

# Prospective Study of Atherosclerotic Disease Progression in the Renal Artery

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**Background**—The aim of this study was to determine the incidence of and the risk factors associated with progression of renal artery disease in individuals with atherosclerotic renal artery stenosis (ARAS).

**Methods and Results**—Subjects with  $\geq 1$  ARAS were monitored with serial renal artery duplex scans. A total of 295 kidneys in 170 patients were monitored for a mean of 33 months. Overall, the cumulative incidence of ARAS progression was 35% at 3 years and 51% at 5 years. The 3-year cumulative incidence of renal artery disease progression stratified by baseline disease classification was 18%, 28%, and 49% for renal arteries initially classified as normal,  $< 60\%$  stenosis, and  $\geq 60\%$  stenosis, respectively ( $P=0.03$ , log-rank test). There were only 9 renal artery occlusions during the study, all of which occurred in renal arteries having  $\geq 60\%$  stenosis at the examination before the detection of occlusion. A stepwise Cox proportional hazards model included 4 baseline factors that were significantly associated with the risk of renal artery disease progression during follow-up: systolic blood pressure  $\geq 160$  mm Hg (relative risk [RR]=2.1; 95% CI, 1.2 to 3.5), diabetes mellitus (RR=2.0; 95% CI, 1.2 to 3.3), and high-grade ( $> 60\%$  stenosis or occlusion) disease in either the ipsilateral (RR=1.9; 95% CI, 1.2 to 3.0) or contralateral (RR=1.7; 95% CI, 1.0 to 2.8) renal artery.

**Conclusions**—Although renal artery disease progression is a frequent occurrence, progression to total renal artery occlusion is not. The risk of renal artery disease progression is highest among individuals with preexisting high-grade stenosis in either renal artery, elevated systolic blood pressure, and diabetes mellitus. (*Circulation*. 1998;98:2866-2872.)

**Key Words:** atherosclerosis ■ kidney ■ arteries ■ stenosis

Renal ischemia resulting from stenosis of the renal artery may result in 2 important sequelae: (1) systemic arterial hypertension, which is frequently difficult to control, placing the individual at increased risk of stroke and myocardial infarction; and (2) renal atrophy and nephron loss, resulting in an increased risk of progression to end-stage renal disease.

Atherosclerotic renal artery stenosis (ARAS) is a frequent and often underappreciated cause of both hypertension and renal insufficiency.<sup>1,2</sup> The appropriate management of patients with ARAS requires accurate knowledge of the natural history of this condition. In patients with ARAS, systemic blood pressure and the risk of renal atrophy are well correlated with the degree of narrowing in the renal artery.<sup>3</sup> Therefore, the rate of progression of disease in the renal artery and factors associated with increased rates of progression are important elements to consider when therapy or follow-up for patients with this disease is being planned.

In January 1990, we began a prospective study of the natural history of ARAS using serial duplex ultrasonography.

The goals of the present study were to estimate the frequency of ARAS disease progression and to assess the importance of several potential risk factors for disease progression. We have previously reported on rates of disease progression in the renal artery.<sup>4,5</sup> The present report provides longer follow-up on  $\approx 2.5$  times as many kidneys as in our most recent previous analysis.<sup>5</sup> The larger sample size in the present report enabled us to estimate progression rates with greater precision and to assess the presence of risk factors for progression with increased power.

## Methods

### Study Population

In 1990, a prospective study of the natural history of atherosclerotic renovascular disease was initiated at the University of Washington. Between January 1990 and March 1997, we recruited 220 subjects who underwent renal duplex scanning. The patients were referred for renal ultrasound evaluation because of hypertension, renal insufficiency, or both. Subjects with  $\geq 1$  stenotic main renal artery who

Received June 2, 1998; revision received September 2, 1998; accepted September 15, 1998.

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were not candidates for immediate renal revascularization were eligible for inclusion in the study. During the course of this study, the patient's primary care and/or referring physicians continued to manage all aspects of care, including blood pressure medication and the decision to intervene on a stenotic renal artery. Informed consent was obtained from all participants with approval from the Human Subjects Review Committee at the University of Washington.

Patients with  $\geq 1$  ARAS and a minimum of 3 months of follow-up were considered for this analysis. Of the 220 patients, 50 were excluded from the analysis for the following reasons: 25 had been studied only once, 15 had undergone prior bilateral renal interventions (renal artery balloon angioplasty, surgical procedures, or nephrectomy); 2 patients with unilateral renal artery occlusion had had an intervention on the opposite side; 7 patients were in the study for  $< 3$  months; and we were unable to classify the disease state in 1 subject.

This provided 170 patients with potentially 340 renal arteries. Of these, an additional 45 arteries were excluded. Twenty-two renal arteries had prior intervention; 21 were occluded at the time of the first visit; and 1 patient had a congenitally absent kidney, and the remaining side had an inadequate duplex evaluation. This left 170 subjects and 295 renal arteries for the present analysis. After the baseline visit, follow-up duplex examinations were performed at 6-month intervals. When a renal artery intervention was performed during the study, all subsequent examinations were excluded from the analysis.

### Exposure Assessment

Clinical data for all subjects were entered at the time of the baseline and subsequent duplex examinations. Demographic data, as well as past and current medical status, were recorded. Risk factors for atherosclerosis, symptoms and signs of atherosclerotic disease elsewhere, current medication use, and any procedure for treatment of arterial disease were noted. Diabetes mellitus was defined as the use of any hypoglycemic agent or insulin.

Blood pressure was measured twice in both arms after  $\geq 15$  minutes of rest in the supine position. The blood pressure determination used for the analysis was an average of measurements made on the arm that had the higher blood pressure. The ankle-arm index (AAI) was also measured at each visit with a continuous-wave Doppler. The AAI is the ankle systolic pressure (the higher of the anterior versus posterior tibial arteries) divided by the higher of the brachial systolic pressures. For the purposes of the analysis, we used the measurement from the leg with the lowest AAI.

Beginning in January 1990, blood was drawn and tested for serum creatinine concentration at the baseline visit. Beginning in August 1994, blood was also drawn for lipid analysis, including total, LDL, and HDL cholesterol; triglyceride; apolipoprotein A and B; and lipoprotein(a) concentrations. All blood draws were performed after an overnight fast.

### Renal Duplex Scanning

The technique of renal artery duplex scanning used at the University of Washington has been reported in detail previously.<sup>6-8</sup> All examinations were performed with an ATL Ultramark 9 or HDI duplex scanner (Advanced Technology Laboratories) using a 2.25- or 3.2-MHz phased array or 3-MHz mechanical sector transducer. All patients were scanned in the supine position after an overnight fast to minimize the presence of bowel gas. The abdominal aorta was imaged first, and the peak systolic velocity (PSV) was measured at or above the level of the superior mesenteric artery. Velocities were then measured from the origin, proximal, middle, and distal segments of each renal artery. The angle between the Doppler ultrasound beam and the renal artery was  $\leq 60^\circ$  for all renal artery velocity measurements.

The severity of ARAS was classified according to previously validated criteria.<sup>6-8</sup> These criteria are based on the highest renal artery PSV and the renal-to-aortic ratio, defined as the highest renal artery PSV divided by the aortic PSV. These criteria permit classification of renal artery diameter reduction by duplex scanning into 4 categories (Table 1): normal,  $< 60\%$  stenosis,  $\geq 60\%$ , and occlusion.

**TABLE 1. Diagnostic Criteria for Classification of Renal Artery Stenosis by Duplex Scanning**

Renal Artery Diameter Reduction	Renal Artery PSV	RAR
Normal	$< 180$ cm/s	$< 3.5$
$< 60\%$	$\geq 180$ cm/s	$< 3.5$
$\geq 60\%$	$<$ or $\geq 180$ cm/s	$\geq 3.5$
Occlusion	No signal	No signal

PSV (peak systolic velocity) indicates the maximum velocity measured by the Doppler spectral waveform analysis; RAR, renal-to-aortic ratio (ratio of highest PSV in the main renal artery to PSV in suprarenal abdominal aorta). If peak systolic velocity in the abdominal aorta is abnormally low ( $< 40$  cm/s), RAR cannot be used, and identification of a  $> 60\%$  renal artery stenosis is based on the finding of a localized high-velocity jet and poststenotic turbulence.

### Outcome Assessment

Renal artery disease progression was defined as any detectable increase in the degree of diameter reduction in the renal artery, including renal artery occlusion. We used the principle that blood flow velocity across a stenosis is approximately proportional to the degree of vessel diameter reduction. An increase in the renal artery PSV of  $\geq 100$  cm/s would represent a statistically significant increase in the flow velocity, beyond the intrinsic measurement variability of the duplex scanner. This 100 cm/s threshold was based on the between-observation variability for renal artery PSV measurements in the present study, a figure obtained by performing simple linear regression of renal artery PSV as a function of time separately for each kidney with  $\geq 3$  observations. The SD of all points about the regression lines was 48 cm/s, an estimate of the within-subject variability that is independent of linear trends in renal artery PSV over time. To be conservative, an increase in renal artery PSV  $\geq 100$  cm/s was considered to be less likely due to chance, a threshold that is  $> 2$  times the SD. Thus, an increase in the renal artery PSV of  $\geq 100$  cm/s would be unlikely in the absence of true renal artery disease progression (assuming normally distributed random observation errors).

In summary, renal artery disease progression was defined as either (1) an increase in the renal artery PSV of  $\geq 100$  cm/s compared with the baseline examination or (2) renal artery occlusion. In separate, secondary analyses, we also estimated the cumulative incidence of renal artery occlusion as well as the incidence of disease progression to a  $\geq 60\%$  diameter-reducing stenosis (for renal arteries classified as normal and  $< 60\%$  stenosis at the baseline examination).

### Statistical Methods

The data analysis was performed with STATA for Windows version 5.0. Summary statistics were calculated, including means and SDs for continuous variables and proportions for categorical variables. The cumulative incidence of renal artery disease progression was estimated by the Kaplan-Meier method. Cox proportional hazards regression was used to identify risk factors for progression. Because of possible dependence of disease progression between the left and right renal arteries within a patient, robust SEs were used to calculate *P* values and 95% CIs.<sup>9</sup>

### Results

Table 2 summarizes the characteristics of the 170 participants at the baseline examination. Mean systolic and diastolic blood pressures at baseline for the entire population were 163 mm Hg (range, 90 to 236 mm Hg) and 82 mm Hg (range, 53 to 110 mm Hg), respectively. One hundred sixty-two patients (95%) were receiving treatment for arterial hypertension, and the average number of antihypertensive medications taken was 2.2 (range, 1 to 5). Mean serum creatinine was 1.5 mg/dL (range, 0.5 to 7.7 mg/dL), and 56 subjects (33%) had

**TABLE 2. Baseline Characteristics of the Study Population**

Characteristic	n*	Value
<b>Demographics</b>		
Age, y (mean±SD)		68±9
Sex, M:F ratio		85:85
<b>Risk factors for atherosclerosis</b>		
Hypertension (% receiving antihypertensive medication)		95%
SBP, mm Hg (mean±SD)		163±25
Diastolic blood pressure, mm Hg (mean±SD)		82±12
Diabetes mellitus (% diabetic)		18%
Cigarette smoking (% current smokers)	169	25%
Pack-years of cigarette smoking	131	43±34
Body mass index (mean±SD)	135	26±5
<b>Lipid and lipoproteins, mg/dL (mean±SD)</b>		
Total cholesterol	144	216±41
LDL cholesterol	144	131±39
HDL cholesterol	144	49±20
Triglyceride	144	183±124
Apolipoprotein A1	143	141±31
Apolipoprotein B	143	116±26
Lipoprotein(a)	144	18±26
<b>Renal function</b>		
Serum creatinine, mg/dL (mean±SD)	167	1.5±0.9
<b>Markers of atherosclerotic disease</b>		
AAI, mean±SD	169	0.87±0.24
Clinical coronary heart disease, % (myocardial infarction, angina, CABG, PTCA)		47%
Clinical cerebrovascular disease, % (stroke, TIA, carotid endarterectomy)		27%

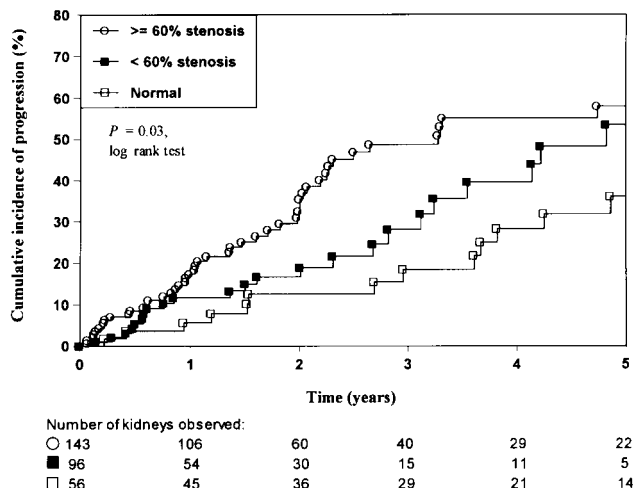
TIA indicates transient ischemic attack.

\*Sample size for variables with missing data; sample size=170 if not specified.

impaired renal function (creatinine ≥1.5 mg/dL) at the baseline examination. Diabetes mellitus was present in 18% of the patients and a history of smoking in 79% (25% were current smokers at the time of the baseline examination). The mean serum total cholesterol was 216 mg/dL (range, 125 to 395 mg/dL).

There were a total of 295 kidneys included in this analysis. Renal artery duplex scanning at the baseline examination demonstrated 56 normal renal arteries, 96 with <60% diameter reduction, and 143 with ≥60% stenosis. The majority of renal arteries showed atherosclerotic lesions at the origin or in the proximal segment of the renal artery. Follow-up averaged 33 months and ranged from 3 months to 7.2 years.

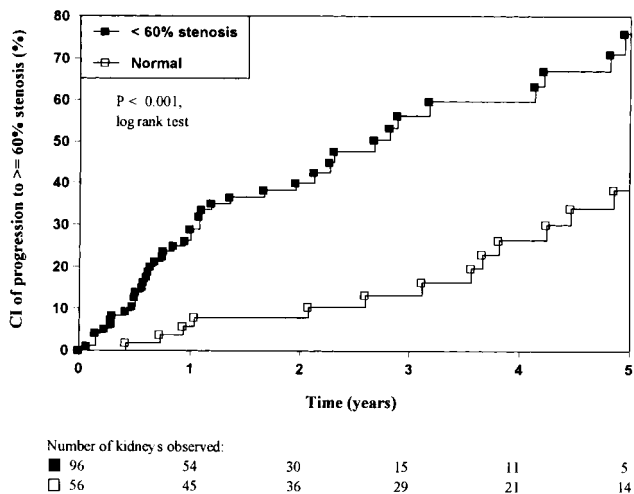
Renal artery disease progression was detected in 91 (31%) of the 295 renal arteries in this study. The cumulative incidence of renal artery disease progression, stratified by the baseline disease classification, is shown in Figure 1. There was a statistically significant association between baseline disease classification and subsequent risk of renal artery disease progression ( $P=0.03$ , log-rank test). The estimated 3-year cumulative incidence of renal artery disease progres-



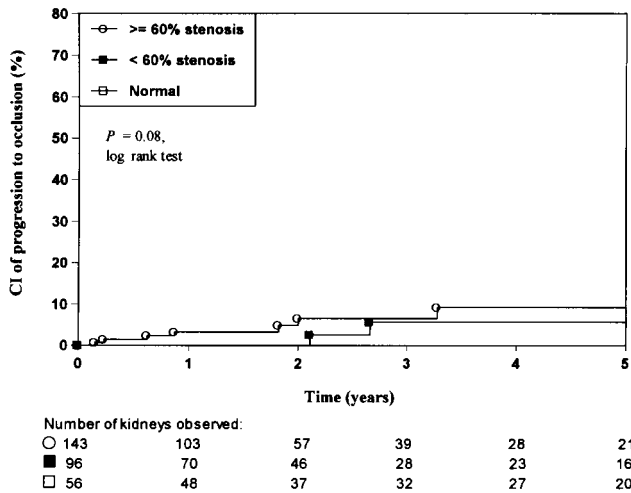
**Figure 1.** Cumulative incidence of renal artery disease progression stratified according to baseline degree of renal artery narrowing. SEs were <10% for all plots through 5 years.

sion stratified by baseline disease classification was 18%, 28%, and 49% for renal arteries initially classified as normal, <60% stenosis, and ≥60% stenosis, respectively.

The cumulative incidences of progression to the ≥60% stenosis category and to occlusion are shown in Figures 2 and 3, respectively. These plots are similarly stratified according to the baseline disease classification. For arteries classified as normal and having <60% stenosis at the baseline examination, the estimated 3-year cumulative incidence of progression to the ≥60% stenosis category was 13% and 56%, respectively. Only 9 of the 295 renal arteries in this analysis progressed to total occlusion during the follow-up period. Seven of these were classified as having ≥60% stenosis at baseline, whereas 2 were initially classified as having <60% stenosis. Progression to ≥60% stenosis was detected in both arteries in the latter group before the detection of renal artery occlusion. None of the arteries classified as normal at the time of the baseline examination progressed to occlusion.



**Figure 2.** Cumulative incidence (CI) of progression to ≥60% renal artery stenosis stratified according to baseline degree of renal artery narrowing. SEs were <10% for all plots through 5 years.



**Figure 3.** Cumulative incidence (CI) of progression to renal artery occlusion stratified according to baseline degree of renal artery narrowing. Occlusion was not observed among renal arteries classified as “normal” at baseline examination. SEs were <10% for all plots through 5 years.

The Cox proportional hazards analysis of risk factors for renal artery disease progression is shown in Table 3<sup>8</sup>. In addition to the baseline disease status in the ipsilateral renal artery, this analysis of one predictor variable at a time identified 5 additional baseline factors associated with renal artery disease progression at the  $P < 0.05$  level: the presence of high-grade ( $\geq 60\%$  stenosis or occlusion) disease in the contralateral renal artery, age, systolic blood pressure (SBP), diabetes mellitus, and a low AAI. There was no statistically significant evidence for effect modification or interaction among these important predictors of renal artery disease progression.

These 6 variables were then entered into a stepwise Cox proportional hazards model. Continuous variables were dichotomized for ease of interpretation. Four factors were retained in the model (Table 4), which suggests that the effect of each of these factors was not explained by correlation with other study variables. SBP remained an important predictor of ARAS progression in this model ( $P = 0.006$ ): an SBP  $\geq 160$  mm Hg corresponded to a 2.1-fold increase in risk. A history of diabetes mellitus was associated with a 2.0-fold increase in risk ( $P = 0.009$ ). Baseline disease status in the ipsilateral ( $P = 0.004$ ) and contralateral ( $P = 0.04$ ) renal arteries was an independent predictor of the risk of renal artery disease progression and was associated with 1.9- and 1.7-fold increases in risk, respectively.

Using this model, we calculated the predicted cumulative incidence of renal artery disease progression at 2 years using the relative risk estimates in Table 4 and the baseline hazard rate for the study population. For renal arteries without high-grade disease in either the ipsilateral or contralateral arteries belonging to nondiabetic patients with baseline SBP  $< 160$  mm Hg, the predicted 2-year cumulative incidence of renal artery disease progression was 7%, whereas it was 65% for arteries with high-grade disease in both the ipsilateral and contralateral renal arteries belonging to diabetic patients with elevated ( $\geq 160$  mm Hg) SBP.

## Discussion

Atherosclerosis affecting the coronary, carotid, and peripheral arteries has been exhaustively studied in terms of incidence, sequelae, treatment, and outcome. This is not true of atherosclerosis of the renal arteries, which has been difficult to detect and even more difficult to monitor over time. Until duplex scanning became available, there were no direct methods available short of arteriography, which has been used sparingly and only in situations in which the information was needed for management of the patient. Although it does provide anatomic information on the location and extent of disease, arteriography is not suitable for long-term studies to document the natural history of the problem.

The present study has potential limitations that should be addressed. First, renal artery duplex scanning has been criticized for its technical difficulty and variable accuracy. However, several centers (including our own) have demonstrated that this technique can be performed with high levels of accuracy and reproducibility in patients with ARAS.<sup>6-8,10,11</sup> Renal artery duplex scanning has the additional advantages of being noninvasive and less expensive than arteriography, making it the best available tool for the prospective study of the natural history of renal artery stenosis.

Second, this study was not adequately powered to detect significant differences in progression rates among subgroups defined by factors that had small effect sizes. For example, the association between lipid levels and the risk of renal artery disease progression was generally as expected in the present study, but the magnitude of the observed effects was not statistically significant. Progression was more frequently observed among individuals with higher concentrations of total and LDL cholesterol, triglyceride, apolipoprotein B, and lipoprotein(a), but evidence that these associations were not due to chance is lacking.

Zierler and colleagues from our laboratory reported the early results of renal artery disease progression detected with duplex ultrasound.<sup>4,5</sup> The current report provides longer follow-up on  $\approx 2.5$  times as many kidneys as that study and is the largest prospective study of renal artery disease progression to date. Furthermore, we used a different primary definition of disease progression in this report; we had previously concentrated our efforts solely on progression to occlusion or to  $\geq 60\%$  stenosis. The use of a threshold renal artery PSV increase allowed us to estimate the incidence of nonocclusive as well as occlusive disease progression among arteries with  $\geq 60\%$  stenosis at the baseline examination.

The most striking finding in the present study of renal artery disease progression is the very rapid rate with which it occurs. The cumulative incidence of progression to high-grade ( $\geq 60\%$ ) stenosis for renal arteries that were normal or  $< 60\%$  stenosed at baseline was relatively high in this study. By 5 years,  $> 33\%$  of renal arteries initially classified as normal had progressed to high-grade stenosis, and 75% of arteries with  $< 60\%$  stenosis at baseline had progressed to the high-grade category. The risk of progression to renal artery occlusion reported from our laboratory has been consistently low and is in general agreement with other published studies.<sup>12,13</sup>

**TABLE 3. Cox Proportional Hazards Analysis of Association Between Baseline Factors and Risk of Renal Artery Disease Progression**

Factor	n	RR (95% CI)	P
Severity of renal artery stenosis			
Ipsilateral renal artery disease class			
Normal*	56	1.0	0.03
<60%	96	1.3 (0.8, 2.3)	
≥60%	143	2.0 (1.2, 3.4)	
Contralateral renal artery disease severity			
Not high grade*	127	1.0	0.04
High grade	167	1.6 (1.0, 2.5)	
Demographics			
Age			
<60*	46	1.0	0.03
60–69	119	1.7 (0.8, 3.5)	
≥70	130	2.5 (1.2, 5.2)	
Sex			
Female*	146	1.0	0.4
Male	149	0.8 (0.5, 1.3)	
Risk factors for atherosclerosis			
SBP, mm Hg			
<140*	45	1.0	0.004
140–159	85	0.8 (0.3, 2.0)	
≥160	165	2.0 (0.9, 4.6)	
Diastolic blood pressure, mm Hg			
<90*	214	1.0	0.4
90–94	48	1.3 (0.8, 2.2)	
≥95	33	1.5 (0.8, 2.7)	
Diabetes mellitus			
No*	233	1.0	0.03
Yes	62	1.9 (1.1, 3.2)	
Current cigarette smoker			
No*	222	1.0	0.6
Yes	72	1.1 (0.7, 1.8)	
Pack-years smoking			
<20*	46	1.0	0.6
20–39	71	1.3 (0.7, 2.4)	
≥40	109	1.3 (0.7, 2.4)	
Body mass index			
<25*	108	1.0	0.7
25–29	90	0.9 (0.5, 1.6)	
≥30	41	1.3 (0.7, 2.5)	
Lipids and lipoproteins, mg/dL			
Total cholesterol			
<200*	90	1.0	0.8
200–239	108	1.2 (0.7, 2.2)	
≥240	56	1.3 (0.6, 2.6)	
LDL cholesterol			
<130*	128	1.0	0.2
130–160	81	0.8 (0.4, 1.3)	
≥160	45	1.5 (0.8, 2.9)	
HDL cholesterol			
≥60*	54	1.0	0.8
35–59	143	1.2 (0.6, 2.3)	
<35	57	1.1 (0.5, 2.5)	

TABLE 3. Continued

Factor	n	RR (95% CI)	P
Triglyceride			
<150*	122	1.0	0.07
150–250	84	0.6 (0.3, 1.2)	
>250	48	1.5 (0.8, 2.7)	
Apolipoprotein A1			
<124*	84	1.0	0.8
124–147	85	0.8 (0.4, 1.6)	
≥148	84	1.0 (0.5, 1.8)	
Apolipoprotein B			
<106*	89	1.0	0.2
106–125	83	0.9 (0.5, 1.6)	
≥126	81	1.4 (0.7, 2.7)	
Lipoprotein(a)			
<4.8*	85	1.0	0.4
4.8–17.8	85	1.2 (0.7, 2.3)	
≥17.9	85	1.5 (0.8, 2.8)	
Renal function			
Creatinine, mg/dL			
<1.2*	119	1.0	0.4
1.2–1.4	79	1.2 (0.7, 2.1)	
≥1.5	92	1.5 (0.8, 2.6)	
Markers of atherosclerotic disease			
AAI			
≥1.0*	127	1.0	0.01
0.7–0.99	80	1.3 (0.7, 2.3)	
<0.7	87	2.1 (1.2, 3.5)	
Clinical coronary heart disease (myocardial infarction, angina, CABG, PTCA)			
No*	157	1.0	0.9
Yes	138	1.0 (0.6, 1.7)	
Clinical cerebrovascular disease (stroke, TIA, carotid endarterectomy)			
No*	217	1.0	0.8
Yes	78	1.1 (0.6, 1.9)	

n indicates number of renal arteries; RR, relative risk; High grade, ≥60% stenosis or occlusion; and TIA, transient ischemic attack.

\*Referent category, P value=test for association.

Six factors associated with the risk of renal artery disease progression were identified in the present study: age, systolic hypertension, diabetes mellitus, a low AAI, and the presence of high-grade (≥60% or occlusion) atherosclerotic disease in either the ipsilateral or contralateral renal artery. When the effects of these factors were considered simultaneously in a Cox proportional hazards model, age and low AAI were no longer statistically significant. Because of the number of

factors (21) screened for inclusion in the final regression model, it is possible that ≥1 of the 4 identified factors is statistically significant by chance alone.

Systolic hypertension, a classic risk factor for the development of atherosclerosis, appears to be both a consequence of and a risk factor for worsening ARAS. As a result of the original experiments of Goldblatt et al,<sup>14</sup> arterial hypertension due to unilateral renal artery stenosis is known to be a cause of bilateral renal damage because of ischemia on the ipsilateral side and hypertension on the contralateral side. The data presented in the present study indicate that poorly controlled blood pressure in turn increases the risk of renal artery disease progression on both sides. Aggressive blood pressure control in patients with ARAS would appear to be a critical element in interrupting this “vicious circle.” The association between age and renal artery disease progression was no longer statistically significant after adjustment for the presence of systolic hypertension; this finding is consistent with the hypothesis that the effect of age is mediated by its association with systolic blood pressure.

TABLE 4. Stepwise Cox Proportional Hazards Analysis of Baseline Risk Factors for Renal Artery Disease Progression

Factor	RR	95% CI	P
SBP ≥160 mm Hg	2.1	(1.2, 3.5)	0.006
Diabetes mellitus	2.0	(1.2, 3.3)	0.009
High-grade ipsilateral ARAS	1.9	(1.2, 3.0)	0.004
High-grade contralateral ARAS	1.7	(1.0, 2.8)	0.04

RR indicates relative risk; High-grade, ≥60% stenosis or occlusion.

Diabetes mellitus, another classic risk factor for the development of atherosclerosis, was also associated with an increased risk of renal artery disease progression in the present study. Although hyperglycemia is the main metabolic abnormality of diabetes, a strong association between glycemic control and macrovascular disease has not been demonstrated.<sup>15</sup> However, control of hyperglycemia is an important element of the treatment of diabetic patients because of the well-demonstrated association between glycemic control and reduction in the risk of microvascular and other complications of this disease.

Another important risk factor identified in the present study was a low AAI, which indicates that individuals who have demonstrated a propensity for atherosclerotic disease progression in other vascular beds appear to be at increased risk for disease progression in the renal artery. The AAI has been well-correlated with mortality and both clinical and subclinical measures of atherosclerotic disease in large population-based epidemiological studies<sup>16-18</sup> and may prove to be a useful, inexpensive screening test for the identification and targeting of high-risk individuals for cardiovascular risk factor reduction.

Finally, the degree of preexisting narrowing in both renal arteries was found to be associated with the subsequent risk of renal artery disease progression in the present study. This finding may have important implications for planning therapy and the frequency of follow-up for patients with ARAS. For patients who would be considered candidates for surgical or endovascular intervention, this information will also be important for planning follow-up of the contralateral renal artery.

The roles of surgical and endovascular therapy for ARAS are not clearly defined. In the past, surgical therapy for this disease has been reserved for patients with poorly controlled hypertension despite multiple medications or those with worsening renal function.<sup>19-22</sup> With proper patient selection, surgical revascularization of the renal artery is durable and is associated with improved blood pressure control in the majority of individuals. However, concern over the risk of perioperative death and complications has led to a more liberal use of endovascular techniques for treating renal artery stenosis. The safety, efficacy, and durability of these techniques has varied widely in reported series.<sup>23-26</sup> Additional studies to better define the association between the degree of narrowing in the renal artery and outcomes such as myocardial infarction, stroke, end-stage renal disease, and death are necessary to improve our understanding of the natural history of ARAS. Randomized clinical trials are also necessary to better elucidate the role of surgical and endovascular interventions in altering the natural history of this disease. The utility of the data presented in this report will likely increase as these issues are more clearly defined.

### Acknowledgment

This work was supported by NIH grant 1 R01 DK48088-01A1.

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