Published in final edited form as:

Prog Cardiovasc Dis. 2009 ; 52(3): 220–228. doi:10.1016/j.pcad.2009.10.001.

Timing and Selection for Renal Revascularization in an Era of Negative Trials: What to do?

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Introduction

Management of atherosclerotic renovascular disease has never been more simple — or more complex. On one hand, advances in medical therapy over the last two decades provide dramatically improved ability to lower blood pressure and medical risk as compared to before. It is likely that many patients with “true” renovascular hypertension remain undetected for years because they are treated successfully and simply with available agents, particularly those that block the renin-angiotensin system. Most of these patients are never subjected to extensive diagnostic studies and one might argue that they are well-treated at limited expense.

During the same time interval, advances in imaging and interventional methods now make detection, monitoring and revascularization more feasible than ever before. As a result, nearly 3–4 fold more endovascular procedures are being performed in the U.S. than a decade ago (1). Some argue that the potential benefits to relieving vascular obstructive lesions are self-evident (2).

Unfortunately, the benefits of revascularization procedures have been ambiguous. It is recognized that only a fraction of patients treated with renal revascularization have improved blood pressure levels or reduced medication requirements, and kidney function after revascularization infrequently improves and sometimes declines (3). The Centers for Medicare and Medicaid Services (CMS) commissioned a review of published reports regarding the value of these procedures and concluded that “data were insufficient to conclude substantial benefit regarding blood pressure control, kidney function or mortality for atherosclerotic renal artery disease” (4). Relatively few prospective, randomized trial data are available—although several trials are in progress. Preliminary reports from the major trial in the United Kingdom (ASTRAL) indicate that no major advantage has yet been evident during follow-up after more than two years (5). Long-term outcome of surgical repair does not show a difference between those revascularized for stabilization of kidney function and those managed medically after more than nine years (6). Some argue that a large fraction of these patients gain little, if any, benefit from vascular intervention. The details of these studies and important differences between previous data and the current trials are discussed elsewhere in this issue of *Progress in Cardiovascular Disease*.

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These ambiguities notwithstanding, clinicians working with hypertensive patients with complex vascular disease and renal dysfunction recognize that some patients, in fact, do experience major benefits from restoring blood flow and circulation, or in some cases from removing ischemic “pressor” kidneys. Case series and specific examples are well recognized that indicate important functional recovery of underperfused kidneys can be achieved in some cases. Since the introduction of “ischemic” renal disease as a diagnostic category in the United States Renal Data Systems in the early 1990’s, this category has been more frequently assigned as a causal factor for patients with end-stage renal disease (ESRD) (7). Those physicians caring for patients with ESRD would like nothing better than to avoid the need for dialytic support or transplantation in this group. Illustrated in FIGURE 1 is a CT angiogram from an individual with widespread atherosclerotic vascular disease, extensive aortic thrombus and calcification with asymmetric kidneys and recently progressive hypertension. At this point, kidney function is adequate and blood pressure is well controlled with only minor medications. Nonetheless, the potential for disease progression cannot be ignored. How should one rationally evaluate and anticipate renal revascularization for such a patient?

This manuscript undertakes to examine our current understanding of methods of functional assessment, timing, and considerations for renal revascularization.

Patient Classification by clinical status

Recent writing groups (8,9) acknowledge that the intensity of evaluation and pressures to intervene depend largely upon the clinical manifestations related to renovascular disease. Clearly, the stakes differ between an individual with well-controlled hypertension with unilateral renal artery stenosis and another with a solitary functioning kidney and declining kidney function. It is helpful to define from the outset the degree to which identification of disease would prompt further characterization and possible revascularization, as both incur major expense and potential hazard. A clinical classification of atherosclerotic renal artery stenosis with guidelines for vascular intervention or surveillance was published in 2008 by the Atherosclerotic Peripheral Vascular Symposium (9). This is summarized in TABLE 1. Others have proposed additional studies to identify whether target organ injury has occurred using additional studies such as individual assessment of kidney size or function with radionuclide studies (3). These observations recognize that current medical therapy with intensive management of dyslipidemia, arterial hypertension, aspirin and tobacco cessation are the mainstays of management and can be effective and sufficient. Common to these classification schemes is the premise that renovascular disease is not static. Atherosclerosis, in particular, can progress to a point where clinical manifestations warrant further evaluation and restoration of blood flow to the kidney.

Different subspecialty groups perceive the risks and benefits of renovascular intervention differently. Remarkably, intense interest in kidney function as a predictor for adverse cardiovascular outcomes seems to have sharpened enthusiasm among cardiologists and interventionalists in recent years, despite limited supporting data. Nephrologists have less enthusiasm for vascular intervention based upon the potential hazards and limited benefit of revascularization from studies to date (10). These differences underscore the need for more systematically collected data regarding characterization of vascular disease and optimized outcomes based upon prospective trials.

Estimating the severity of obstructive vascular lesions

Renal blood flow—in similar fashion to other vascular beds—is often unaffected by minor obstructive lesions. Studies using latex casts to characterize the luminal occlusion indicate no measurable changes in either pressure or flow at levels below 60%, and indicate that the “break point” at which hemodynamic effects develop is between 75–85% of luminal occlusion (11).

Hence, most clinical studies report lesions defining “renal artery stenosis” as lesions more than “50%” obstructed almost certainly are diluted by many lesions that had minimal hemodynamic effect. Recent studies aimed at detecting the degree of obstruction required to release renin again confirm that a substantial trans-lesional gradient is required for measureable effect. The magnitude of renin release was related to the magnitude of the post-stenotic gradient during these acute studies (12). (FIGURE 2). Renal vein renin sampling confirms that clinically detectable lateralization of renin production appear to require 80% stenosis (13). Hence, even lesions that are estimated at 60–70% lumen obstruction by a clinical test, such as duplex ultrasonography, may be non-functional. These observations were confirmed recently by results from the STent placement in patients with Atherosclerotic Renal artery stenosis (STAR) trial. Nearly 15% of patients identified with “more than 50%” stenosis by non-invasive screening were disqualified at angiography because no functional stenosis could be identified (14). Visual estimates of stenosis obtained from two-dimensional angiograms are notoriously imprecise and prove difficult to confirm using quantitative angiographic estimates. Measurement of Doppler velocity provides a general correlation with severity of stenosis, but the relationship is approximate, at best. Whereas initial criteria suggest that peak systolic velocities above 200 cm/sec usually represent at least 60% stenosis, this value has been challenged. Studies of the Cardiovascular Outcomes of Renal Atherosclerotic Lesions (CORAL) require the velocity to be above 300 cm/sec so as to avoid this pitfall (15).

Some authors measure “functional flow reserve”, usually defined as the ability to dilate after administration of a potent vasodilator such as papaverine. This provides less information regarding the severity of vascular occlusion, but theoretically addresses the potential for post-stenotic small vessels to respond favorably to restoring proximal blood flow and recover kidney function. Its clinical value is discussed in detail elsewhere in this issue.

Functional Assessment of kidneys with vascular lesions

Sodium excretion and rennin release: Estimating the hemodynamic effects of vascular occlusion and the potential for recovery warrant consideration within a historical perspective. Most of the early studies were geared to define benefit in terms of relief of the malignant hypertension commonly encountered at the time.

Unilateral kidney disease often induces functional hypertrophy in the contralateral kidney, making measurement of total glomerular filtration rate (GFR) a delayed or insensitive estimate of its effect. For that reason, early studies of individual kidney function were developed to identify changes in blood flow, GFR, sodium excretion and other measures of renal tubular function that could be examined using clearance studies from each kidney (16). These methods require bilateral ureteral cannulation and are cumbersome, but do indicate that reduced perfusion to a functioning kidney capable of completely reabsorbing sodium generally could predict benefit regarding blood pressure response to surgical revascularization. Observations from these studies that some kidneys with reduced estimated renal plasma flow—measured using clearance of hippuran that requires intact tubular secretion—failed to improve after technically successful revascularization set the precedent that some kidneys were beyond salvage (17). Because surgical repair of renal artery lesions carries considerable morbidity and some mortality, the goal was to identify individuals with convincing indications of likely benefit.

Later studies were based on demonstrating a primary causal role for renin release and activation of the renin-angiotensin-aldosterone system. Experimental studies had established unilateral renovascular disease as a prototype of “angiotensin-dependent” hypertension (18). A series of studies in the 1970’s and 1980’s sought to establish criteria to identify “curable” renovascular hypertension on the basis of renin-sodium profiling, measurement of renin after diuretic or

ACE inhibition as a stimulatory maneuver, or measurement of renal vein renin values (19). These studies provide attractive applications of physiology to real clinical problems and are persuasive when “positive”. Some of these proposed that pressure responses to angiotensin blockade could predict the final blood pressure following surgical revascularization (20) (21).

Unfortunately, testing conditions profoundly affect renin release. Measurements of plasma renin activity change dramatically depending upon sodium balance, arterial perfusion pressure, levels of sympathetic activation, age, and many antihypertensive agents that alter sympathetic or other pathways (22). Attempts to apply renin measurements as diagnostic studies for individual patients routinely produce large numbers of “false positive” and “false negative” results as predictors to blood pressure responses to therapy (23) (24). As a result the positive and negative predictive values of peripheral renin measurements are reported in the 35–60% range, not useful in many cases (25)..

Measurement of renin values from each renal vein merits further consideration. A careful review of this literature series demonstrates a close relationship between pressure responses and the magnitude of “lateralization”, i.e. the relative difference of one renal vein level to the other, usually expressed as a ratio of stenotic/non-stenotic for unilateral disease. As a result, demonstrating a relative overproduction of renin (by a factor more than 1.5), especially when corrected for the arterial level of renin activity, predicts a clinically positive outcome for renal revascularization in more than 90% of cases (23,26). In essence, this is a special instance of “useful when positive” and confirms the primary role of a specific kidney in producing angiotensin-dependent hypertension. It remains a reliable predictor of the likely blood pressure response in some cases, particularly when one is considering unilateral nephrectomy for a “pressor” kidney (27). These measurements are further refined by demonstrating “suppression” of renin release (i.e. subtracting the “arterial” level of renin (usually estimated as the value of inferior vena cava below the renal veins) from the contralateral kidney (28). The case illustrated in FIGURE 3(A) demonstrates the value of renal vein measurements in a specific case of previously treated renovascular disease with in-stent restenosis, distal fibromuscular disease and a question of a contralateral “pressor” kidney.

Why not rely upon renal vein renin measurements as a regular part of a diagnostic evaluation today? Several major limitations became apparent as these tests were adopted widely. 1) Demonstration of renin levels and relative release from each kidney changes dramatically depending on drug therapy. A broad array of stimulating maneuvers was developed, including furosemide stimulation, hydralazine or nitroprusside reduction of systemic arterial pressures, administration of an ACE inhibitor such as captopril, and others (29). Most of these were aimed to increase release so as not to overlook lateralizing effects from one kidney. As the potential hazards of iodinated contrast rose to the fore, most radiologists adopted protocols for “hydration” that include administration of saline or other volume expanders. Careful studies confirm that lateralization of renin can disappear during administration of saline (22). 2) the role of renin itself as a major mediator of sustained hypertension appears to be temporary. While experimental renovascular hypertension requires an intact renin-angiotensin system (and does not develop if this system is blocked or if angiotensin receptor are not present), actual levels of renin activity gradually fall and alternative systems are recruited to sustain elevated pressure (30). As a result, renal vein values can be “useful when positive”, but are frequently negative in proven cases of renovascular hypertension.

Functional studies of the post-stenotic kidney: Captopril Renography

Radionuclide studies now using Tc-Mag3 primarily have been advocated as a functional means to examine individual kidney function. Analysis includes the time to cortical accumulation of the isotope, cortical retention and finally excretion as a function of glomerular filtration (31). Changes in the profile of cortical retention after administration of an agent that blocks the

action of angiotensin, specifically an ACE inhibitor such as captopril or enalapril, illustrate the role of this system in maintaining glomerular filtration in the presence of pre-glomerular limitation of blood flow. Development of a change in cortical retention in the post-captopril images is taken to suggest functional impairment of blood flow typical of renovascular disease that may be improved by restoring blood supply. A drawback of this approach is the requirement for repeated renography, with and without administration of captopril. Implicitly, identifying a change in GFR might translate into a clinical improvement in kidney function and blood pressure control, the original goal of these investigations.

Several studies proposed that diagnostic accuracy of abnormal captopril renograms for predicting the blood pressure response after revascularization may exceed 90% (32,33). Many of these are small series from centers focusing attention on treatment resistant hypertension. Early consensus statements reflect high enthusiasm for this approach (34). A review of this field in 2000 suggests that for patients with normal kidney function, the sensitivity and specificity for captopril renography again exceeds 90% (35). These figures deteriorate substantially, however, in patients with abnormal kidney function to levels closer to 50%. Smaller series examining mathematical models to predict the clinical outcomes of percutaneous transluminal renal angioplasty suggest that specificity and sensitivity were closer to 36–43% in patients suspected of having atherosclerotic disease (24). As with many functional tests, results depend heavily upon conditions of the measurement, including pre-treatment with ACE inhibitors and calcium channel blocking drugs (36–38). Both of these classes have been suspected of diminishing the accuracy of captopril-induced changes (35).

An obvious limitation of captopril renography is the focus on function without providing detailed anatomical information. For patients with other parenchymal renal disease such as ureteral obstruction, previous scarring, infarction, etc. the scans are commonly asymmetric and may have functional changes after ACE inhibition that do not reflect large vessel disease primarily. Because the decision regarding renal revascularization has shifted substantially towards preservation of renal function, more patients than before are undergoing evaluation with reduced GFR and therefore less chance of gaining information from renography.

Estimates of tissue oxygenation and blood flow using functional magnetic resonance (MR)

Computed tomographic (CT) angiography and MR angiography have enjoyed wider use than ever before to characterize the vascular supply to the kidney. These methods provide stunning detail of the large vessels and can provide a general idea of the function of each kidney based on filtration and excretion of contrast. These methods carry drawbacks regarding the toxicity of contrast agents, specifically the nephrotoxicity of iodinated contrast for CT and the potential for nephrogenic systemic fibrosis (NSF) attributed to gadolinium exposure. Most importantly, they do not provide detailed information on the adequacy of blood supply regarding the metabolic needs of the organ or whether the post-stenotic kidney is injured beyond recovery.

Recent studies indicate that Blood Oxygen Level Dependent (BOLD) MR may provide a tool to examine relative levels of deoxyhemoglobin within cortex and medulla of the kidney. Because deoxyhemoglobin is paramagnetic but oxyhemoglobin is not, one can detect alterations in local relaxation times reflecting the level of tissue oxygenation (39). BOLD MR is capable of detecting reduced oxygenation within the medullary region of the kidney that is dependent upon active tubular solute transport, specifically inhibited by furosemide (40). Experimental studies demonstrate a rise in deoxyhemoglobin during acute reductions in blood flow to the kidney manifest as a rise in the BOLD signal, designated $R2^*$ (41). (FIGURE 3B). Remarkably, initial studies in humans with atherosclerotic renal artery stenosis demonstrate preserved levels of cortical and medullary oxygenation, consistent with a substantial excess of delivered oxygen under most conditions (42). Under severe ischemic stress, $R2^*$ rises (See Figure 3(B)). Total occlusion and loss of kidney viability can be associated with minimal

deoxyhemoglobin and no response to administration of a tubular transport inhibitor. Similar observations have been made during acute loss of kidney tubular transport functions associated with cellular allograft rejection (43). Exactly how best to use these tools to more precisely identify viable kidney tissue as a means to select candidates for renal revascularization is an area of active research.

Clinical Trials: Why are we still uncertain about patient selection?

While seminal studies demonstrate the role of reduced kidney perfusion as a stimulus to developing renovascular hypertension and reduced function, the optimal timing and role for renal revascularization remain controversial, as we have discussed (44). Other contributions in this issue of *Progress in Cardiovascular Disease* highlight this ambiguity in detail. Will results of several prospective, randomized trials now in progress resolve these questions?

Balk and colleagues reviewed the published data regarding endovascular revascularization since 1993 (4). These authors carefully applied rules of evidence-based medicine to examine the strength and level of supporting data. The majority consisted of observational, retrospective series. Remarkably few comparative treatment trials were available, each of which was limited in patient enrollment. The largest of these included 106 subjects. None of these trials provide strong evidence to demonstrate a preference for either revascularization or for the medical therapy applied. Initial results from the largest prospective trial to this point, ASTRAL trial performed in the United Kingdom were presented in 2008 that again failed to demonstrate important differences in blood pressure control, measures of kidney function, hospitalization or mortality in 806 subjects (5). Table 2 summarizes the central points of six prospective trials of either surgical or endovascular revascularization as compared to medical therapy. Additional trials are now in progress. It should be emphasized that substantial improvement and/or reduction in antihypertensive drug therapy requirements occurred only in some patients subjected to revascularization. Important reduction in drug therapy is not reported in subjects assigned to medical therapy alone. Similarly, clinical improvement in kidney function, albeit uncommon, was limited to patients undergoing revascularization. Some authors in the field place major emphasis on the crossovers in these trials, indicating that this likely reflected patients that were poorly responsive to medical management alone and thereby required vascular intervention (45).

As with most clinical series, group mean data may not accurately reflect important clinical benefits to specific subsets. TABLE 3 identifies several important limitations that render results of study populations only poorly generalizable to specific patients. Patient selection for the prospective trials in progress may not resolve these issues. In the recently reported ASTRAL trial, for example, patients were enrolled based upon the “uncertainty” criterion, i.e. they were considered if the attending clinicians were materially “uncertain” as to the best management (46). Of course, this implies that a clinician sometimes may be “certain” of the best course, but the basis for certainty is not defined. Despite attention to these details in CORAL, enrollment in the U.S. has been slower than expected for many reasons. One reason may include the fact that individual clinicians have strong preconceptions about the benefits and risks of either medical or interventional management and are therefore less likely to invite patients to consider randomized therapy. Exactly how representative the final study population will be as compared to the universe of patients with atherosclerotic renovascular disease overall will warrant careful review. Although it is certain that robust baseline and outcome data will result from these studies, one is left with the concern that group average results of the present trials may not resolve the balance of risks and benefits for individual patients.

It should be emphasized that medical therapy for atherosclerotic renal artery stenosis is not completely standardized. Opinions differ as to whether blockade of the renin-angiotensin

system should be a requirement (this set of medications was excluded in some of the prospective studies). Recent data underscore the potential for ACE inhibitors to improve overall cardiovascular outcomes, however. Both an Italian series and a Canadian administrative database indicate improved survival for patients treated with these agents (47,48), despite renal arterial stenosis. On clinical and theoretical grounds, removal of the neurohormonal hazards associated with activation of the renin-angiotensin system is desirable and allows better blood pressure control than previously available. This group of patients is recognized to have high cardiovascular risk as compared to essential hypertension. Intensive administration of statins, aspirin and removing tobacco use is warranted. These strategies should be employed in all patients with diffuse atherosclerosis.

Exactly how medical therapy will control hypertension and alter cardiovascular outcomes over the long-term is less certain. Evaluation of cardiovascular outcomes is the major objective of CORAL (49). Most of the prospective trials to date are limited to brief periods of follow-up, ranging from six months to several years. Part of managing individual patients, of course, depends heavily upon the likelihood of adverse events in the near future and the potential for vascular disease progression if revascularization is not undertaken. Studies in the 1990's suggest that progression of atherosclerotic disease to more severe levels of occlusion is relatively common, although it only rarely leads to intractable hypertension or measurable declines in kidney function. Nonetheless, careful identification of parenchymal kidney injury and/or progressive hemodynamic compromise must remain high priorities for clinician deciding when to move forward with vascular intervention.

Taken together, these developments suggest that management of atherosclerotic renal artery disease will remain challenging. While optimizing medical therapy will require redoubled efforts for all such patients, careful follow-up to define the subset with progressive disease and salvageable kidneys will be essential. Because this population carries substantial age-related risk and other comorbidities, each patient will require careful consideration before starting down a path inevitably leading to vascular intervention. The possibility that negative and/or ambiguous trials in this field will magnify the risk of delaying diagnosis in those that can benefit cannot be ignored. We believe that thoughtful surveillance and application of functionally meaningful diagnostic studies should continue to be a major area of research.

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Figure 1A

Figure 1B

Figure 1.

(A) CT angiographic reconstruction from a 67 y.o. with extensive aortic atherosclerosis, a high-grade stenosis affecting the right renal artery (Doppler velocity > 400 cm/sec), and a small kidney. (B) Coronal view of CT angiogram demonstrating adjacent aortic thrombus, wall dilatation and extensive vascular calcification. This individual had previous peripheral atheroembolism. Blood pressure levels remain in the 122/70 mm Hg range with therapy based upon ACE inhibitor and calcium channel blocker therapy with serum creatinine 0.9 mg/dL. The left renal artery appears widely patent. This patient faces potential hazards with endovascular therapy and may not derive much benefit at this point in time. Developing an optimal strategy to monitor and re-evaluate the course of this disease in the future presents a major clinical challenge (see text).

Figure 2.

Levels of plasma renin activity measured from the stenotic and contralateral kidneys at various levels of reduction in perfusion pressure across an artificial lesion produced by an inflated balloon catheter. These data argue that measurable renin release requires a reduction in pressure of at least 10–20 mm Hg between the aorta and post-stenotic site. Such a gradient only develops when luminal occlusion exceeds 70–75% of lumen diameter. Recreated from De Bruyne with permission (12).

Figure 3.

(A) CT angiogram obtained in a 58 y.o. smoker with labile hypertension studied after stenting the right renal artery. The left kidney demonstrates only minimal flow and function. The right kidney also has evident distal fibromuscular dysplasia (FMD). Unexpectedly, renal vein measurements for plasma renin activity during therapy with diuretics and ACE inhibition demonstrated substantial lateralization to the right kidney, confirmed by dilation of in-stent restenosis and PTRAs of the distal FMD. (B) Blood Oxygen Level Dependent (BOLD) magnetic resonance study of these kidneys demonstrated markedly elevated deoxyhemoglobin (expressed as $R2^*$ sec⁻¹) in the medullary, but not cortical, segments of the left kidney with no change after administration of furosemide. Despite the presence of additional stenosis in

the right kidney, cortical and medullary $R2^*$ levels are at normal levels and medullary levels fall after administration of furosemide. Functional measurements of oxygen consumption indicate that tissue oxygenation is well-preserved in the viable right kidney, but is not in the left kidney under these conditions. It is likely that identifying patients likely to recover kidney function after revascularization will depend upon some form of tissue evaluations such as these.

Table 1**(A). Functional Classification for Atherosclerotic Renal Artery Stenosis**

Grade I: Renal artery stenosis present, but no clinical manifestations (normal blood pressure and normal renal function)
Grade II: Renal artery stenosis present, but patients have medically controlled hypertension and normal renal function
Grade III: Renal artery stenosis present and patients have evidence of abnormal renal function, medically refractory hypertension, or evidence of volume overload

Table (B)

Factors favoring medical therapy and revascularization for renal artery stenosis

- progressive decline in GFR during treatment of hypertension
- failure to achieve adequate blood pressure control with optimal medical therapy
- rapid or recurrent decline in the GFR in association with a reduction in systemic pressure
- decline in GFR during therapy with ACE inhibitors or ARBs
- Recurrent congestive heart failure in a patient in whom the adequacy of left ventricular failure does not explain the cause

Factors favoring medical therapy and surveillance of renal artery disease

- controlled blood pressure with stable renal function
- stable renal artery stenosis without progression on surveillance studies (e.g. serial duplex ultrasound)
- advanced age and/or limited life expectancy
- extensive comorbidities that make revascularization too risky
- high risk or previous experience with atheroembolic disease
- other concomitant renal parenchymal diseases that cause progressive renal dysfunction (e.g. diabetic nephropathy)

From the writing group for Atherosclerotic Peripheral Vascular Disease Symposium (9).

Table 2
Prospective Trials Comparing Medical Therapy to PTR $\pm$ Stenting or Surgery in Atherosclerotic Renal Artery Stenosis

Source/Patients	Features	Outcomes
Webster 1998: J. Human Hyper.	Run-In Medical Rx	No difference in BP, renal function, four-year survival; ? Crossover
N=55	Random Zero BP	
Unilateral=27	No ACE inhibitors	
Plouin 1998: Hypertension	Multicenter	No difference in BP, slightly fewer meds in PTR $\pm$ A group. More complications: Crossover in Med Rx: 7/26 (27%)
N=49	ABPM at 6 months	
All unilateral	No ACE inhibitors	
Van Jaarsveld 2000: NEJM	Multicenter, office and automated BP	No difference in BP at 12 months Crossover in Med Rx: 22/50 (44%)
N=106		
Unilateral	Lateralization studies (scan, renal vein renin)	
Uzzo 2002: Transplant Proc.	High-grade stenosis entire renal mass (>75% stenosis)	Stop points BP, doubling Cr ESRD, CV event or death.
N=52	Creatinine = 4.0 mg/dL	Median f/u: 74 mo: No difference 67% reached stop point
Kabra: ASTRAL 2008: (Abstract)*	"Uncertainty" qualifications	No difference in BP, serum creatinine mortality, CHF at 27 months
N=806	Primary endpoint-CKD progression	
Bax 2009: STAR* 2009: Annals of Internal Medicine	RAS>50%	Med failure: 4/74 (only 46/64 randomized to stent were treated) No benefit: 16% vs. 22% had fall in CC, complications with stenting
N=140	Clearance <80 mL/min/1.73 m ²	
Bilateral 46/50%	Endpoint $\geq$ 20% change in clearance	
2-year followup	ACE/ARB in 54–60%	

* ASTRAL: = Angioplasty and Stent Therapy for Renal Artery Lesions

STAR = Stent placement in patients with Atherosclerotic Renal Artery Stenosis

Table 3**Limitations of Clinical Trials in Atherosclerotic Renal Artery Stenosis**

1	Patient selection:
	<ul style="list-style-type: none"> a. Most severe stenosis not considered for randomization b. Most severe hypertension and progressive renal disease not included c. Limited selection of antihypertensive drug therapy <ul style="list-style-type: none"> i. ?Role of renin-angiotensin system blockade ii. Non-standardized measurement of outcomes: BP levels d. Non-standardized therapy for dyslipidemia/comorbid disease
2	Outcome measurement
	<ul style="list-style-type: none"> a. Widely variable definitions of blood pressure goals, achieved levels b. Variable measurement of renal function c. Circulatory congestion/volume control/drug selection d. Crossovers from medical to interventional arms: 20–44% e. Short duration of follow-up:
3	Confounders limiting interpretation
	<ul style="list-style-type: none"> a. Roles and magnitude of comorbid disease: diabetes, pre-existing cardiovascular disease b. Age/timing of intervention/timing of detection of disease c. Intermixing degree of renal involvement/tissue at risk: roles of unilateral and bilateral disease unevenly addressed d. Rates of development of disease, including renal dysfunction/blood pressure changes. e. Definition of treatment “resistance”