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Severity of renal vascular disease predicts mortality in patients undergoing coronary angiography

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Severity of renal vascular disease predicts mortality in patients undergoing coronary angiography.

Background. Renal artery stenosis (RAS) is a relatively uncommon but potentially reversible cause of renal failure. In a previous report, we demonstrated that the presence of RAS is independently associated with mortality in a group of patients undergoing coronary angiography. Our current study expands on this cohort, investigating the effect of the severity of RAS on all-cause mortality.

Methods. A total of 3987 patients underwent abdominal aortography immediately following coronary angiography. For the purpose of survival analysis, significant RAS was defined as ≥75% narrowing in the luminal diameter.

Results. Significant RAS was present in 4.8% of patients studied and was bilateral in 0.8%. Factors associated with the presence of RAS included female gender, older age, hypertension, congestive heart failure, elevated serum creatinine, and congestive heart failure. The four-year unadjusted survivals for patients with and without significant RAS were 57 and 89%, respectively ($P < 0.001$). Using the Cox proportional hazards model, the factors independently associated with decreased survival were the presence of RAS, increased age, the severity of coronary artery disease, the presence of comorbid disease, reduced ejection fraction, symptoms of congestive cardiac failure, and the mode of treatment of coronary artery disease. In the multivariate model, the presence of RAS conferred a hazard ratio of 2.01 (95% CI, 1.51 to 2.67, $P < 0.001$). We demonstrated an incremental effect on mortality according to the severity of RAS at baseline. Four-year adjusted survival for patients with 50%, 75%, and ≥95% stenosis was 70%, 68%, and 48%, respectively. In addition, bilateral disease was associated with four-year survival of 47% as compared with 59% for patients with unilateral disease ($P < 0.001$). The impact of RAS on survival remained robust regardless of the manner of treatment of coronary artery disease [that is, medical, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass graft (CABG)].

Conclusions. In this patient population, the presence of RAS is a strong independent predictor of mortality. Increasing severity of RAS has an incremental effect on survival probability.

Key words: renovascular disease, death, CABG, coronary angiography, CAD, arterial stenosis, end-stage renal disease, chronic renal failure.

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Renal artery stenosis (RAS) is emerging as a common and frequently unsuspected cause of chronic renal failure and end-stage renal disease (ESRD) [1, 2]. The vast majority of cases in the expanding older population are due to atherosclerotic disease, usually in the presence of widespread disease affecting the coronary vessels, cerebrovasculature, and/or the vessels supplying the lower limbs [3, 4]. In recent years, abdominal aortography at the time of coronary angiography has been used to study the prevalence of RAS [5]. Using this technique, incidental RAS has been discovered in 15 to 20% of patients. In patient groups undergoing aortography at the time of lower limb angiography, the prevalence has been reported as 14 to 35% [6]. Progression in the severity of luminal narrowing is known to occur in 9 to 16% of cases, this being more likely to occur when the stenosis is ≥75% [7]. The proportion of patients with ESRD attributable to atherosclerotic RAS has been reported as between 5 and 15%, a number that has risen substantially in recent years [8].

We have previously studied the prevalence of RAS using an abdominal aortogram at the time of coronary angiography, with RAS being defined as a 50% or greater luminal narrowing [5, 9]. Our previous studies have defined the presence of RAS as a luminal narrowing of 50% or greater on abdominal aortography. We have now extended these observations to include a larger patient population and employed the more rigorous definition of RAS of 75% luminal narrowing on aortography. In addition, patients were stratified as to their treatment of coronary artery disease (CAD).

METHODS

Patient population

Over the course of 78 months, 7758 patients underwent elective diagnostic cardiac catheterization. Of these, 3987 were screened for the presence of renal artery disease through the use of single-plane abdominal aortography. Demographic data, medical history, physical findings, and blood chemistries were entered prospectively into

a database before the catheterization was performed. Peripheral vascular disease was defined as a history of claudication, previous vascular procedure, and/or physical examination evidence of femoral or abdominal bruit. Cerebrovascular disease was defined as a history of stroke or transient ischemic attack and/or carotid bruit on examination. Congestive heart failure symptoms were classified according to the New York Heart Association criteria. Hypercholesterolemia and hypertension were respectively defined as a total cholesterol of >5.5 mmol/L and diastolic BP >90 mm Hg or the use of antihypertensive medications before catheterization.

Angiographic methods

Coronary angiography was performed via the femoral artery approach using the Judkins technique. Coronary artery lesions graded as ≥75% luminal narrowing were classified as significant. For the purposes of survival analysis, the severity of CAD was graded according to the CAD Prognostic Index. After left ventriculography, the pigtail catheter was withdrawn into the abdominal aorta and positioned a few centimeters caudal to the renal arteries. Aortography was performed in the anterior–posterior projection with nonionic contrast, power-injected at a rate of 20 mL/min to a total of 30 to 40 mL. The injection was recorded on cine film at 30 frames per second.

Aortographic analysis

Aortograms were reviewed by a single observer who was blinded to the clinical information. Narrowing of the luminal diameter of a major renal artery was quantified as <25%, 25 to 49%, 50 to 74%, 75 to 94%, 95 to 99%, and 100% and as bilateral or unilateral. Because of the difficulty in assessing minor degrees of arterial narrowing, patients with normal renal arteries or any degree of luminal narrowing <50 were included with the <50% group. For survival purposes, RAS was considered significant if there was ≥75% luminal narrowing. Accessory renal arteries were classified as major if it was estimated that they supplied more than one third of the renal mass. Lesion location was defined as ostial, main artery (>2 cm beyond the ostial segment), or branch vessel (beyond the first bifurcation of the renal artery). Patients were considered to have bilateral disease if they had 75% luminal narrowing in both renal arteries. Stenotic lesions were designated as athereosclerotic if they did not manifest the distinctive "string-of-beads" appearance characteristic of fibromuscular hyperplasia. No complications related to the aortogram were observed.

Follow-up

All patients were followed prospectively using the Duke Databank for Cardiovascular Disease for a median of 3.2 years. Follow-up information was collected using mailed questionnaires six months, one year, and annually thereafter. Patients who did not respond were contacted by telephone by trained interviewers. Data were recorded regarding survival status, the development of cardiac events and admission to hospital.

Statistical analysis

All categorical factors are described as number and percentage of patients with the factor. All continuous measures are described with median as the measure of central tendency, with 25th and 75th percentiles included for measures of variability.

Comparisons of binary factors with the occurrence of a renal arteriogram and with the presence of significant RAS were made using likelihood ratio chi-square statistics. For categorical and continuous factors, Wilcoxon rank-sum tests were used.

Cox proportional hazards regression modeling techniques were used in evaluating the prognostic significance of the factors of interest. A long-term clinical and catheterization survival model developed previously by Mark et al used similar inclusion criteria [10]. The variables from that model were used as covariates in the adjusted survival models.

As has been shown previously, the adjusted mortality is worse initially with coronary artery bypass graft (CABG) from the procedural deaths [11]. However, for the patients who survive the procedure, adjusted mortality is better for CABG patients. As we were interested in the effect of RAS on long-term survival, patients were considered to be in the CABG or percutaneous transluminal coronary angioplasty (PTCA) treatment arms if the therapeutic procedure was performed within 30 days of catheterization. If they received both within the first 30 days, they were assigned to the treatment that they received first. If neither was used within the first 30 days, they were assigned to the medically treated arm. Initiation into the study began 30 days after the time of the procedure for the CABG and PTCA arms. It began 30 days after catheterization for the medical arm. In this way, all early "in-hospital" deaths were equally excluded for all three arms.

Univariable analyses of RAS, bilateral renal disease, and creatinine levels were performed first. RAS, creatinine levels, and the interactions of RAS with treatment, CAD disease, and creatinine were added to the previously developed clinical and catheterization model using Cox proportional hazards techniques. Backward variable selection techniques were used to determine which of the additional renal variables and interactions added prognostically significant information.

The unadjusted survival for the RAS subgroups are illustrated using Kaplan-Meier survival curves. In the adjusted plots, survival estimates are calculated for the average patient in this study using the clinical and catheterization model plus renal stenosis, creatinine, and the interactions of renal stenosis with procedural treatment and CAD disease.

Table 1. Baseline characteristics of the patient population according to whether or not they underwent aortographic screening for renal artery stenosis (RAS)

		Renal arteriogram		
	N	No (*N* = 3771)	Yes (*N* = 3987)	*P* value (*N* = 7758)
Male	7758	65 (2462)	69 (2752)	<0.001
Age	7758	51/61/69	52/61/69	0.685
Canadian Heart class				
0	5289	13 (355)	12 (308)	<0.001
1		1 (33)	2 (50)	
2		10 (274)	26 (643)	
3		17 (470)	15 (367)	
4		41 (1170)	32 (784)	
5		18 (521)	13 (314)	
Smoker	7758	67 (2523)	67 (2675)	0.860
Hypertension	7758	55 (2076)	58 (2296)	0.024
Hyperlipidemia	7758	49 (1864)	52 (2074)	0.023
History of MI	7758	46 (1733)	53 (2111)	<0.001
CHF	7737	13 (473)	14 (568)	0.029
CHF (NYHA)				
0	7733	88 (3306)	87 (3440)	0.057
1		1 (23)	1 (37)	
2		2 (92)	3 (122)	
3		3 (112)	3 (119)	
4		3 (104)	2 (99)	
5		3 (120)	4 (159)	
Serum creatinine *mg/L*	4708	0.9 /1.1 /1.3	0.9 / 1.0 /1.2	<0.001

Values are given as % (number) and median with 25th, 75th percentiles. Abbreviations are: MI, myocardial infarction; CHF, chronic heart failure; NYHA, New York Heart Association.

RESULTS

There were several significant differences in the baseline variables (Tables 1 and 2) between those patients who underwent aortography ($N = 3987$) and those who did not ($N = 3771$). Patients were less likely to undergo an aortogram if they had severe anginal symptoms, a low ejection fraction, raised serum creatinine, or a history of congestive heart failure. On the other hand, patients were more likely to undergo aortography if advanced coronary disease was found at the time of coronary angiography.

One hundred ninety-one (4.8%) of the patients with renal arteriograms had renal artery luminal narrowing of ≥75% (Table 3). Bilateral disease was present in 33 patients (0.8%). Patients with renal stenosis were at higher risk of cardiovascular disease than were those with less significant or no renal stenosis (Tables 4 and 5). These patients were more often female, older, more hypertensive, more likely to have chronic heart failure (CHF), had higher serum creatinine, and more extensive coronary disease. Percutaneous coronary interventions were more prevalent in the patients with <75% than those with ≥75% renal stenosis (37% vs. 19%). CABG and no interventional therapy occurred more often in those with increased renal stenosis (39% vs. 31% and 41% vs. 32%, respectively).

Patient survival

The unadjusted survival probability, according to the presence or absence of ≥75% RAS, is depicted in Figure 1. The four-year survival of patients with and without significant RAS was 57 and 89%, respectively. The variables found to be associated with increased mortality in the previously developed Cox proportional hazards model [10] as well as the significant renal factors are summarized in Table 6. The interactions of RAS and of serum creatinine with procedural treatment of CAD were not statistically significant. Thus, the effects of RAS and creatinine on outcome were not found to have changed according to the mode of treatment of CAD or the severity of disease.

The presence of significant RAS, increased age, the severity of CAD, the presence of co-morbid disease, reduced ejection fraction, symptoms of congestive cardiac failure, and the mode of treatment of coronary disease were all independently associated with reduced survival in this study. Gender and mitral regurgitation were no longer statistically significant ($P = 0.504$ and $P = 0.785$, respectively) in the multivariate model. The finding of increased mortality in the presence of significant RAS remained robust regardless of whether CAD was treated medically, with PTCA or CABG (Figs. 2 and 3). In the multivariate model, RAS conferred a hazard ratio for death of 2.01 (95% CI, 1.51 to 2.67, $P < 0.001$).

There was an incremental effect on mortality with respect to the severity of RAS. Four-year survival in patients with 50 to 75%, 75 to 95%, and >95% was 70%, 68%, and 48%, respectively (Fig. 4). Patients with significant unilateral RAS had a four-year survival of 59%, while those with significant bilateral disease had a four-year survival probability of 47% (Fig. 5).

DISCUSSION

This study of a large cohort of patients undergoing abdominal aortography at the time of coronary angiography provides a number of observations. First, we have confirmed the frequent association of significant RAS with patients with underlying coronary disease. Second, we demonstrated that the presence of asymptomatic RAS is associated with a profound effect on long-term survival, regardless of the method of treatment of coronary disease.

This study notes a number of important differences from our previous studies (although the current study includes patients from our earlier work [5], they are in addition many more in this cohort) in which RAS was defined as 50% or greater luminal narrowing. In particular, these earlier reports did not demonstrate an association between 50% luminal narrowing and the presence of hypertension. Using the more stringent definition of 75% luminal narrowing, hypertension is strongly associ-

Table 2. Severity of coronary artery disease (CAD) according to whether or not the patient underwent aortographic screening for renal artery stenosis (RAS)

		Renal angiogram		
	N	No (*N* = 3771)	Yes (*N* = 3987)	*P* value (*N* = 7758)
Number of vessels	7758			
1 VD		61 (2288)	43 (1711)	<0.001
2 VD		27 (1013)	30 (1183)	
3 VD		12 (470)	27 (1093)	
LAD disease (≥75%): Yes	6442	79 (1954)	68 (2716)	<0.001
CAD index	7758			
1 VD ≥75%		12 (448)	11 (426)	<0.001
1 VD ≥95%		42 (1580)	28 (1097)	
2 VD		14 (535)	10 (405)	
2 VD, 2 severe		2 (92)	5 (180)	
1 VD, ≥95% proximal LAD, or 2 VD, ≥95% LAD		14 (534)	16 (632)	
2 VD, ≥95% proximal LAD, or 3 VD		3 (128)	4 (174)	
3 VD, 1 severe		8 (317)	18 (728)	
3 VD, ≥75% proximal LAD		2 (60)	4 (152)	
3 VD, ≥95% proximal LAD		2 (77)	5 (193)	
Ejection fraction %	5220	38/49/60	46/56/64	<0.001

Values are expressed as % (number) and median with 25th and 75th percentiles. Abbreviations are: VD, vessel disease; LAD, left anterior descending artery.

Table 3. Breakdown of patient numbers according to severity of renal artery stenosis (RAS) (*N* = 3987)

Degree of stenosis	No. of patients	Proportion of all patients undergoing aortography
<50%	3625	90.9%
50–75%	171	4.3%
75–95%	99	2.5%
95–99%	75	1.9%
Total occlusion	17	0.4%
Bilateral disease	33	0.8%

Table 4. Baseline characteristics of the patient population according to the presence or absence of significant renal artery stenosis (RAS)

		Renal stenosis		
	N	<75% (*N* = 3796)	≥75% (*N* = 191)	*P* value (*N* = 3987)
Male	3987	70 (2662)	47 (90)	<0.001
Age	3987	51/60/69	63/70/76	<0.001
Canadian Heart class	2466			
0		12 (288)	16 (20)	0.095
1		2 (50)	0 (0)	
2		27 (623)	16 (20)	
3		15 (345)	17 (22)	
4		32 (743)	33 (41)	
5		12 (291)	18 (23)	
Smoker	3987	67 (2547)	67 (128)	0.981
Hypertension	3987	57 (2150)	76 (146)	<0.001
Hyperlipidemia	3987	52 (1984)	47 (90)	0.165
History of MI	3987	53 (2019)	48 (92)	0.175
CHF	3978	13 (500)	36 (68)	<0.001
CHF (NYHA)	3976			
0		88 (3314)	66 (126)	<0.001
1		1 (34)	2 (3)	
2		3 (112)	5 (10)	
3		3 (100)	10 (19)	
4		2 (86)	7 (13)	
5		4 (139)	10 (20)	
Serum creatinine *mg/L*	3304	0.9/1.0/1.2	1.0/1.2/1.5	<0.001

Values are given as % (number) or median with 25th, 75th percentiles. Abbreviations are: MI, myocardial infarction; CHF, chronic heart failure; NYHA, New York Heart Association.

ated and probably reflects the greater hemodynamic significance of 75% luminal narrowing. We also controlled for the mode of treatment of CAD, a factor that has a large impact on overall mortality. Additionally, our current study found that increasing the severity of RAS was independently associated with an incremental increase in all-cause mortality. Survival after four years varied from 48% in patients with >95% luminal narrowing up to 90% in patients with no RAS on abdominal aortography. On the whole, significant RAS, defined as ≥75% narrowing, was associated with a four-year survival rate of 57%. Our study was not designed to examine the association between RAS and the development of ESRD, as it was not included on the data set.

Our study was performed on a select group of patients who were undergoing coronary angiography and therefore deemed to be at high risk for atherosclerotic disease. Consequently, the results may not be generally applicable to other patient groups. In addition, the likelihood of undergoing aortography at the time of coronary angiography was lower in the presence of a raised serum creatinine or severe angina, and higher when severe coronary disease was present. These factors may have affected the prevalence of RAS, although they tend to push the prevalence in opposing directions so the net effect was likely to be small.

These findings are consistent with previous studies, virtually all of which have found RAS to be an independent marker of increased mortality. In a precursor to the present study, it was found that four-year all-cause

Table 5. Severity of coronary artery disease (CAD) according to the presence or absence of significant renal artery stenosis (RAS)

		Renal stenosis		
	N	<75% (*N* = 3796)	≥75% (*N* = 191)	*P* value (*N* = 3987)
Number of vessels	3987			
1 VD		44 (1661)	26 (50)	<0.001
2 VD		29 (1119)	34 (64)	
3 VD		27 (1016)	40 (77)	
LAD disease (≥75%): Yes	3969	68 (2568)	78 (148)	0.015
CAD index	3987			
1 VD ≥75%		11 (413)	7 (13)	<0.001
1 VD ≥95%		28 (1064)	17 (33)	
2 VD		10 (382)	12 (23)	
2 VD, 2 severe		5 (176)	2 (4)	
1 VD, ≥95% proximal LAD, or 2 VD, ≥95% LAD		16 (595)	19 (37)	
2 VD, ≥95% proximal LAD, or 3 VD		4 (170)	2 (4)	
3 VD, 1 severe		18 (680)	25 (48)	
3 VD, ≥ 5% proximal LAD		4 (137)	8 (15)	
3 VD, ≥95% proximal LAD		5 (179)	7 (14)	
Ejection fraction %	3941	46/56/64	39/52/65	0.116

Values are expressed as % (number) or median with 25th and 75th percentiles. Abbreviations are: VD, vessel disease; LAD, left anterior descending artery.

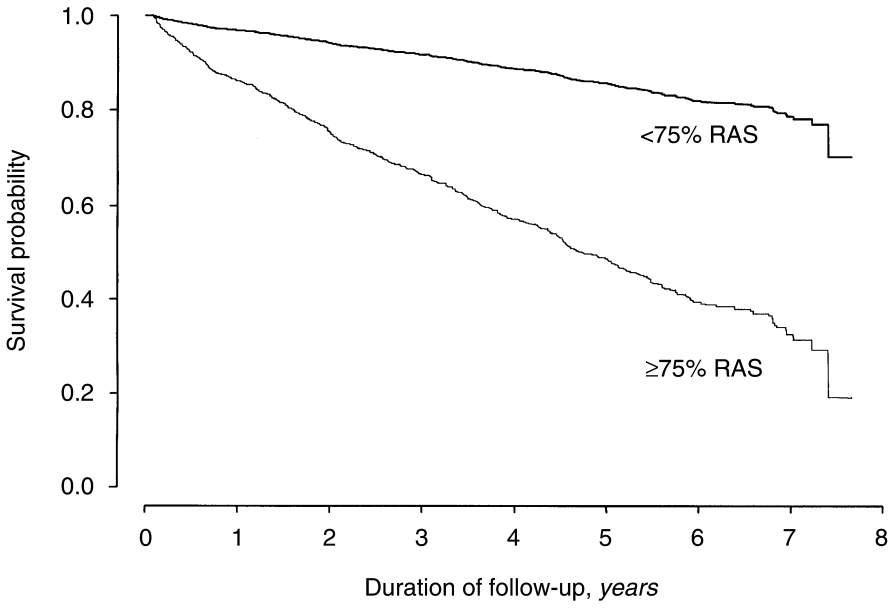

Fig. 1. Kaplan-Meier survival curve showing unadjusted survival according to the presence or absence of significant renal artery stenosis (RAS; $P < 0.001$). Symbols are: (thick line) <75% RAS; (thin line) ≥75% RAS.

Table 6. Effect of clinical- and catheterization-derived variables on mortality as assessed by the Cox proportional hazards model

Variable	Hazard ratio (95% CI)	*P* value
CAD index (63 vs. 32)	2.54 (1.68–3.85)	<0.001
≥75% RAS	2.01 (1.51–2.67)	<0.001
Age (69 years vs. 52 years)	1.99 (1.69–2.34)	<0.001
Treatment of CAD (CABG vs. medical)	0.54 (0.39–0.74)	<0.001
Treatment of CAD (PTCA vs. medical)	0.61 (0.48–0.78)	<0.001
Ejection fraction (64% vs. 46%)	0.73 (0.64–0.83)	<0.001
Presence of co-morbid illness (yes vs. no)	1.34 (1.21–1.47)	<0.001
Serum creatinine (1.2 vs. 0.9) *mg/L*	1.24 (1.14–1.34)	<0.001
CHF (V vs. 0)	1.57 (1.18–2.09)	0.002
Mitral regurgitation (yes vs. no)	1.10 (0.82–1.48)	0.504
Gender (male vs. female)	1.03 (0.84–1.25)	0.785

Abbreviations are: CAD, coronary artery disease; RAS, renal artery stenosis; CABG, coronoary artery bypass graft; PTCA, petcutaneous transliminal coronary angioplasty.

mortality in those with >50% luminal narrowing was 67% compared with 88% in those without it [9]. Our findings confirm and expand on those results. They demonstrate that the strong association of RAS and increased mortality remain robust regardless of the method of coronary revasularization. The finding of a consistent incremental increase in mortality with increasing severity of RAS strengthens the case for a true biological relationship. In addition, patients with ESRF due to ischemic nephropathy have a very high mortality rate. One study by Mailloux et al found a five-year survival rate of 18%, with a median survival after commencing dialysis of 25 months [12]. This prognosis is among the worst of all patient groups presenting with ESRF.

Valentine et al demonstrated that asymptomatic RAS was a stronger predictor of mortality following abdomi-

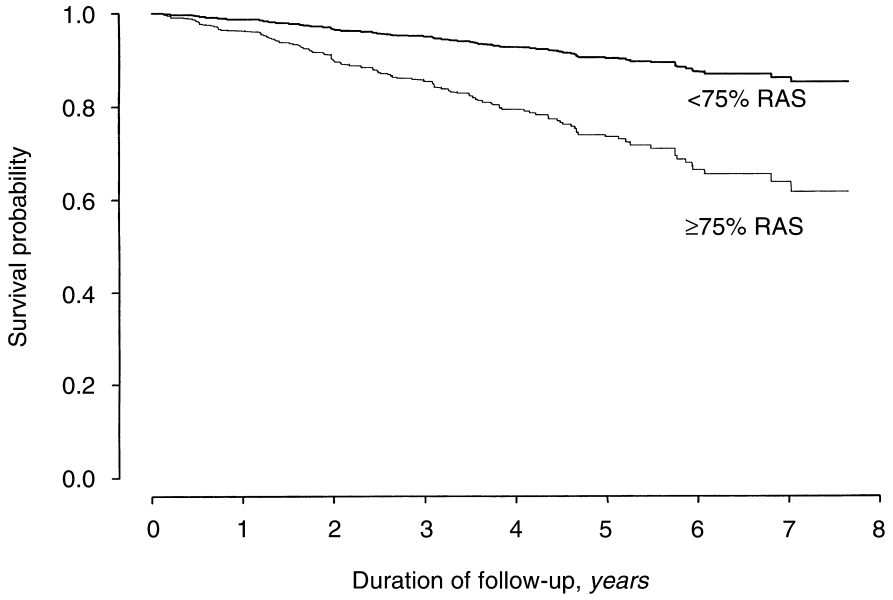

Fig. 2. Adjusted survival according to the presence or absence of significant renal artery stenosis (RAS) in patients treated with percutaneous transluminal angioplasty (PTCA) ($P < 0.001$). Symbols are: (thick line) <75% RAS; (thin line) ≥75% RAS.

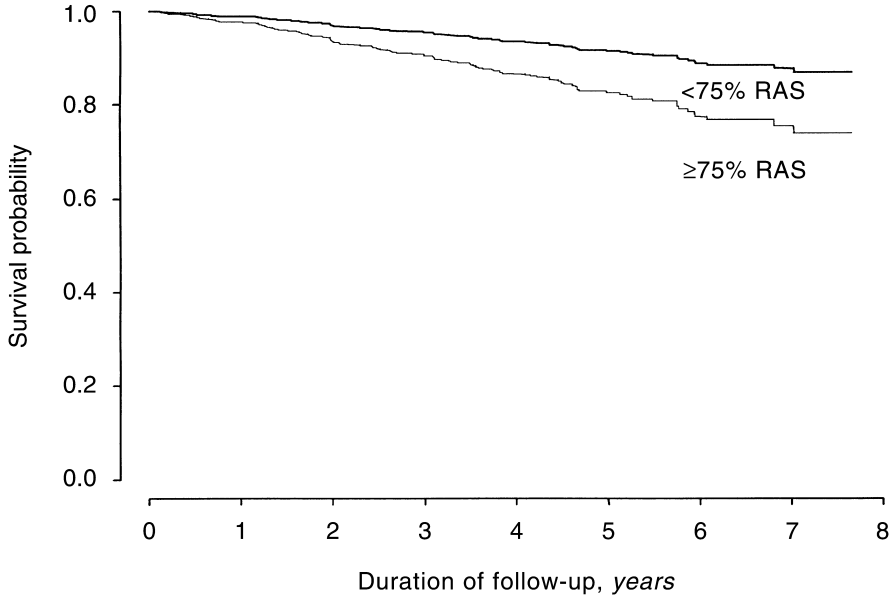

Fig. 3. Adjusted survival according to the presence or absence of significant renal artery stenosis (RAS) in patients treated with coronary artery bypass graft (CABG) ($P < 0.001$). Symbols are: (thick line) <75% RAS; (thin line) ≥75% RAS.

nal aortic surgery than clinically overt CAD [4]. In their and other similar studies, death most frequently was due to cardiovascular or cerebrovascular disease rather than renal failure [13, 14]. In addition, studies of percutaneous or surgical revascularization of ischemic kidneys have largely failed to show a clinically significant improvement in blood pressure or survival benefit [15, 16]. Consequently, there has been much debate as to the nature of the link between atherosclerotic RAS and mortality, a link that appears to be as strong as that for CAD. It is probable that unsuspected atherosclerotic RAS is a marker for aggressive atherogenesis in many vascular beds. This increased risk appears to be independent of traditional markers of progressive atherosclerosis, such as hyperlipidemia, hypertension, diabetes mellitus, and male gender [9]. The ischemic kidney is known to produce increased amounts of renin, with consequent angiotensin II production [17]. The latter is a potent vasoconstrictor and has been implicated in the activation of cell proliferation systems [18]. High levels of angiotensin II are associated with accelerated atherogenesis [19] and left ventricular hypertrophy [20]. This model is certainly too simplistic to explain fully the excess mortality in patients with RAS although it does provide a conceptual starting point from which to address the question.

From a practical point of view it seems attractive to attempt revascularization of these ischemic kidneys. As mentioned, however, the outcomes in most studies looking at this have been unimpressive with respect to both improvement in blood pressure and prevention of pro-

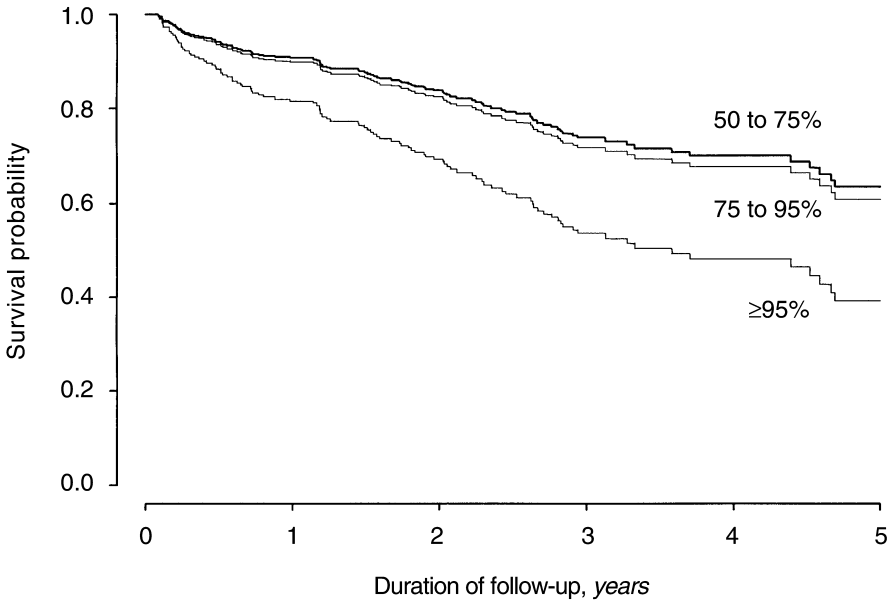

Fig. 4. Adjusted survival stratified for the severity of renal artery stenosis (RAS) ($P < 0.001$ for trend). Symbols are: (thick line) 10 to 75% RAS; (medium line) 75 to 95% RAS; (thin line) ≥95% RAS.

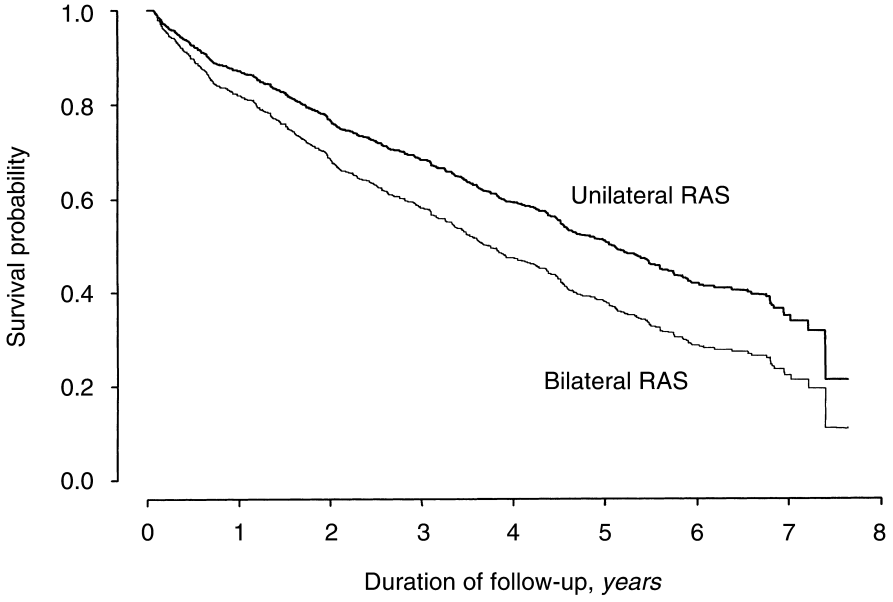

Fig. 5. Adjusted survival according to the presence of unilateral (thick line) or bilateral (thin line) renal artery stenosis (RAS) ($P < 0.001$).

gressive renal failure [21]. However, despite the lack of immediate therapeutic potential, in view of the frequent coexistence of RAS with atherosclerosis elsewhere, it would be prudent to screen for its presence in patients undergoing procedures such as coronary arteriography, peripheral vascular surgery, and carotid artery endarterectomy. This would allow identification of a subgroup with a particularly adverse prognosis for whom treatment could be tailored appropriately.

In summary, patients with RAS discovered incidentally at coronary angiography were found to have a much worse prognosis than those with no renal artery narrowing. This finding was independent of other risk factors of mortality. In addition, increasing severity of RAS incrementally increased mortality.

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