Controversies in Renal Artery Stenosis: 
A Review by the American Society of Nephrology Advisory Group on Hypertension

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Introduction

There are gaps in understanding ‘incidental’ renal artery stenosis (RAS) found during cardiac catheterization. RAS lesions often must be evaluated based on limited dimensional images, often in the presence of severe vascular disease, and commonly in the face of diminished renal function. Patients with atherosclerotic RAS face increased risk from cardiovascular events and progressive renovascular occlusion. The role and timing of renal revascularization is controversial. Recent studies indicate that the benefits of renal revascularization are nearly balanced by the potential adverse effects, leading to what has been defined as ‘clinical equipoise’. The purpose of our manuscript is to synthesize key knowledge and identify critical gaps in caring for patients with incidental RAS. Several prospective studies are planned or are in progress to determine the best medical therapy compared to interventional treatments for RAS patients. The studies include patients who have been evaluated for suspected RAS, or who are undergoing investigation for resistant hypertension. The practice may be hazardous and should be critically examined. A dialog and closer cooperation between cardiologists and nephrologists is warranted and organized programs should be formulated to address this problem.

Key Words
Renal artery stenosis • Renal vascular disease • Ischemic nephropathy • Renal artery angioplasty • Renal artery stenting

Abstract
Renovascular hypertension is a recognized secondary potentially curable cause of hypertension since the work of Harry Goldblatt. Operative treatments for renal artery stenosis (RAS) have been offered for decades and percutaneous interventions have been widely available for 20 years. Stenting has largely obviated recurrence and modern techniques have contributed greatly to the safety of the procedure. Nevertheless, controversy abounds and prospective randomized trials have not successfully documented the value of intervention in patients with atherosclerotic RAS. The patient population has also changed remarkably. Whereas earlier patients with RAS were identified on clinical grounds, RAS is now commonly found serendipitously during angiography for other reasons. Whether or not these patients benefit from drive by stenting is unknown. The practice may be hazardous and should be critically examined. A dialog and closer cooperation between cardiologists and nephrologists is warranted and organized programs should be formulated to address this problem.
Literature was identified and selected based on medline search, using key words renovascular disease and any of the following: outcomes, clinical trials, progressive renal disease, hypertension, renal artery stenosis, interventions. Both review articles and original studies were collected: recent review articles were also cross referenced to ensure completeness. Studies were reviewed by the authors, using a standard critical appraisal framework, in the context of whether they could suitably answer key questions currently posed regarding the topic of interest: the natural history and outcomes of renal artery stenosis in the context of cardiac catheterization. This was not intended as a systematic review.

Chronic Kidney Disease

The prevalence and incidence of chronic kidney disease (CKD) are increasing. Dialysis start rates have increased steadily over the last 2 decades. Current dialysis initiation rates per year per million population are 168 in Canada and >250 in the USA [4, 5]. The morbidity and resource utilization of these patients exceeds that of most other chronic diseases. It is of importance to search for reversible causes of CKD. The most common cause of CKD and dialysis starts in Canada and the USA is diabetes mellitus (>33%). However, concomitant hypertension and vascular diseases (cardiac and peripheral) are highly prevalent. Renovascular disease is more common than previously believed. The estimates range between 8 and 10%.

Atherosclerotic RAS is associated with peripheral vascular disease and cardiovascular disease as part of a systemic illness characterized by endothelial dysfunction, accumulative atherosclerotic plaque formation, and subsequent target organ ischemic damage.

In this review, we focus on atherosclerotic disease rather than other causes of RAS such as fibromuscular hyperplasia. Recent data underscore the importance of minor renal dysfunction in predicting adverse cardiovascular outcomes [6–11]. In patients with mildly compromised renal function, there are higher incidences and poorer outcomes from stroke, myocardial infarction, and congestive cardiac failure. Since RAS is a potentially reversible type of CKD, it has been implied that correction of ischemic lesions can reverse decrease in renal function and improve CV outcomes. This hypothesis has not been tested in clinical studies.

What Do We Know about Outcomes and Renovascular Disease?

Despite the association of reduced renal function and cardiovascular disease, the relationship between vascular compromise, renal dysfunction, glomerular filtration rate (GFR) decline, and the extent of renal dysfunction that is due to ischemia, has not been well studied. Invasive cardiologists commonly examine renal arteries during cardiac catheterization in a procedure labeled ‘drive-by angiography’ by nephrologists. Reduction of flow below critical perfusion pressures in kidneys causes ischemic damage with including activation of fibrotic processes, and ultimately loss of function [12]. While RAS is common; it is unknown whether RAS in an individual patient causes hypertension or contributes to declining renal function. Diagnostic tests to delineate this dilemma are not available. Guidelines regarding timing, evaluation, treatment, and follow-up are not formulated. The literature is confusing because of variable definitions of RAS and differences in studied populations. For instance, patients at risk for RAS are not distinguished from those in whom the diagnosis is strongly suspected. While the presence of RAS is a risk factor for poor renal function and for renal failure, little information exists of rationale screening programs or treatment strategies for this disease [13].

What Is a Useful Definition of Ischemic Nephropathy?

The definition of ‘ischemic nephropathy’ is unclear. We will use ‘impairment of renal function beyond occlusive disease of the main renal arteries’ [12]. However, deterioration of renal function in the presence of RAS may not reflect ‘ischemia’. Under normal conditions blood flow to the kidney is far in excess of metabolic needs [14]. Thus, moderate absolute reductions in blood flow as in RAS may not be the sole or even a major contributor to reduced renal function. Furthermore, given the ability of the kidney to compensate with an increased single nephron GFR, even the loss of a single kidney from reduced or occluded vascular supply should not adversely affect renal function in the absence of additional insults. Thus, the view that reduction in renal blood flow directly results in ischemic damage is overly simplistic. Since the prevalence of RAS depends on definition and methodology, the true prevalence is not known. Given the increased survival of patients with cardiac disease and the known association
between atherosclerotic disease and RAS, the true prevalence of anatomical RAS may be increasing. Alternatively, the condition may be increasingly identified.

Atherosclerotic RAS, defined as >50% narrowing of the renal artery, is reported to occur in 11–42% of renal artery studies. In autopsy studies, RAS was found in 4–50% of subjects, with much higher prevalence in those >60 years of age, compared to those <60 years of age (16.4 vs. 5.5%). In individuals undergoing aortic angiography, RAS was reported in 38% of patients with aortic aneurysm, 33% in those with aortic occlusive disease, and in 39% of those with lower limb occlusive disease [15]. More recent reports of RAS found during cardiac catheterization describe a 14–29% prevalence in individuals with coronary disease and <10% of individuals with normal coronary arteries [16]. RAS occurred in 30% of individuals undergoing coronary angiography; 15% had trivial RAS, 11% had significant unilateral ostial RAS, and 4% had significant bilateral ostial RAS. A total of 34% of 86 heart failure subjects had RAS. Those patients also had higher creatinine values than non-RAS patients (2.8 vs.1.9 mg/dl) and more peripheral vascular disease (31 vs. 9%) [17]. The prevalence of RAS lesions is a function of both age and risk factors such as smoking, hypertension, dyslipidemias and diabetes [18]. In the Dutch Renal Artery Stenosis Intervention Cooperative Study (DRASTIC) [19] the most powerful predictors for detecting lesions of at least 50% were age, symptomatic vascular disease, elevated cholesterol and the presence of an abdominal bruit. The authors developed a scoring system that estimated the pre-angiographic probability of finding lesions of 50% or more with accuracy equal to radionuclide angiography. Buller et al. [20] describe a patient cohort undergoing cardiac catheterization that was at risk for RAS. Criteria included: uncontrolled hypertension, unexplained impaired kidney dysfunction, (GFR<60 ml/min), flash pulmonary edema, or diffuse atherosclerosis, 28% of the cardiac catheterization population were identified at risk. A total of 14% had significant RAS lesions.

**Does RAS Cause CKD or ESRD?**

RAS is a putative cause of end-stage renal disease (ESRD) in approximately 5% of ESRD patients [21, 22]. However, this number is questionable since the diagnostic criteria are not consistent. In some series, the diagnosis was confirmed by pathology. In others, the diagnosis was based on history of hypertension, bland urine sediment, and asymmetrical kidney size. Unfortunately, most registry data citing ‘ischemic nephropathy’ as the etiology for ESRD has not been rigorously validated. Nevertheless, it has been concluded that incidence of RAS as an ESRD cause has increased from 3 per million in 1991 to 6 per million in 1997 [23]. There may be racial differences in the prevalence of RAS [24]. In whites undergoing investigation for secondary hypertension, RAS was diagnosed in 27% of patients compared to 18% in black patients. Other series cite the prevalence as 30% lower in Native Americans, and 17% lower in African-Americans, compared to white patients. Ascertainment bias, survival bias, and various other biases make these data suspect. Most importantly, the demonstration of RAS is necessary but not sufficient to conclude that decreases in GFR are caused by renal artery narrowing. The anatomic demonstration of RAS does not prove functionality of the lesion.

**Do We Know the Natural History of RAS?**

Most studies have reported on selected populations or populations from an era prior to the use of vascular protection strategies, such as adequate blood pressure control or statin therapy. Furthermore, there is limited information on individuals with incidental RAS found at the time of cardiac catheterization. Moreover, it is difficult to ascertain the natural history of RAS because many studies lack a consistent, agreed upon primary outcome. Surrogate outcomes including decrease in renal artery diameter, decline in GFR and renal atrophy have been used.

Internal renal artery diameter is commonly assessed by angiography or duplex scans. Estimates of progression are between 11 and 60% and occlusion, 0.01 and 3% of renal arteries [25–27]. Progression appears to be dependent on the extent of the initial lesion, the follow-up time, the methods used to study renal artery diameter, and the study indications. For example, patients undergoing renal arteriography studies during cardiac catheterization appear to have less progression and occlusion than those undergoing evaluation for CKD, PVD or during a workup for secondary hypertension. Crowley et al. described renal artery stenosis progression in patients undergoing cardiac catheterization followed for an average of 2.6 years [25]. They found that 13.4% of individuals had lesions ≥50%, opposed to 2–11% at the initial study. In contrast, Caps et al. [26, 27] report that in those undergoing duplex scanning to assess renal artery diameter for evaluation of hypertension and/or impaired renal function, the 3-year cumulative incidence of renal artery narrowing stratified by baseline RAS severity was 18, 28 and 49% for renal arteries.
initially classified as normal, <60% stenosis or ≥60% stenosis, respectively. These important studies illustrate the problems understanding the natural history of RAS. Whereas the Crowley Study used angiography and incidental identification during cardiac catheterization, the CAPS study used duplex scanning in high-risk individuals. While the differences in progression may be ‘real’ alternatively the differences may simply be related to the inclusion criteria used for the two study groups, or differences in mortality risk. Possibly, those who remain alive after cardiac catheterization have less severe disease than those in whom RAS is suspected clinically and in those who have a high prevalence of peripheral vascular disease but are not undergoing cardiac catheterization. Importantly, both studies are in agreement that progression to complete occlusion is rare. Four patients in the Crowly and co-workers study and 9 patients in the study by Caps’ group developed complete occlusion [25–27]. Large cohort studies, systematically evaluating specific populations by both noninvasive and invasive techniques to characterize the natural history of RAS have not been done.

Loss of GFR may be a more useful endpoint for ischemic nephropathy progression. Importantly, there does not appear to be a tight relationship between renal artery diameter and loss of GFR [12]. There are several reasons that diameter and GFR loss may not be tightly related. For example, RBF exceeds renal metabolic demands so that relatively large decreases in flow would still meet these demands. Alternatively, atherosclerotic process may affect smaller vessels leading to atherosclerotic changes within the kidney with relatively small changes in large vessel diameter.

Leertouwer et al. [28] analyzed the need for renal replacement therapy in patients with untreated RAS ≥50% stenosis (n = 126), compared to controls without RAS (n = 260) matched for age and gender. Despite RAS ≥50% stenosis no patient developed ESRD during a 10-year follow-up. Serum creatinine levels, although approximately 20% higher in patients with RAS compared to controls, remained stable during follow-up. In another series of 68 patients with ‘incidental’ RAS ≥70% ‘clinical’ progression leading to ESRD or revascularization occurred in <12% [29]. Incidental RAS does not necessarily progress to ESRD.

There may be no relationship between the extent of proximal narrowing and GFR decline [30, 31]. For example, when renal arteries were characterized from <50% to >70%, of normal, GFR ranged from 30 to 36 ml/min and was unrelated to diameter size. Cheung et al. [31] assessed time to ESRD progression in individuals with unilateral renal artery occlusion and contralateral RAS. Time to ESRD progression was not related to ipsilateral renal artery anatomy. The time to ESRD or death in 142 patients was not related to renal artery anatomy. Progression was the same irrespective of whether non occluded artery was normal or had stenosis of varying severity of paradoxically, the Cox proportional hazard analysis for risk of ESRD or death indicated that RAS <50% was more of a risk (OR 3.39) than more severe RAS (RR 0.95). The data suggest that while RAS is necessary to cause progressive loss of GFR, additional factors operating within the kidney must determine progression. In fact, Cheung et al. [31] showed that dialysis-free survival or death was best predicted by low baseline GFR rather than renal vascular anatomy. A corollary to this finding is the observation that RAS repair may not stabilize GFR in the presence of distal parenchymal disease. One could hypothesize that less severe lesions allow transmission of high pressures to compromised renal vasculature, thereby exacerbating the sclerotic process by activating local tissue factors associated with endothelial shear stress. If so, then aggressive treatment of less severe lesions may important to prevent progressive parenchymal injury. Such a paradigm would be in contrast to other ‘ischemic models’. Prevailing opinion holds that intervention in lesions <70% is not helpful. However, if relatively less severe lesions affected downstream events, it would seem reasonable to intervene earlier in the course of RAS.

Renal atrophy is a better indicator of the functional consequence of RAS. Changes in kidney size should be a late outcome to measure the effect of flow reduction. Clear definitions of ‘renal atrophy’ are lacking. Reduction in kidney size would be expected to occur more frequently in kidneys with renal arteries ≥60% stenosed. For example, Caps et al. [26, 27] showed that the 2-year cumulative incidence of renal atrophy was 5.5, 11.7, and 20.8% in kidneys with baseline renal artery diameters classified as normal, <60% stenosis, and ≥60% stenosis, respectively. Thus, while there was a relationship between renal artery diameter and atrophy, there was progression in kidney disease with <60% stenosis as well. The extent of fibrosis and sclerosis on biopsy may be a helpful predictor of progression. In a small series, Wright et al. [32] found a robust relationship between decreases in creatinine clearance over time and renal damage score from biopsy samples. However, whether or not renal size is truly a surrogate for fibrotic scores on kidney biopsy remains unclear. Studies are required to determine whether change in renal size is truly a reliable early marker of atrophy. While renal resistive index appears to be a good surrogate mark-
er for renal sclerosis, these results have not been confirmed in a larger series [33].

Another marker for ischemic damage in RAS patients may be proteinuria. RAS causes a number of functional consequences to the kidney, including hypertension, sodium retention, decreased GFR and proteinuria. Sodium retention is mediated by activation of the renin-angiotensin-aldosterone system, other hormonal mediators, as well as by intrarenal factors. While proteinuria is not common with RAS <50%, when GFR is reduced to less than 25% of normal, proteinuria (even in the nephrotic range) has been reported in ischemic RAS. It is not known whether proteinuria is directly related to narrowing of the renal artery or to secondary glomerular sclerosis. Some case reports demonstrate remission of proteinuria after revascularization.

In summary, knowledge about the natural history of atherosclerotic RAS is limited due to the variation in study cohorts, potential bias for selection, and follow-up of survivors. From the data available, the best predictor of progression to ESRD may be GFR at presentation and/or biopsy proven renal fibrosis score. It is clear that progressive loss of GFR cannot be related to RAS alone. Thus, the diagnosis of ischemic nephropathy requires more than the demonstration of RAS. Clearly, there is a need for studies that examine the relationship between the extent of RAS and the degree of sclerosis. Functional measure of sclerosis, measured directly or indirectly by means of resistive index or severity of proteinuria, is required.

**How Often Are Therapeutic Interventions Performed in Patients with RAS?**

The introduction of stenting increased renal artery interventions from 13,380 to 21,600 for Medicare beneficiaries between 1996 and 2000 [34]. Interventional cardiologists perform most of these procedures. In contrast, because of the perceived risk of systemic atheroemboli with potentially catastrophic results especially in patients with extensive disease, many nephrologists remain conservative [35]. Technical advances, including the introduction of various protective devices, may diminish risks. Nevertheless, the outcomes for these patients remain uncertain. Since the incidence of ischemic nephropathy appears to be increasing and techniques to diagnose and reversely stenotic lesions are available, it is important that interventionalists (cardiologists, interventional radiologists, and vascular surgeons) collaborate with nephrologists in choosing selected patients in whom stenting would prevent progression of ischemic nephropathy.

The summary of three prospective randomized trials comparing medical therapy for renovascular hypertension to percutaneous renal artery angioplasty (PTRA), presented in table 1 are small, and contained selected patient populations, none of which were incidentally discovered RAS. However, they sought to standardize blood pressure outcome measurement and to randomize patients prospectively. Each was different, but all found less major benefits accrued in PTRA groups than reported by observational studies alone. Crossover rates from medical to angioplasty arms were significant, however, and emphasize the importance of restoring blood supply in selected patients, particularly those with bilateral disease.

**What Is the Concomitant Vascular Disease Burden in Patients with RAS?**

Disturbances of endothelial function, as determined by forearm blood flow studies, develop with either fibromuscular dysplasia or atherosclerotic RAS. Endothelial dysfunction is potentially reversible after successful angioplasty [13]. Loss of GFR develops almost exclusively in patients with atherosclerosis, often superimposed upon vascular changes related to aging, essential hypertension, smoking and diabetes mellitus. Renal injury and fibrogenesis related to renal atherosclerotic disease develop as a result of multiple macrovascular injury mechanisms [12, 13, 34, 36, 37]. Candidates for revascularization of ‘ischemic nephropathy’ usually require extensive medical therapy for atherosclerotic disease elsewhere. Many of the interventions recommended for the reduction of mortality related to CVD will lead to improvement in the atherosclerotic process affecting the kidneys. Some authors suggest that the increasing incidence of renal artery stenoses may, in fact, be related to the reduced mortality from atherosclerosis in other vascular beds. Medical treatment may allow progression of renal artery lesions to reach critical severity in such patients that might otherwise have died of other atherosclerotic causes [38].

Since the introduction of angiotensin-converting enzyme (ACE) inhibitors, several authors reported successful blood pressure control in 82–96% of patients with renovascular hypertension [40]. Thus, many patients treated with renin-angiotensin system blockers who have early renovascular lesions are probably never identified. Patients who fail medical therapy represent an important subgroup to be considered for revascularization. Recent studies have established the benefit of angiotensin (Ang) II receptor blockers (ARB) and ACE inhibitors in patients...
with coronary artery disease, congestive heart failure or chronic renal disease of various sorts. Cardiovascular mortality and renal disease progression were diminished in these studies. Numerous patients participating in these studies may have had some degree of RAS. Whether or not renin-angiotensin system blockade results in slowing of RAS is unknown. However, cardiovascular mortality in patients with renovascular disease is reduced in patients receiving these drugs [41].

**When Should Renal Revascularization for Ischemic Nephropathy Be Considered?**

A detailed examination of the effects of surgical, angioplasty, and endovascular stent series is beyond the scope of this review. Few studies have examined outcomes in the current era of vascular protective strategies and more aggressive diagnosis of RAS in the context of cardiac catheterization. Many of the renal functional outcomes of these series are summarized elsewhere [42, 43]. There are continued developments in endovascular stent technology that appear to reduce re-stenosis and acute procedural complications. The studies report ambiguous clinical results from composite clinical outcomes after interventional procedures [44].

In most series, GFR is minimally changed during long-term follow-up. Some individuals dramatically recover kidney function [44]. Many patients have little or no change in renal function but in the absence of CKD progression, may be at lower risk of subsequent progressive vascular occlusion and for cardiovascular events. Vascular intervention in RAS patients is associated with a small but inevitable subset of patients, about 25% in most series, who develop worsening renal function soon after revascularization [45, 46]. The outcome in these patients is uniformly worse, with some reporting more than 35% progression to dialysis and accelerated mortality [47].

The problems with generalizing these studies are several: (1) criterion for patient selection; (2) criterion for the diagnosis of RAS; (3) definition of outcome measures, and (4) lack of comparable control groups. When faced with the situation that ‘about one-third gets better, one-third gets worse, and one-third stays about the same’, clinical decision making becomes a hazardous undertaking.

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**Table 1. Prospective, randomized trials of medical vs. interventional therapy for atherosclerotic renal artery stenosis [48–50]**

<table>
<thead>
<tr>
<th>Author/patients</th>
<th>Inclusion/BP measurement</th>
<th>BP outcome, mm Hg</th>
<th>Renal outcome</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Webster, 1998</td>
<td>n = 55 (unilateral = 27) n = 135 eligible</td>
<td>BP ≥95, 2 drugs exclusion: CVA, MI RAS &gt;50%</td>
<td>unilateral: PTRA: 173/95 med Rx: 161/88 bilateral: PTRA: 152/83 med Rx: 171/91 p &lt; 0.01</td>
<td>creatinine (μmol/l) bilateral PTRA: 188 med Rx: 157 unilateral PTRA: 14 med Rx: 168</td>
</tr>
<tr>
<td>Plouin, 1998</td>
<td>n = 49 (unilateral ASO) RAS &gt;75% or &gt;60%, lateralizing study</td>
<td>BP: random zero device No. ACEI allowed</td>
<td>PTRA: 140/81 med Rx: 141/84 No. drugs (DDD): PTRA 1.0 med Rx: 1.78, p &lt; 0.01 crossover to PTRA: 7/26 (27%)</td>
<td>creatinine clearance ml/min: (6 months) PTRA: 77 med Rx: 74 renal artery occlusion: PTRA: 0 med Rx: 0</td>
</tr>
<tr>
<td>Van Jaarsveld, 2000</td>
<td>n = 106 ASO RAS &gt;50%</td>
<td>DBP ≥95 mm Hg or creatinine rise with ACEI exclusion: Creat ≥2.3 solitary kidney/total occlusion kidney &lt;8 cm BP: random zero device</td>
<td>BP outcomes at 3 months: PTRA 169/89 med Rx: 163/88 at 12 months: PTRA: 152/84 med Rx: 162/88 No. drugs: 1.9 vs. 2.4 p &lt; 0.01</td>
<td>creatinine Cl (3 months) ml/min: PTRA: 70 med Rx: 59 (p = 0.03) abnormal renograms PTRA: 36% med Rx: 70% (p = 0.002) renal artery occlusion PTRA 0 med Rx 8</td>
</tr>
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</table>

DDD = Defined daily doses.
The DRASTIC study is the most extensive prospective controlled trial of angioplasty versus medical therapy for RAS [48]. No difference between the two treatments could be found in this intention-to-treat analysis. However, the cross over of patients from the medical to the angioplasty group was numerous so that the study results are uninterpretable. The Essai Multicentrique Medicaments versus Angioplastie (EMMA) study group concluded that in unilateral atherosclerotic renal artery stenosis, angioplasty is a drug-sparing procedure that involves some morbidity [49]. Previous uncontrolled and unblinded assessments of angioplasty overestimated its potential for lowering blood pressure. The Scottish and Newcastle Renal Artery Stenosis Collaborative Group concluded that in hypertensive patients with atheromatous RAS, percutaneous renal angioplasty results in a modest improvement in systolic blood pressure compared with medical therapy alone [50]. This benefit was confined to patients with bilateral disease. No patient was ‘cured’, renal function did not improve, and intervention was accompanied by a significant complication rate. Other than these three controlled trials, no others are available.

CORAL is a prospective, multicenter unblinded two arm-randomized trial of the clinical outcomes of medical therapy plus stenting of atherosclerotic renal artery stenosis, compared to medical therapy alone [1]. The goal is to enroll 1,080 patients by the first quarter of 2007. Entry will require hypertension (defined as systolic BP >155 mm Hg during therapy with two or more drugs) and at least one non-occluded artery with at least 60% stenosis. Such stenosis must exhibit a trans-lesional gradient ≥20 mm Hg or more. Those stenosis exceeding 80% stenosis will not require a gradient measurement. Both arms will feature a ‘forced’ medical therapy to lower target blood pressure levels ≤140/90 mm Hg, based on anti renin-angiotensin system therapy and additional drugs as needed. After informed consent is obtained and the RAS lesion is confirmed, patients will be randomly assigned to receive stent placement or not. Those receiving stents will also have a ‘distal protection device’ employed (Angiogard) to minimize atheroembolic complications. Follow-up time will be 3.5–5 years. The primary endpoint in CORAL is a composite endpoint, defined as ‘event-free survival’ from cardiovascular and renal adverse events. Events are cardiovascular or renal death, stroke, myocardial infarction, hospitalization for heart failure, and progressive renal insufficiency, defined as doubling serum creatinine or requiring dialysis. The investigators are intent on maintaining treatment groups for the duration of the trial and to avoid ‘crossovers’ for difficult blood pressure control. This trial seeks to truly establish the prevalence of restenosis, the benefits and risks of endovascular procedures in technically capable centers, and to determine whether or not stent placement materially improves cardiovascular and renal outcomes. Two other studies in preparation have similar study design and outcome measures, and are being performed in different populations, but with similar premises as the CORAL study [2, 3].

### A Need for Extended Clinical Studies

We propose that a comprehensive program of systematic evaluation and investigation should be conducted to understand the natural history and impact of RAS and renovascular disease in high-risk patients. Clear, unambiguous definitions are necessary to permit a true assessment of the problem, its magnitude, and rational interventional approaches. These definitions and outcome measures should be clearly understood by all participants prior to embarking on observational or interventional studies. The natural history of and functional consequences of RAS found at the time of cardiac catheterization should be ascertained. The most useful markers of renal function, markers of acute and chronic damage, and fibrosis should also be defined. A novel marker cystatin-C that predicts renal injury after interventions with surprising precision is now available [51]. This marker should be included so as to predict potential hazards of any interventions. As a collaborative effort of clinicians and researchers, we could answer these questions within 5 years.

### Key Questions to Be Answered

Most observational and interventional studies available in the literature have been conducted in patients with RAS suspected on clinical grounds. Outcomes data are based on this same population; however, because of the time differential, the studies were conducted with various technologies, and were very heterogeneous in terms of concomitant therapies. Patients with RAS identified at the time of cardiac catheterization differ substantially from patients with RAS suspected on clinical grounds. The current practice of ‘drive-by’ angiography identifies a potentially different group of patients than those previously studied. While there may be some theoretical rationale for treatment of serendipitous lesions, many key questions remain unanswered. A team of cardiologists
and nephrologists should prospectively address these questions.

- What is the prevalence of RAS in age-adjusted subgroups, namely patients with coronary disease, peripheral vascular disease, systolic and diastolic heart failure, proteinuric and nonproteinuric renal disease?
- How should ischemic nephropathy be defined so that agreement can be reached regarding who needs treatment and which strategy should be employed?
- What is the current natural history of RAS and what measures will most accurately detect progression of kidney disease?
- Which patients with RAS will benefit from revascularization? Specifically, do stents: (a) reduce BP; (b) slow progression of renal disease, and (c) prevent CVD outcomes.

An assessment should be conducted to prospectively compare nonselective overviews of the renal arteries with selective arteriography, magnetic resonance imaging angiography, and computerized tomography to determine the sensitivity, specificity, positive and negative predictive values of the brief overviews obtained during cardiac catheterization [52]. In other words, is ‘drive by’ renal angiography a justifiable diagnostic test? We still do not know whether the treatment allows an improved outcome when these patients have their renin-angiotensin systems interrupted.

Given the increase in cardiac and renal angiography procedures, and the fact that RAS as a cause of ischemic nephropathy and CKD is potentially reversible it is important to develop an integrated and informed approaches to diagnose and treat RAS discovered incidentally at the time of cardiac catheterization.

**Key Points**

1. Renal artery stenosis is associated with two clinical syndromes: hypertension and ischemic nephropathy.
2. Renal artery narrowing is necessary but not sufficient to cause progressive loss of GFR. There is not a ‘tight’ relationship between the extent of arterial narrowing and loss of GFR.
3. The most useful predictor of progressive loss of GFR is the initial GFR and renal atrophy.
4. Renal artery stenting may not result in prevention of loss of GFR because of irreversible, progressive parenchymal injury.
5. Prospective studies on the incidence, natural history, best practices for treating incidentally diagnosed renal artery stenosis are required.

**American Society of Nephrology**

*Hypertension Advisory Group*


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### References


Levin et al.