Predictors of Renal and Patient Outcomes in Atheroembolic Renal Disease: A Prospective Study

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Abstract. Atheroembolic renal disease (AERD) is part of a multisystemic disease accompanied by high cardiovascular comorbidity and mortality. Interrelationships between traditional risk factors for atherosclerosis, vascular comorbidities, precipitating factors, and markers of clinical severity of the disease in determining outcome remain poorly understood. Patients with AERD presenting to a single center between 1996 and 2002 were followed-up with prospective collection of clinical and biochemical data. The major outcomes included end-stage renal disease (ESRD) and death. Ninety-five patients were identified (81 male). AERD was iatrogenic in 87%. Mean age was 71.4 yr. Twenty-three patients (24%) developed ESRD; 36 patients (37.9%) died. Cox regression analysis showed that significant independent predictors of ESRD were long-standing hypertension (hazard ratio [HR] = 1.1; $P <$ 0.001) and preexisting chronic renal impairment (HR = 2.12;

$P = 0.02$); use of statins was independently associated with decreased risk of ESRD (HR = 0.02; $P = 0.003$). Age (HR = 1.09; $P = 0.009$), diabetes (HR = 2.55; $P = 0.034$), and ESRD (HR = 2.21; $P = 0.029$) were independent risk factors for patient mortality; male gender was independently associated with decreased risk of death (HR = 0.27; $P = 0.007$). Cardiovascular comorbidities, precipitating factors, and clinical severity of AERD had no prognostic impact on renal and patient survival. It is concluded that AERD has a strong clinical impact on patient and renal survival. The study clearly shows the importance of preexisting chronic renal impairment in determining both renal and patient outcome, this latter being mediated by the development of ESRD. The protective effect of statins on the development of ESRD should be evaluated in a prospective study.

AERD is part of a multisystemic disease caused by showers of cholesterol emboli from atherosclerotic aorta to many organs. It may occur spontaneously or more often as a complication of major medical or surgical procedures. The disease is usually associated with poor renal and patient survival. In the last decade, some clinical studies have increased our understanding of AERD, enabling us to make premortem diagnosis. The presence of a triad characterized by a precipitating event, subacute renal failure, and peripheral cholesterol embolization strongly suggests the diagnosis, which can be confirmed by the biopsy of the target organs (1–6).

Although the clinical features of the AERD have been well delineated, the predictors of the outcomes of the disease have never been studied in a large population of patients. In addition to the traditional risk factors for atherosclerosis, other factors may be associated with the outcomes, including comorbidities, precipitating factors, and clinical severity of the disease. How-

ever, the different and relative contribution of each factor is unknown. In the present study, we prospectively followed up 95 consecutive patients with diagnosis of AERD to gain insight into the interrelationship of potential predictors of both renal and patient mortality.

Materials and Methods
Patient Population
After the retrospective analysis of our first series (7), we undertook a longitudinal cohort study mainly aimed at identifying predictors of outcome in patients with AERD. Patients attending the Renal Department of Brescia, Italy, who had diagnosis of AERD from 1995 to 2002 were included in the study and prospectively followed.

Study Design
Data collection was prospective, which formed the basis of this observational study. Demographic data, risk factors for atherosclerosis, comorbidities, and exposure to precipitating factors were recorded at time of diagnosis of AERD. In all patients, serum creatinine concentration was available shortly before the precipitating event for iatrogenic forms and before the onset of symptoms for spontaneous forms; at time of diagnosis of AERD; during the course of the acute or subacute phase of disease. At follow-up clinic visits, serum creatinine concentration, clinical signs, and comorbidities were reassessed. Demographic, clinical, and biochemical data recorded at different times were entered into an electronic database after obtaining patient informed consent.

Definition of Comorbid Conditions

Comorbid conditions were evaluated at time of diagnosis of AERD. Coronary artery disease was defined as symptomatic angina, positive exercise stress-test result, positive coronary angiography, or evidence of previous myocardial infarction. Cerebrovascular disease was defined as clinical signs or radiologic confirmation of a transient ischemic attack or cerebrovascular accident. Peripheral vascular disease was defined as symptoms of intermittent claudication, previous surgery for lower-limb arterial insufficiency, and/or angiographic evidence of significant stenosis in one or more blood vessels supplying the lower limbs. Congestive heart failure was defined either as symptoms of relative pump failure, including episodes of pulmonary edema, or echocardiographic description of systolic dysfunction or cardiomegaly at chest x-ray. The presence of an abdominal aortic aneurysm or of a renal artery stenosis ($> 50\%$ in one or both renal arteries) was demonstrated by means of an angiographic examination. Patients were considered to have diabetes if they had been given either oral antidiabetic drugs or insulin. Patients were considered as smokers both in case of actual or previous smoking habit. All smokers were cigarette smokers with a consumption of more than 10 cigarettes per day and with duration of smoking of > 10 yr. Total cholesterol serum level as well as the time of exposure to the hypertensive status were available for all patients. Hypercholesterolemia was defined by presence of total cholesterol levels ≥ 220 mg/dl or by concomitant administration of statins. Hypertension was defined as systolic or diastolic BP of ≥ 140 mmHg or ≥ 90 mmHg, respectively, or if anti-hypertensive drugs had been given.

Diagnostic Criteria

Patients were considered as having iatrogenic AERD if the following criteria had been met: (1) renal function deterioration occurring in atherosclerotic patients; (2) simultaneous ischemic changes to the lower abdomen or extremities; (3) presence of one or more precipitating factors. Histologic confirmation was available for the majority of iatrogenic cases. Spontaneous form of AERD was diagnosed only when skin, gastrointestinal, or renal biopsy documented cholesterol clefts or, alternatively, when the funduscopic examination disclosed retinal emboli. Signs of central nervous system involvement, gastrointestinal symptoms, presence of eosinophilia as well as the rate of renal function deterioration were considered to evaluate the severity of the disease. Detailed description of diagnostic criteria have been reported elsewhere (2).

Definition of Renal Failure

Renal function was estimated using serum creatinine level (mg/dl) and GFR, calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) formula (8). A preexisting chronic renal impairment was defined by the presence of serum creatinine levels of ≥ 1.5 mg/dl in men and ≥ 1.3 mg/dl in women; it was also very conservatively defined as a calculated GFR ≤ 50 ml/min. With respect to the clinical presentation of AERD, renal failure was defined as acute if a sudden 50% increase of serum creatinine level was evident within 1 wk after the precipitating event; as subacute if the same amount of deterioration occurred in a stepwise fashion over 2 to 6 wk; as chronic if the patient had a stable impairment (2).

Variables of Interest and Outcome Measures

The major outcomes included end-stage renal disease (ESRD), defined as need for permanent dialysis therapy, and death. Zero time for survival analyses was the time of precipitating event for iatrogenic forms of AERD and the date of the onset of symptoms for spontane-

ous ones. The covariates considered to test the potential association with the development of ESRD and death included: (1) variables present before zero time, including traditional risk factors for atherosclerosis (age, gender, hypertension, cholesterol levels, diabetes, smoking) and comorbid conditions (coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure, abdominal aortic aneurysm, renal artery stenosis, chronic renal impairment); (2) factors acting closer to the onset of the AERD, such as exposure to one or more precipitating factors; (3) markers of clinical severity of the AERD, including degree of renal functional impairment, defined as peak serum creatinine, modality of kidney function deterioration (chronic *versus* acute and subacute renal failure), involvement of organ systems other than kidney and skin, such as gastrointestinal tract and central nervous system; (4) selected therapeutic variables including statins, which have a potentially protective effect on plaque disruption, and steroids, used for the antiinflammatory properties in a subset of patients with a short interval between the procedure and onset of the disease.

Statistical Analyses

Baseline clinical characteristics of patients were compared by using Pearson χ^2 test for categoric variables and t test or Mann-Whitney U test for continuous variables, as appropriate. Logistic regression analysis was planned to determine the independent association between the above-mentioned covariates with the development of ESRD. The Kaplan-Meier product-limit technique was used to describe patient and renal survival, and the log-rank statistics to test equality for strata. Patients were censored if dialysis free or alive on the final observation time (December 31, 2002). Cox proportional hazards regression models were planned to assess the independent effect of each factor on the instantaneous probability of ESRD or death. Patients were censored as in the descriptive analyses. The proportionality of the covariates was evaluated using log minus log plots. All multivariate models were developed by using both forward and backward elimination techniques, including traditional risk factors for atherosclerosis, comorbidities, exposure to precipitating events, and markers of clinical severity of the AERD. In the final models, all covariates were considered for controlling the effect of significant independent variables. Estimated relative risks along with corresponding 95% confidence limits and results of two-tailed likelihood ratio test of association are reported for all regression covariates. $P < 0.05$ for two-sided tests were considered statistically significant. All calculations were made using a standard statistical package (SPSS version 11; SPSS Inc., Chicago, IL).

Results

Baseline Characteristics

From 1995 to 2002, AERD was diagnosed in 95 patients (mean age, 71.4 yr; SD, 7.3; median, 71.7 yr; IQR, 67.1 to 76.5 yr) who were subsequently followed-up by the renal unit at Brescia Hospital. The population included 81 men (85%). In the 87 hypertensive patients (91.6%), the mean number of years of exposure to hypertension were 10 (SD, 9 yr), with a median of 7 yr (IQR, 4 to 15 yr). The mean total cholesterol levels were 217 mg/dl (SD, 53 mg/dl); hypercholesterolemia was found in 38 patients (40%), and 23 (24%) were on statin treatment. Excluding hypertension, any cardiovascular disease was present in 90% of the patients, and 14.7% were had diabetes ($n = 14$). AERD was spontaneous in 12 patients (13%). Of 83 patients with iatrogenic form, 29% had a single

precipitating factor, 44% had two precipitating factors, and 14% had three precipitating factors. The most common precipitating factor was angiography via the femoral artery (77.9%). The diagnosis was clinical in 21 patients (22%); 72 patients (76%) had histologically proven diagnosis (skin biopsy, 58 patients; renal biopsy, 5 patients; gastrointestinal biopsy, 4 patients; nephrectomy, 2 patients; autopsy, 2 patients; bone marrow biopsy, 1 patient); in 2 patients (2%), the diagnosis was confirmed by the only finding of retinal emboli. Demographic and clinical characteristics of the 95 patients are summarized in Table 1.

Table 1. Baseline patient characteristics, risk factors, and clinical findings[a]

Demographics and comorbidities	
age (yr)	71.4 ± 7.3
male	81 (85%)
hypertension	87 (91%)
smokers	78 (82%)
diabetes	14 (15%)
hypercholesterolemia	38 (40%)
statin treatment	23 (24%)
coronary artery disease	69 (73%)
peripheral vascular disease	51 (54%)
cerebrovascular disease	35 (37%)
abdominal aorta aneurysm	40 (42%)
congestive heart failure	30 (32%)
chronic renal failure	57 (60%)
renal artery stenosis	27 (28%)
cardiovascular disease (excluding HTN)	86 (90.5%)
Precipitating factors	
angiography	74 (78%)
PTCA	24 (25%)
cardiovascular surgery	15 (16%)
anticoagulation/fibrinolysis	31 (33%)
Clinical presentation	
iatrogenic forms	83 (87%)
acute renal failure	33 (35%)
subacute renal failure	44 (46%)
chronic renal failure	18 (19%)
cutaneous findings	82 (86%)
extrarenal (CNS and/or GIT)	24 (25.3%)
neurological changes	5 (5%)
gastrointestinal changes	12 (13%)
retinal emboli	10 (11%)
eosinophilia (>500)	72 (76%)
steroids	14 (15%)
Diagnosis	
clinical	21 (22%)
histologically proven	72 (76%)
retinal emboli	2 (2%)

[a] Variable values expressed as mean ± SD and N (%), as appropriate.

Renal Function

Mean serum creatinine concentration shortly before the precipitating event or before the onset of disease (in spontaneous forms) was 1.77 mg/dl (SD, 0.77 mg/dl; median, 1.5 mg/dl; IQR, 1.2 to 2.0 mg/dl). The mean estimated GFR was 46.3 ml/min (SD, 18.6 ml/min; median, 45.4 ml/min; IQR, 30.4 to 63.5 ml/min). At that time, chronic renal impairment, based on abnormal serum creatinine, was present in 57 patients (60%); 55 patients (58%) had an estimated GFR lower than 50 ml/min. At the time of diagnosis, mean serum creatinine concentration was 3.77 mg/dl (SD, 1.7 mg/dl; median, 3.5 mg/dl; IQR, 2.4 to 4.6 mg/dl). The mean peak serum creatinine was 5.84 mg/dl (SD, 2.8 mg/dl; median, 5.1 mg/dl; IQR, 3.7 to 7.7 mg/dl), corresponding to a mean estimated GFR of 14 ml/min (SD, 13.3 ml/min; median, 10.1 ml/min; IQR, 6.8 to 17.5 ml/min). Thirty-five patients (37%) required dialysis therapy. The treatment modality for the majority of the patients was hemodialysis (23 patients; 66%); peritoneal dialysis was preferred in 12 patients. Twenty-one patients remained on maintenance dialysis therapy, and 14 recovered sufficient renal function to stop dialysis. Because of declining in renal function during follow-up, two additional patients required maintenance dialysis.

Renal Survival

A final diagnosis of ESRD was made for 23 patients (24%). These patients were more likely to have an abnormal basal serum creatinine (34 *versus* 10%; $P = 0.011$) and renal artery stenosis (40.7 *versus* 19.6%; $P = 0.045$) and were less likely to be under statin treatment (4.3 *versus* 30.6%; $P = 0.011$). Patients who reached ESRD had significantly lower GFR at baseline, being the median values (IQR) 33.7 (15.4) *versus* 49.8 (30.6) ml/min (rank sum $P = 0.003$; arithmetic mean difference, 12.9 ml/min; 95% CI, 5.3 to 20.5 ml/min; $P = 0.001$). Furthermore, they had a significantly longer history of arterial hypertension, being the median values (IQR) 10 (14) *versus* 5.5 (7) yr (rank sum $P = 0.008$; arithmetic mean difference 5.5 yr; 95% CI, 1.1 to 9.7 yr; $P = 0.013$). Logistic regression showed that preexisting chronic renal impairment, evaluated using both serum creatinine levels and GFR, and the years of exposure to hypertension significantly predicted ESRD, independently of all the other confounders (gender, presence of diabetes, and the other comorbidities). We then manually added each variable of interest (precipitating factors, use of steroids and statins, and markers of clinical severity of AERD) to test if they improved the model fit. Only the use of statins was retained in the final model (OR, 0.01; $P = 0.01$). The same results were obtained considering peak serum creatinine instead of the preexisting chronic renal impairment (Figure 1). The results were also confirmed considering time to event by both univariable analysis and multivariable modeling. At univariable analysis, patients with preexisting chronic renal impairment (0.68 *versus* 0.90; $P = 0.0005$), presence of renal artery stenosis (0.61 *versus* 0.82; $P = 0.0259$), and those who were not given statins (0.74 *versus* 0.94; $P = 0.0192$) had a significantly lower 1-yr cumulative survival. The hazard for ESRD was increased by 8.6% per each year of previous exposure to arterial hypertension, 82.8% per each mg/dl of serum creatinine increase, while the use of statins conferred a significant protective effect, reducing the hazard ratio

(HR) to 0.031%. The presence of renal artery stenosis was associated with a marginally significant increased risk of chronic dialysis. Figure 2 graphically depicts the HR for ESRD, adjusted for gender, age, diabetes, comorbidities, use of steroids, precipitating factors, and markers of clinical severity of AERD. When the peak serum creatinine (or the worse estimated GFR) was introduced in the equation, this independent variable was the only covariate retained in the model (adjusted HR associated with each mg/dl of worse serum creatinine, 1.48; 95% CI, 1.23 to 1.80; $P <$ 0.001).

Patient Survival

The mean follow-up of the cohort as a whole was 61.53 mo (95% CI, 48.28 to 74.78 mo), with a median survival of 49.05 mo (95% CI, 29.25 to 68.86 mo) and 487 patient-years at risk. During the study, 36 patients (37.9%) died, and 59 patients remained under active follow-up (7 event % patient-years at risk). Of 36 patients who died, cause of death was ascertained for 32 patients. Cardiovascular disease was the main cause of mortality, accounting for 26 deaths (72%); 19 patients (52.7%) died as a result of cardiac causes (myocardial infarction, 11 patients; arrhythmia, 3 patients; heart failure, 3 patients; sudden death, 3 patients) and 7 (19.4%) due to vascular causes (stroke, 3 patients; atheroembolic intestinal infarction, 4 patients). Other causes of death in the study cohort were cachexia (2 patients), infection (1 patient), acute severe pancreatitis (1 patient), malignancy (2 patients). One-year cumulative survival was significantly longer in men than in women (0.86 *versus* 0.52; $P = 0.0036$) and in patients without preexisting chronic renal impairment (0.91 *versus* 0.76; $P = 0.0003$) (Figure 3). Conversely, shorter survival was borderline associated with a history of diabetes (0.6 *versus* 0.86; $P = 0.0650$) and heart

failure (0.75 *versus* 0.85; $P = 0.0441$) and significantly associated with the development of ESRD (0.61 *versus* 0.88; $P = 0.0342$). A beneficial effect of statins was also observed on patient survival, although not statistically significant (0.9 *versus* 0.81; $P = 0.102$). In the Cox regression model, only gender, age, and diabetes were retained. Precipitating factors and markers of clinical severity of AERD did not significantly improve the model fit when added. Conversely, the development of ESRD was independently associated with more than doubling the risk of death (Figure 4). Even considering the peak serum creatinine (or the worse GFR estimate), the final equation did not change.

Discussion

There have been few studies of outcomes in patients with AERD (2,3,6). They are all retrospective and do not resolve the confusing relationships among traditional risk factors for atherosclerosis, vascular comorbidities, and severity of AERD in determining renal and patient outcome. Our study is the first prospective study addressing this issue and provides important insights into the likelihood of renal and patient mortality in patients with AERD.

With respect to the ESRD outcome, the key findings were threefold. First, preexisting chronic renal impairment was the chief variable independently associated with increased probability of ESRD. The association of preexisting chronic renal impairment with ESRD outcome in AERD patients is not surprising, because the presence of renal dysfunction at disease diagnosis is usually a predictor of poor renal outcome in all renal diseases. In patients developing AERD, the preexisting renal impairment is usually due to ischemic atherosclerotic nephropathy, which frequently co-clusters with AERD (9).
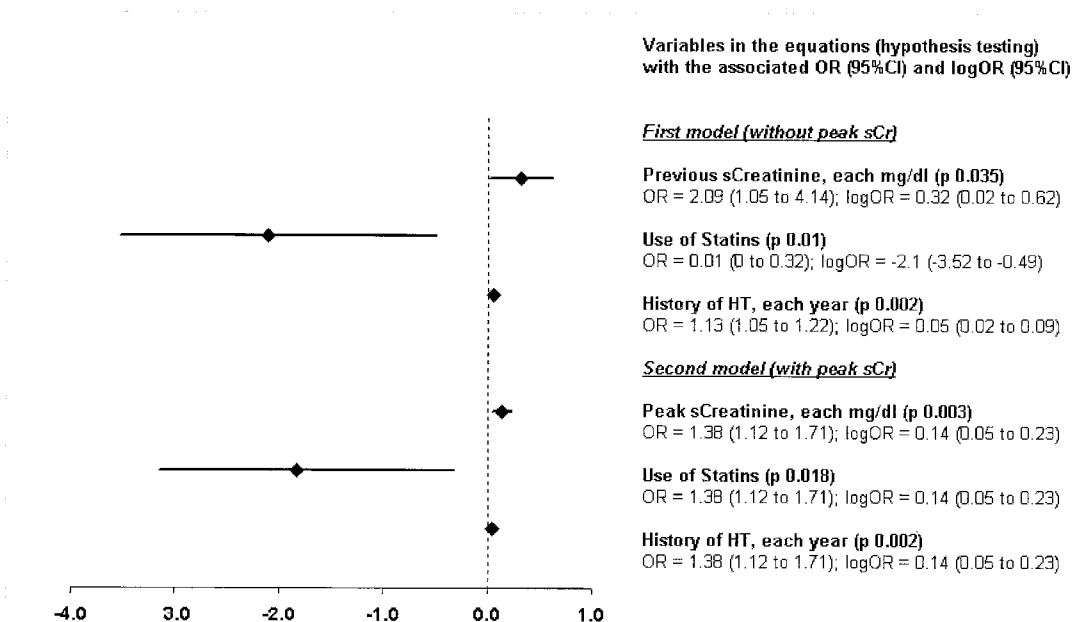

Figure 1. Logistic regression models: odds ratios (OR) for ESRD adjusted for age, gender, smoking, cholesterol, comorbidities (heart failure, diabetes, vascular diseases), eosinophilia, precipitating factors, markers of clinical severity, and use of steroids.

This was confirmed in our study, where a number of patients (28%) had renal artery stenosis. Of note, renal artery stenosis was associated with an increased, although NS, risk of developing ESRD. Of interest, the second important finding of our study was that long-standing hypertension exerted a significant, negative effect on ESRD outcome. The deleterious impact of each 10 yr of hypertension was comparable to that of each mg/dl higher basal serum creatinine level. The adverse effect of hypertension, a key factor affecting progression of renal dysfunction in all chronic renal diseases (10), reinforces the importance of the preexisting intrarenal vascular damage in determining ESRD outcome. These findings seem to support the view that the preexisting intrarenal vascular parenchymal damage is the arbiter of renal outcome in patients developing AERD. We can hypothesize that cholesterol embolic event acts as a "second ischemic hit," aggravating the preexisting intrarenal vascular lesions and contributing to the development of ESRD on ischemic grounds.

The third major finding was a protective benefit of statins, because patients on statin treatment had a significant lower risk for developing ESRD. To date, the role of statins in AERD remains uncertain, because only occasional cases have responded to lovastatin and simvastatin (11,12). Because deterioration in renal function over several weeks observed in the majority of patients with AERD suggests an ongoing embolic process, strategies should be developed to stabilize ulcerated atherosclerotic plaques showering cholesterol emboli into renal circulation. Recent studies have demonstrated that statins possess, beyond cholesterol-lowering, antiinflammatory, and immunomodulatory properties,

which may contribute to plaque stabilization (13). We might speculate that the beneficial effects observed with statin treatment in our patients could be explained in the context of the emerging evidence of statin-induced plaque stabilization and regression (14,15).

Historically, patients with AERD are considered to have a dismal outlook (1,2). An aggressive therapeutic approach, however, with patient-tailored supportive measures, may be associated with a more favorable clinical outcome (3). In our study, the 1-yr and 2-yr patient survival rates were 82% and 73%, respectively. The major cause of death was cardiovascular. This was not surprising, considering the atherosclerotic background of these patients. Most patients died from traditional cardiovascular events usually injuring the elderly atherosclerotic patients. In a minority of patients, however, cause of death was gastrointestinal ischemia, which occurred as a direct consequence of disseminated microvascular obstruction by cholesterol crystals. The proportional hazard analyses identified age, female gender, diabetes, and ESRD as the most salient predictors of death. As expected, older age and diabetes, which are well-recognized risk factors for atherosclerosis, were associated with increased risk of death. However, the relationship between female gender and patient mortality was an unexpected finding, because male gender is one of the traditional markers of complicated atherosclerosis. The implication of this finding, however, needs to be tempered by the small number of female patients enrolled in the study. Undoubtedly, the most important finding was the independent role of ESRD as a strong predictor of mortality, being associated with a more than doubled risk of death. In the present cohort, its effect was
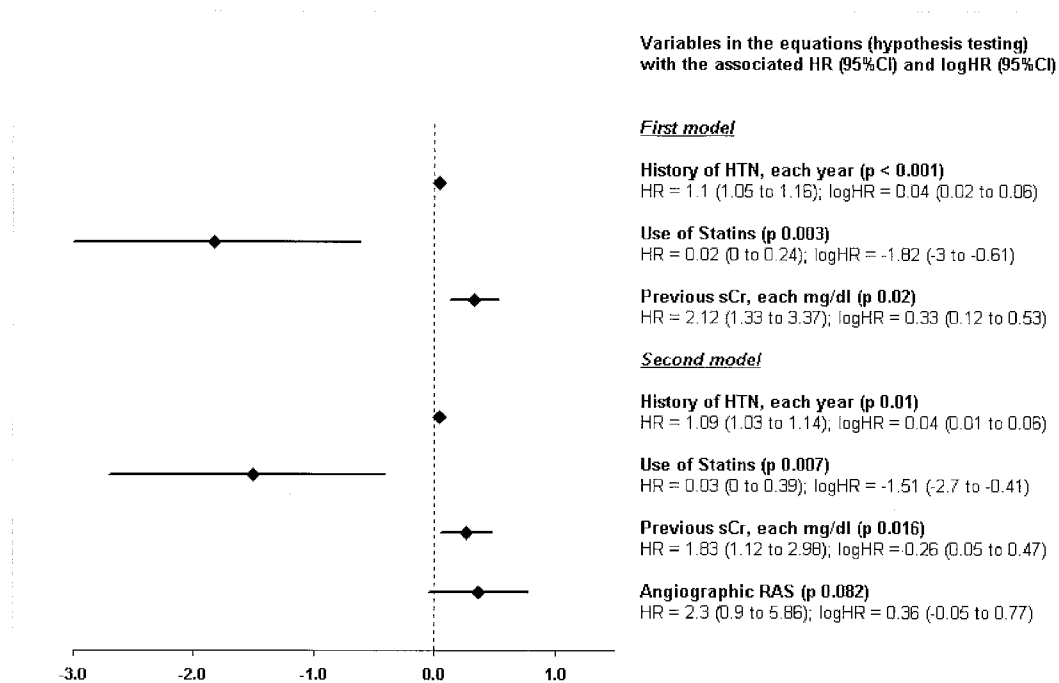

Variables in the equations (hypothesis testing)
with the associated HR (95%CI) and logHR (95%CI)

First model

History of HTN, each year (p < 0.001)
HR = 1.1 (1.05 to 1.16); logHR = 0.04 (0.02 to 0.06)

Use of Statins (p 0.003)
HR = 0.02 (0 to 0.24); logHR = -1.82 (-3 to -0.61)

Previous sCr, each mg/dl (p 0.02)
HR = 2.12 (1.33 to 3.37); logHR = 0.33 (0.12 to 0.53)

Second model

History of HTN, each year (p 0.01)
HR = 1.09 (1.03 to 1.14); logHR = 0.04 (0.01 to 0.06)

Use of Statins (p 0.007)
HR = 0.03 (0 to 0.39); logHR = -1.51 (-2.7 to -0.41)

Previous sCr, each mg/dl (p 0.016)
HR = 1.83 (1.12 to 2.98); logHR = 0.26 (0.05 to 0.47)

Angiographic RAS (p 0.082)
HR = 2.3 (0.9 to 5.86); logHR = 0.36 (-0.05 to 0.77)

Figure 2. Cox proportional hazards regression models: hazards ratios (HR) for ESRD adjusted for age, gender, smoking, cholesterol, comorbidities (heart failure, diabetes, vascular diseases), eosinophilia, precipitating factors, markers of clinical severity, and use of steroids.
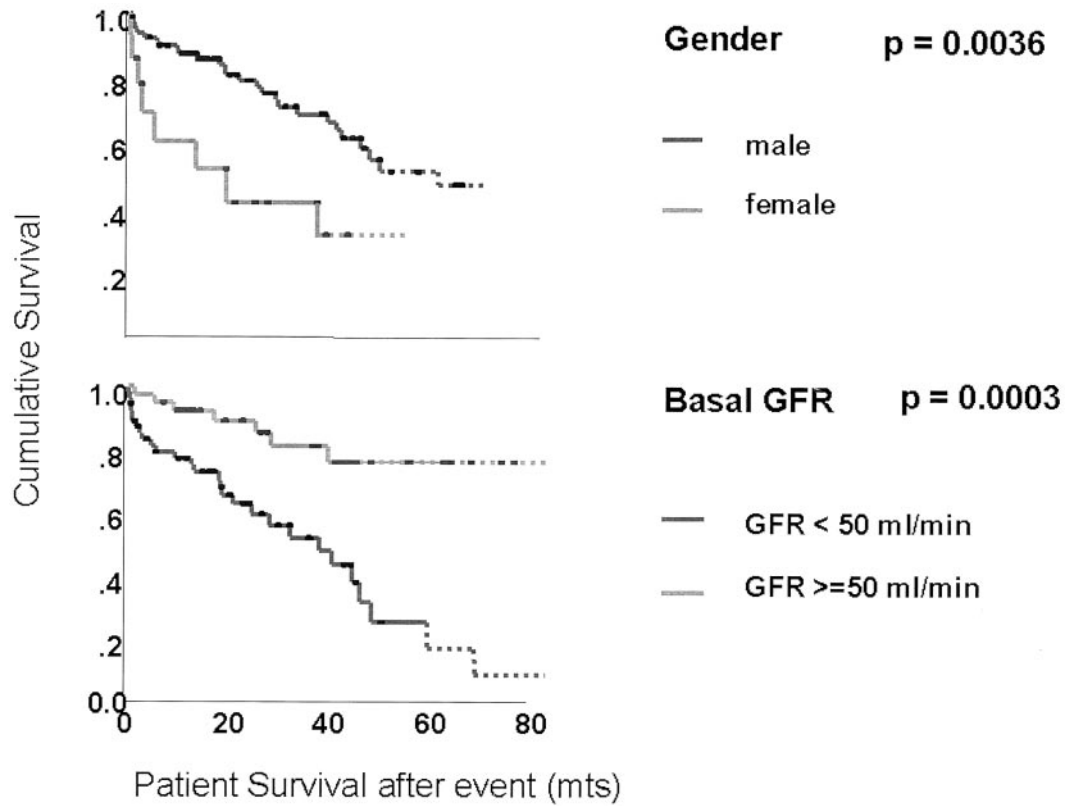
Figure 3. Crude survival plots by gender and preexisting chronic renal impairment. Crosses mark points of censor.
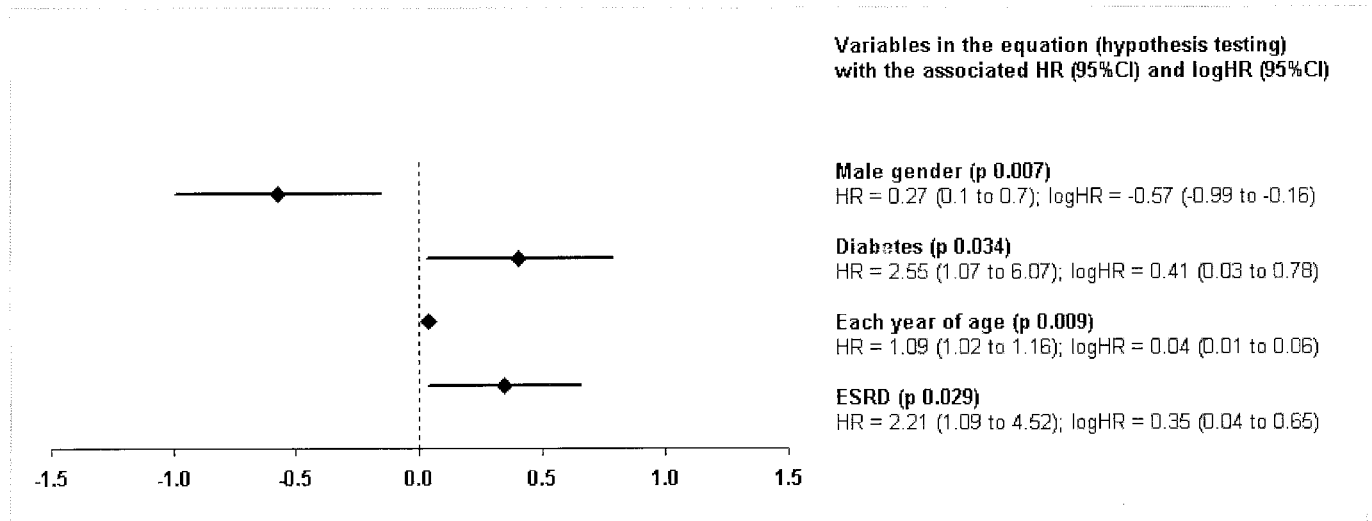

Figure 4. Cox proportional hazards regression models: hazards ratios (HR) for death adjusted for hypertension, smoking, cholesterol, comorbidities (heart failure, vascular diseases), eosinophilia, precipitating factors, markers of clinical severity, and use of statins and steroids.

similar to that of diabetes and of 12 yr of age. It is not surprising that the patients developing ESRD should have increased mortality. The occurrence of ESRD is associated with a higher prevalence of traditional cardiovascular risk factors and with nontraditional, specific risk factors related to uremia, including increased extracellular fluid volume, electrolyte imbalance, anemia, and higher levels of homocysteine (16). Finally, it should be reminded

that preexisting chronic renal impairment was the most striking predictor of ESRD, which for its part, was found to be a key determinant of patient mortality. This clearly emphasizes the indirect role of preexisting chronic renal impairment in determining also patient outcome.

No difference was found in renal and patient survival between spontaneous and iatrogenic forms of AERD, and the

exposure to more than one precipitating factor had no prognostic impact. These findings contrast with those of some authors (1,6) who suggest that iatrogenic forms were associated with worse prognosis. A possible explanation is that patients with spontaneous form can have a more severe and complicated underlying atherosclerosis that does not require any precipitating factors to determine the showers of emboli. Our study showed the high burden of cardiovascular morbidity borne by patients with AERD, but we were unable to show that the overall burden of cardiovascular comorbidity might increase the risk for death or need for dialysis. We acknowledge the limitations of this aspect of our analysis, because no attempt was made to grade the severity of comorbid vascular conditions. Our results may have been also influenced by the patient population studied, because we studied patients with severe AERD, representing the "tip of the iceberg" (2).

In summary, we found that AERD has a strong clinical impact on both the patient and renal survival. Preexisting chronic renal impairment seemed the most striking predictor of ESRD, which in turn was found to be a key determinant of patient mortality. These data clearly show that chronic renal impairment at baseline can be considered the key to predict the individual patient's outcome. Our prospective observational study precludes the establishment of causality. However, the results can be used to develop interventional studies on the basis of biologically plausible associations of specific risk factors. The protective effect of statins suggests that these drugs can be effective in altering the course of disease, and a possible role of such a therapy should be evaluated in a proper prospective study.

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