an analysis of published information regarding the benefits of revascularizing the kidney for atherosclerotic RAS by the Agency for Healthcare Research and Quality. The results of this analysis were published in December 2006. The authors of this review concluded that available information was insufficient to support benefits regarding mortality, progressive kidney disease, or cardiovascular events. Thus, the published literature cannot support the observed, massive expansion of endovascular intervention.

During the same time interval, at least four prospective, randomized trials for atherosclerotic RAS were started to examine the role of medical therapy alone as compared with medical therapy plus stent revascularization. In the United States, the National Heart, Lung, and Blood Institute of the National Institutes of Health is funding the Cardiovascular Outcomes for Renal Atherosclerotic Lesions (CORAL) trial. This trial seeks to randomly assign 1080 patients to “optimal medical therapy” with or without renal artery stenting and evaluate clinical events including death, stroke, coronary artery disease events, congestive heart failure, kidney failure, and uncontrolled hypertension. A central premise of CORAL is that neurohormonal activation (mainly of the renin-angiotensin and sympathoadrenergic system) largely determines the morbidity from RAS. This trial has had difficulty meeting enrollment goals despite the increasing application of stent procedures. That the National Institutes of Health and more than 70 institutional review boards accept that management of atherosclerotic RAS is currently in “equipoise” regarding the added value of renal revascularization again challenges the expanding use of interventional therapy. How CMS will ultimately cover reimbursement for renal artery stenting has yet to be settled.

How did we reach this divergence between medical subspecialties, and how
Figure 1. Milestones in identification and treatment of renovascular hypertension and ischemic nephropathy: Renal revascularization was possible first in the 1960s and was the only effective antihypertensive therapy for severe renovascular disease. The introduction of agents that block the renin-angiotensin system (angiotensin-converting enzyme [ACE] inhibitors and angiotensin receptor blockers [ARBs]) changed the landscape dramatically. Surgery has been mostly replaced by endovascular stent therapy for atherosclerotic disease. The introduction of intensive medical therapy including ACE/ARB and calcium channel blockers, plus statins, aspirin, and diabetes management, has allowed effective therapy for many patients considered untreatable before. Recent small, short-term, prospective trials have failed to identify major benefits of revascularization as compared with medical therapy (see text). Larger, prospective trials are enrolling higher risk patients who will be followed for longer periods of time. HTN, hypertension; STAR, STent placement and BP and lipid-lowering for progression of renal dysfunction caused by Atherosclerotic ostial stenosis of the Renal artery; RAVE, Renal Athersosclerotic reVascularization Evaluation; PTRA, Percutaneous Transluminal Renal Angioplasty.

does it affect clinical nephrology? Renovascular disease has always presented troublesome issues, different in fundamental respects from vascular occlusive disease affecting the heart, brain, or extremities. The interactions between vascular disease and kidney function, arterial pressure, and volume control are complex. Clinical syndromes associated with RAS now arise more frequently than ever for patients who have other vascular disease involving the coronary and peripheral vascular beds. Some estimate that up to 5% of patients who reach ESRD may have renal artery stenosis as their primary kidney disorder. This lingering concern means that for any single patient with worsening hypertension and declining kidney function, nephrologists are forced to consider the potential role of large-vessel atherosclerotic disease. Although many patients can be treated effectively and safely with current medical therapy, selection of individuals who will benefit from renal revascularization and for whom its risks are warranted poses a major clinical challenge.

In some respects, these developments reflect stunning successes of basic and clinical research. Diagnostic imaging and therapeutic options have advanced rapidly in the past two decades. Major milestones in the evolution of our understanding of renovascular hypertension and ischemic nephropathy are summarized in Figure 1. Early observations that placement of a renal artery clip produces a rise in systemic arterial pressure was among the first evidence firmly linking the kidney to cardiovascular control. For many years, patients with severe hypertension were examined for the presence of renovascular hypertension with the goal of either removing the offending kidney or revascularizing the kidney using surgical techniques. Available antihypertensive drug therapy (mainly sympatholytic agents such as methyldopa, reserpine, or guanethidine) often fail to control dangerous, sometimes “malignant phase” hypertension in such individuals. In extreme cases, patients underwent bilateral nephrectomy as a life-saving measure to prevent episodes of recurrent hypertensive encephalopathy or pulmonary edema. These reports coincide with the introduction of renal replacement therapy with dialysis.

Studies of the mechanisms by which a renal artery clip produces hypertension paved the way to define the renin-angiotensin-aldosterone system (RAAS) and were fundamental to development of pharmacologic tools to block this system. The first agents available (Sar-1-Ala-8-angiotensin, or saralasin) to block the angiotensin receptor were targeted primarily at renovascular hypertension. Since then, many studies have identified complex interactions between angiotensin and kidney function, vascular remodeling, recruitment of additional pressor mechanisms, and neurohormonal activation. Studies of genetic knockout models free of the angiotensin receptor (AT1a knockout) extend these observations to demonstrate critical roles for both kidney and systemic receptor activation for angiotensin II–dependent hypertension. The development of oral agents that interrupt the RAAS provided for the first time well-tolerated drugs that improved BP control and reduced cardiovascular risk for patients with renovascular hypertension. Wider application of renin-angiotensin system blockade now provides hope that many forms of progressive kidney injury, congestive heart failure, and vascular disease may be relieved to a degree never imagined by those first studying renovascular hypertension.

RAAS blockade, statins, and antiplatelet therapy are now bedrocks for the clinical management of atherosclerotic disease, including RAS. Although the benefits of restoring blood flow to the kidney may seem to be obvious, vascular stenting carries well-recognized risks of atheroembolic disease, restenosis, and local complications, such as vessel dissection and thrombosis, that remain problematic; therefore, whether endo-
Table 1. Interactive mechanisms underlying hypertension and kidney injury in atherosclerotic RAS

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Underperfusion</th>
<th>Recurrent Local Ischemia</th>
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<tbody>
<tr>
<td>Activation of renin-angiotensin system</td>
<td>ATP depletion</td>
<td>Tubulointerstitial injury</td>
</tr>
<tr>
<td>Altered endothelial function (endothelin, NO, prostaglandins)</td>
<td>Microvascular damage</td>
<td>Immune activation</td>
</tr>
<tr>
<td>Sympathoadrenergic activation</td>
<td>Vascular remodeling</td>
<td></td>
</tr>
<tr>
<td>Increased reactive oxygen species</td>
<td>Interstitial fibrosis</td>
<td>RAAS</td>
</tr>
<tr>
<td>Cytokine release/inflammation (NF-κB, TNF, TGF-β, PAI-1, IL-1)</td>
<td>Symptathoadrenergic activation</td>
<td>Endothelin</td>
</tr>
<tr>
<td>Impaired tubular transport functions</td>
<td>Disturbances of &quot;oxidative stress&quot;</td>
<td>Oxidized LDL</td>
</tr>
<tr>
<td>Apoptosis/necrosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1.

Table 2. Issues central to determining role for renal revascularization in atherosclerotic RAS

<table>
<thead>
<tr>
<th>Questions</th>
<th>Tools for Evaluation</th>
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<tbody>
<tr>
<td>Severity of vascular occlusion?</td>
<td>Quantitative angiography, translesional gradients, intravascular ultrasound</td>
</tr>
<tr>
<td>Treatable?</td>
<td>Vessel location, associated disease, accessory vessels, aneurysm, occlusion</td>
</tr>
<tr>
<td>Responsible for disease?</td>
<td>Evident activation of pressor systems (e.g., renin) Duration of change (e.g., BP) renal function; other measures of tissue ischemia (e.g., BOLD MR, PET energy consumption); activation of fibrogenic, inflammatory, or oxidative pathways</td>
</tr>
<tr>
<td>Benefit from revascularization?</td>
<td>Rapidity of evolution, preexisting 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 for disease progression, salvageability of kidney function (resitive index, BOLD MR)</td>
</tr>
</tbody>
</table>

*BOLD MR, blood oxygen level dependent magnetic resonance; PET, positron emission tomography.

Vascular stenting provides additional benefit beyond meticulous management of BP, blockade of neurohormonal activation, and management of other risk factors is controversial. This is the basic question underlying current prospective treatment trials such as CORAL and ASTRAL (Angioplasty and STent for Renal Artery Lesions). Nephrologists have moved toward a more conservative clinical stance in recent years, perhaps as a pragmatic counterweight to enthusiastic interventional cardiologists and radiologists. The challenge facing thoughtful clinicians in this arena is to prevent such conservatism from interfering with the best interests of patients who could benefit from renal artery revascularization to a major degree.

Among the problematic features of atherosclerotic RAS has been the 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 GFR. 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, and the atherosclerotic milieu produced by dyslipidemia (Table 1). It is unclear 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 living animals 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. 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. 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 consumption induce cytokine release or toxic oxidative stress is an important question that warrants further study.

It is almost certain that many, if not most, patients now being subjected to endovascular stenting of the renal arteries have only limited benefit, regarding either BP response or improvement in kidney function. Equally important to recognize is that a subset of patients with “critical” renal artery stenosis stand to have major clinical benefit from restoring kidney perfusion and major adverse outcomes if not detected and treated. Summarized in Table 2 are a series of clinical issues that address whether patients are likely to warrant renal revascularization. Most imaging procedures focus on the first two items—the anatomic severity and approachability of renal vascular lesions. It is likely that the third and fourth items— diagnostic measures to evaluate the role of vascular occlusive lesions in generating disease and the likelihood of clinical benefit after restoration of vessel patency—are more important. Further studies in the renal vasculature should be aimed at defining these char-
characteristics more fully. A recognized drawback of clinical treatment trials, of course, is the intermixure of high-risk and low-risk patients into the “average” of the entire cohort. Although prospective, randomized trials are essential, clinicians remain in sore need of better tools to identify renal parenchyma at true risk for “ischemic injury” and to identify when kidney function can be (or can no longer be) improved with renal revascularization.

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DISCLOSURES

None.

REFERENCES