Albumin excretion in acute myocardial infarction: A guide for long-term prognosis

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Background Albumin excretion rate has been found to be associated with increased risk of mortality in several clinical settings. We assessed the relationship between urinary albumin and 7-year mortality in a cohort of patients with acute myocardial infarction (AMI).

Methods In this prospective study, we examined 505 white patients admitted with AMI to the intensive care unit of 3 hospitals. Main end points were nonearly all-cause and cardiovascular (CV) mortality. Albumin-to-creatinine ratio (ACR) was measured by radioimmunoassay on the first, third, and seventh days after admission. Risk estimates were made using Cox proportional-hazard model and relative odds. Forty patients (7.9%) died early inhospital, and 175 (34.7%) died during the rest of the follow-up (nonearly mortality).

Results The ACR measured on the third day predicted the occurrence of 7-year nonearly all-cause and CV mortality. Hazard ratios for ACR ≥0.97 mg/mmol were 3.0 (95% confidence limit 2.2-4.1), $P < .0001$, for nonearly all-cause mortality and 3.5 (95% confidence limit 2.5-5.0), $P < .0001$, for CV mortality. Correspondent fully adjusted hazard ratios were 1.9 (95% CI 1.4-2.6), $P < .0001$, and 2.2 (95% CI 1.5-3.2), $P < .0001$, respectively. By adding ACR to the 18-variable predictive model, ACR improved significantly both the goodness of fitting of the model for nonearly all-cause ($P < .0001$) and CV mortality ($P < .0001$) and the C-statistic value ($P < .0001$ and $P = .002$ for nonearly all-cause and CV mortality, respectively). Similar results were obtained for ACR measured on the first day or the seventh day.

Conclusions An early increase of urinary albumin in AMI is a strong independent predictor of long-term adverse clinical outcome. The ACR improved clinical prediction over and above baseline traditional multivariable risk models. (Am Heart J 2008;156:760-8.)

A body of evidence has shown that microalbuminuria is an independent predictor of cardiovascular (CV) events and mortality in diabetic, hypertensive, and also nondiabetic nonhypertensive populations.[1-3]

It has been 15 years since Gosling et al[4] observed a transient increase in albumin excretion rate during acute myocardial infarction (AMI) attributed to a systemic increase in vascular permeability as part of the early acute inflammatory process accompanying AMI. Thereafter, other studies confirmed the sharp increase of albumin excretion during AMI; and some data from our group and other authors showed that urinary albumin is associated with increased risk for short-term mortality in patients with AMI.[5-8] However, the predictive value of microalbuminuria is not well defined in the long term; and it is not known whether the prognostic information provided by this index is additive to that yielded by traditional risk markers.

This study was performed to assess the relationship of albumin excretion rate measured at baseline with nonearly all-cause and CV mortality in a cohort of AMI patients after 7 years of follow-up. We also aimed to evaluate whether measurement of urinary albumin yields prognostic information above that of traditional multivariable risk models.

Methods

Patients

This prospective study included 557 unselected consecutive white patients admitted with definite AMI to the intensive

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Dr Berton and Dr Palatini designed the study. Dr Berton and Dr Cordiano contributed to original data collection. Dr De Toni contributed to laboratory assays. Dr Berton contributed to the creation of data set. Dr. Mazzuco and Dr. Katz contributed to data analysis. Dr Berton and Dr Palatini contributed to data analysis and interpretation, and to the preparation of this report. All authors critically reviewed and approved the final version of the article.

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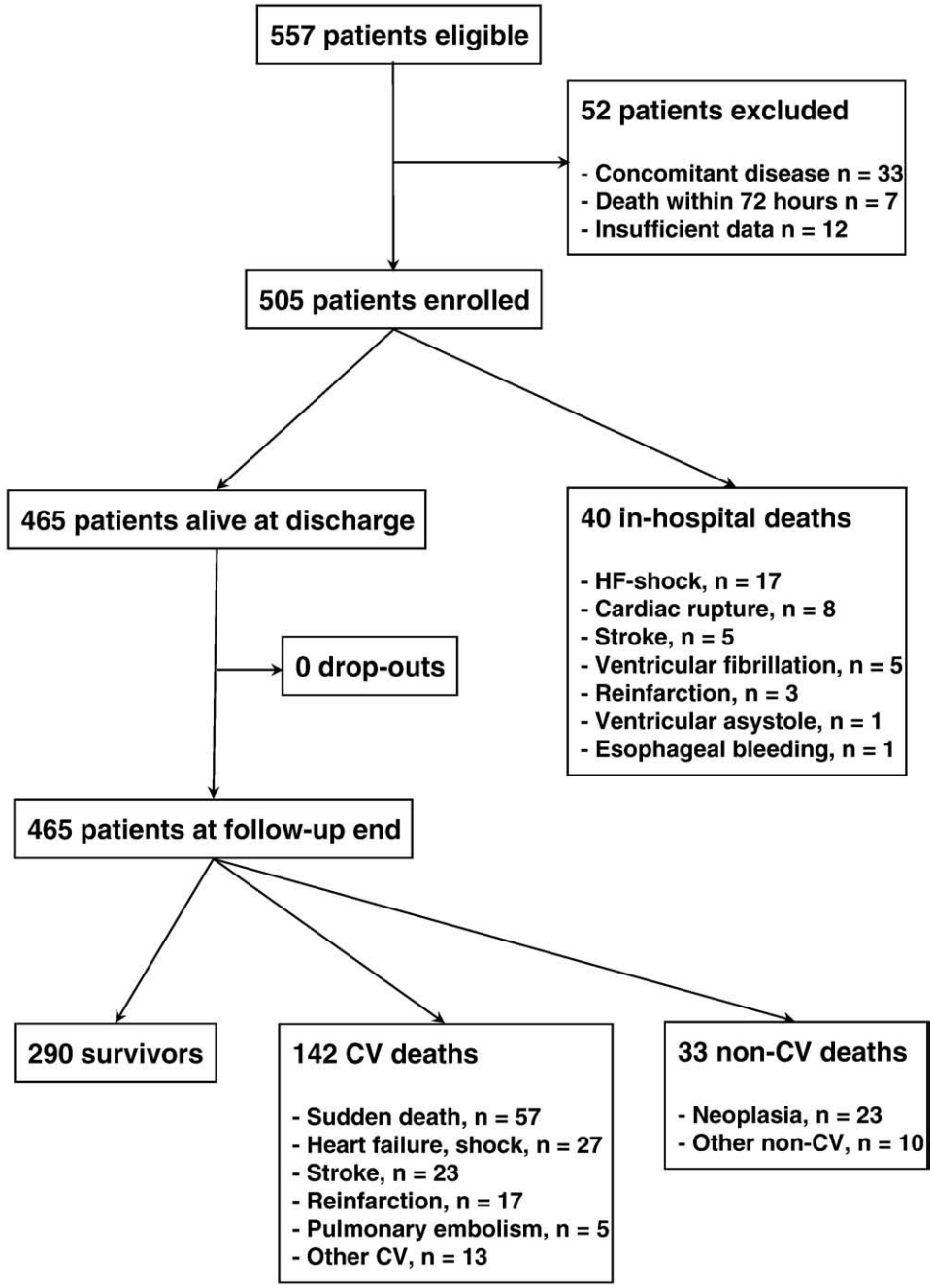
Figure 1



Flow diagram of subject progress during long-term follow-up. *HF*, Heart failure; *CV*, cardiovascular.

care units of 3 hospitals in Northeast Italy from June 21, 1995, to January 19, 1998 (Figure 1). Acute myocardial infarction was diagnosed when at least 2 of the following were present: central chest pain lasting >30 minutes, characteristic changes in serum enzymes (total creatine kinase [CK] and MB isoenzyme of CK), and electrocardiographic changes with pathological Q waves and/or localized ST-T changes in at least 2 contiguous leads.

Twenty-nine patients with urinary tract infections were excluded. These situations included *chronic renal failure* (defined as having history of glomerular filtration rate <60 mL/min per 1.73 m^2 for ≥3 months, with or without

kidney damage) (n = 3), nephrotic proteinuria (n = 2), dialytic treatment (n = 1), myocardial reinfarction within 7 days after admission (n = 3), surgical treatment of bone fractures (n = 2), bronchial infection (n = 1), recent surgery (n = 2), and menstrual flow (n = 1). Additional patients were excluded because of neoplastic disease (n = 4), death within 3 days of admission (n = 7), and insufficient data collection (n = 12). The final analysis was performed in 505 patients. In 53 patients, seventh-day data were not available because of early discharge or death. Written informed consent was obtained from all patients, and the study was approved by each hospital's Ethics Committee.

Measurements

In all patients, a thorough medical history was taken from medical records and patient interview. All clinical and laboratory data were obtained during the first 7 days of hospitalization. Upon admission and every 4 hours thereafter, serum enzyme levels and 12-lead electrocardiogram were obtained. From the third day after admission, these examinations were performed daily. On the first day of hospitalization, venous blood was drawn for determination of serum levels of total and high-density lipoprotein cholesterol, triglycerides, and creatinine. First-, third-, and seventh-day creatinine clearance was computed from creatinine excretion in a 24-hour urine collection and serum creatinine level; and the data were normalized by body surface area. Blood pressure and heart rate were measured between 7:00 AM and 8:00 AM, and the mean of 3 recordings was used. The presence and degree of heart failure were assessed according to the Killip classification. Left ventricular ejection fraction was assessed by 2-dimensional echocardiography between the third and seventh day after enrollment according to the Simpson method. Left ventricular ejection fraction was missing for 39 patients who underwent echocardiography after discharge from the intensive care units and another 20 patients. Forty-four subjects in whom the echocardiographic images were technically unsatisfactory were discarded from the analysis. Thus, left ventricular ejection fraction was available in 402 patients. The records were examined by 2 physicians who had no knowledge of patient clinical data.

Albumin excretion rate

Three 24-hour urine collections, on the first, third, and seventh days after admission, were performed under control of trained nurses to minimize errors in diuresis measurement. After collection, the volumes were measured; and urine specimens were frozen (−20°C) and sent to the University of Padova. Albumin was measured by radioimmunoassay using a Human ALB KIT double antibody (Techno Genetics, Cassina De Pecchi, Milan, Italy).[9] The detection limit of the method was 0.5 mg/L, and the between-batch coefficient of variation was 5%. For each 24-hour urine sample, creatininuria was measured using the Jaffè method.[10] Urinary albumin excretion was then expressed both as albumin excretion rate (micrograms per minute) and as the ratio of albumin (milligrams per liter) to creatinine (millimoles per liter) (ACR) as milligrams per millimole. Standard urinalysis was performed at the time of urinary sample collections.

Follow-up

Every year for 7 years after recruitment, each patient was called for a clinical checkup; and all patients had exactly 7 years of follow-up length. No patient was lost to follow-up. For those who died during a hospital stay, the date and cause of death were obtained from public administration and hospital records (including postmortem report where available). For those who died out of hospital, the data were obtained from the family physician and death certificate. End points were nonearly all-cause and CV mortality. Causes of death were classified as CV and non-CV death (Figure 1). All deaths were classified by 2 physicians blinded to baseline information. In the present article, we refer to *early mortality* as that which occurred during the hospitalization after enrollment and to *nonearly mortality* as that which occurred after discharge to the end of the 7-year follow-up. Angiotensin-converting enzyme (ACE) inhibitor, β-blocker, statin, antiplatelet, and anticoagulant treatments during hospital stay and during follow-up were used as dichotomous covariables. Coronary artery bypass graft surgery and percutaneous coronary angioplasty performed during follow-up were used as time-dependent covariables.

Statistical analysis

Statistical analysis was completed using S-PLUS 6.2 (Insightful Corporation, Seattle, WA) and JMP 4 (SAS Institute Inc, Cary, NC). To correct for positive skewed distributions, log transforms were used as appropriate. The ACR was analyzed as a continuous variable, as quartiles, and as a dichotomous variable using the cutoffs derived from receiver operating characteristic (ROC) curve analysis. For continuous variables, comparison between groups were made using unpaired Student *t* test and repeated-measure analysis of covariance with Tukey post hoc tests when data from all 3 days of observation were simultaneously assessed. The χ^2 test was used for categorical variables. Differences in event rates across risk index ranges were assessed using the χ^2 test for trend.

Univariable and multivariable survival analyses were done using the Cox proportional-hazard regression models.[11] The variables found to be associated with nonearly all-cause or nonearly CV mortality at univariable survival analysis and/or believed to be of prognostic importance were age, ACR, creatinine clearance, Killip class, heart rate, left ventricular ejection fraction, presence of diabetes mellitus, prehospital time delay, atrial fibrillation, gender, current smoking, history of hypertension, body mass index, previous myocardial infarction, history of angina, sedentarity, non–ST-elevation myocardial infarction, tachyarrhythmias, systolic blood pressure, and CK-MB peak. We refer to the model including all these variables as the *baseline traditional risk factor model*. This model was reduced by removing each variable that was nonsignificant and/or causing the least change in significance. This procedure was continued until no further variables could be removed without producing a significant change of the model.[11] This final model was determined to be the *parsimonious multivariable model*. The test on proportionality assumption was based on the scaled

Table I. Clinical characteristics and nonearly mortality rate of the patients according to quartile of ACR measured on the third day of hospitalization

	1st (<0.34 mg/mmol) n = 127	2nd (0.34-0.77) n = 126	3rd (0.78-2.26) n = 126	4th (>2.26) n = 126	*P*
Age (y)	61 (52-70)	66 (58-72)	67 (61-76)	74 (67-82)	<.0001
Female gender (%)	17	18	32	47	<.0001
Body mass index (kg/m^2)	26.1 (24.2-28.7)	25.7 (24.2-28.7)	25.2 (23.8-29.0)	25.4 (22.8-28.4)	.03
Previous myocardial infarction (%)	20	25	15	25	.13
History of angina (%)	20	21	18	21	.96
Current smoking (%)	39	48	39	28	.01
Hypertension (%)	46	32	50	59	.0002
Diabetes mellitus (%)	17	17	21	40	<.0001
Prehospital time delay (min) *	232 (116-534)	178 (95-312)	198 (110-487)	345 (117-727)	.0009
Total cholesterol (mmol/L)	5.4 (2.9-6.2)	5.4 (4.6-6.0)	5.2 (4.3-6.3)	5.2 (4.3-6.1)	.06
HDL cholesterol (mmol/L)	1.1 (1.0-1.3)	1.2 (0.8-1.3)	1.1 (1.0-1.3)	1.1 (1.0-1.3)	.56
Systolic blood pressure (mm Hg)	118 (110-122)	120 (109-132)	123 (112-132)	125 (111-135)	.005
Diastolic blood pressure (mm Hg)	78 (71-83)	70 (66-78)	76 (69-81)	82 (72-87)	.20
Heart rate (beats/min)	69 (59-80)	68 (61-78)	72 (63-82)	80 (67-92)	<.0001
Creatinine clearance (mL/s × 1.73 m^2) *	1.5 (1.0-2.0)	1.3 (1.0-1.7)	1.1 (0.9-1.6)	0.9 (0.7-1.2)	<.0001
CK-MB peak (U/L) *	106 (59-196)	124 (69-249)	152 (68-274)	133 (78-241)	.09
Non-ST elevation (%)	24	22	23	32	.21
Killip class = 2 (%)	24	22	34	42	<.0001
Killip class = 3 (%)	1	3	3	15	<.0001
Killip class = 4 (%)	0	0	3	7	<.0001
LVEF (%) (n = 402)	57 (48-63)	54 (45-61)	50 (42-60)	46 (34-52)	<.0001
Arrhythmias (%) †	17	36	26	36	.001
Atrial fibrillation (%)	8	4	17	22	<.0001
Therapy at enrollment (1st wk)					
Thrombolysis (%)	40	46	45	29	.01
Antiplatelets (%)	94	90	93	84	.04
Anticoagulants (%)	98	98	99	95	.18
β-Blockers (%)	50	43	38	27	.001
ACE inhibitors (%)	35	33	40	57	.0003
Statins (%)	2	6	3	1	.08
Therapy during follow-up					
Antiplatelets (%)	89	80	79	53	<.0001
Anticoagulants (%)	9	12	15	10	.49
β-Blockers (%)	49	43	40	20	<.0001
ACE inhibitors (%)	50	45	61	41	.01
Statins (%)	35	35	34	18	.02
7-y mortality rate					
Nonearly all-cause mortality (%) ‡	21.3	29.4	35.7	52.4	<.0001
Nonearly CV mortality (%) ‡	14.2	23.0	28.6	46.8	<.0001

Data are median and IQ or percentage. *P* values for analysis of variance. *HDL*, High-density lipoprotein; *LVEF*, left ventricular ejection fraction.
* *P* values were calculated on log-transformed data.
† Tachy- and bradyarrhythmia excluding perithrombolytic period.
‡ *P* values for trend. To convert ACR values to conventional units (milligrams per gram), multiply by 1/0.0884.

Schoenfeld residuals. Because of early mortality, the proportional-hazards assumption of the Cox model for ACR was violated ($P = .01$). The typical effect of this violation is to make statistical comparisons more conservative and confidence limits (CLs) on the hazard ratios (HRs) wider.[12] After censoring early mortality cases, the proportional-hazards assumption was verified ($P = .30$). The risk was quantified as an HR with 95% CI.

To ascertain whether ACR provides additive information to that yielded by traditional risk markers, the goodness of fit test and the C-statistic test were used.[13,14] Analogous to the area under the ROC curve, the C-statistic ranges from 0.5 (ie, no discrimination ability) to 1.0 (maximum discrimination ability).[14]

Survival curves were constructed by the Kaplan-Meier method and compared by the log-rank test. Baseline characteristics are summarized with medians and interquartile ranges (IQs) for continuous variables and with numbers and percentages for categorical variables. For all hypotheses tested, 2-tailed *P* values < .05 were deemed significant.

Results

Albumin excretion rate (first day median [IQ] 19 [6-55] μg/min, third day 8 [3-24], seventh day 4 [2-11]) and ACR (first day median [IQ] ACR 2.03 [0.71-6.63] mg/mmol, third day 0.80 [0.35-2.74], seventh day 0.53 [0.18-1.41])

Table II. Albumin-to-creatinine ratio median levels and IQ (milligrams per millimole) during the first week of hospitalization according to nonearly 7-year mortality

	1st-day ACR	3rd-day ACR	7th-day ACR	*P* (sbjs)	*P* (trend)
Survivors n = 290	1.47 (0.58-3.86)	0.54 (0.22-1.13)	0.40 (0.18-0.78)		
All-cause mortality n = 175	2.94 (1.03-8.84)	1.37 (0.54-4.44)	0.67 (0.29-2.33)	.001	<.0001
CV mortality n = 142	3.26 (1.24-10.47)	1.56 (0.60-5.10)	0.80 (0.33-3.21)	<.0001	<.0001
Non-CV mortality n = 33	1.63 (0.53-3.04)	0.70 (0.29-2.18)	0.54 (0.23-0.93)	.32	.19

Data are median and IQ. Data in patients who died during the follow-up and survivors were compared by repeated-measure analysis of covariance using log-ACR adjusted for age, gender, presence of diabetes and/or hypertension, log–CK-MB peak, heart failure, ACE inhibitor, and thrombolytic therapy. Patients who died inhospital (early mortality) were excluded. *P* values are versus survivors; *P* (sbjs) is *P* value for between-subject difference, and *P* (trend) is *P* value for trend. To convert ACR values to conventional units (milligrams per gram), multiply by 1/0.0884.

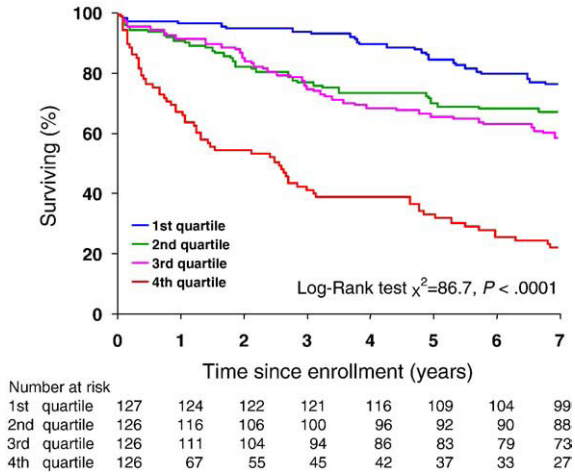
values were closely correlated in all 3 days of measurement ($r = 0.97$, $r = 0.97$, and $r = 0.97$ on the first, third, and seventh day, respectively; $P < .0001$ for all). As 24-hour albumin excretion rate and ACR measurements gave virtually identical results, in the present article, data for ACR are shown.

Clinical characteristics of the AMI patients according to quartile of ACR on the third day of admission are shown in Table I. Patients with ACR in the upper quartile were older, were more frequently women, and were more likely to have a history of hypertension and diabetes. Furthermore, they had more frequently clinical signs of heart failure and presence of atrial fibrillation. Systolic blood pressure and heart rate were higher among the patients of the top ACR quartile than the patients of the other quartiles, whereas left ventricular ejection fraction and creatinine clearance were lower in the former. A negative correlation between log-creatinine clearance and log-ACR was observed ($r = -0.38$, $P < .0001$; $r = -0.33$, $P < .0001$; and $r = -0.38$, $P < .0001$ on the first, third, and seventh day of study). Use of antiplatelets and anticoagulants had similar prevalence across the quartiles of ACR, whereas β-blockers were less frequently used and ACE inhibitors were more frequently used in the top quartile than in the lower ones. During follow-up, antiplatelets, β-blockers, ACE inhibitors, and statins were used less by the patients in the top ACR quartile.

ACR and modes of death

After 7 years, 217 (43.0%) patients had died. Of these, 40 patients (7.9%) died during the hospital stay soon after AMI, all but one for a CV cause (Figure 1). Data for 2 patients who had died in a car accident were censored at the time of the event. Hence, in the following analyses, 215 (42.6%) deaths were considered, of whom 175 (34.7%) represented the nonearly mortality (causes of death are reported in Figure 1). Data of all the survivors were censored at deadline of 7 years, except for 1 patient who had undergone a heart transplantation, whose data were censored at that time.

Figure 2



Kaplan-Meier estimates of the probability of nonearly all-cause mortality in the patients stratified by quartiles of ACR on the third day after admission. Patients who died inhospital (early mortality) were censored at the day of death. For values of ACR in each quartile, see Table I.

The ACR level was higher throughout the week of hospital stay in the subjects who died after discharge from hospital than in the survivors (Table II). However, in the patients who died from nonearly non-CV causes, ACR did not differ from that in the survivors. There was a clear trend to a decline for ACR from the first to the seventh day, except in the subjects who died from non-CV causes

Table III. Univariable and multivariable HRs for nonearly all-cause and CV mortality based on third-day data after hospitalization (n = 505)

	Univariable		Multivariable	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
All patients (n = 505)				
All-cause mortality				
Age (y)	3.1 (2.6-3.9)	<.0001	2.1 (1.7-2.6)	<.0001
ACR (mg/mmol) *	2.1 (1.8-2.6)	<.0001	1.5 (1.3-1.8)	<.0001
Diabetes mellitus (yes/no)	2.3 (1.7-3.2)	<.0001	1.8 (1.3-2.4)	.0007
Heart rate (beats/min)	1.4 (1.3-1.6)	<.0001	1.2 (1.1-1.4)	.004
Previous myocardial infarction (yes/no)	2.1 (1.5-2.9)	<.0001	1.7 (1.2-2.4)	.006
History of angina (yes/no)	2.0 (1.4-2.0)	.0001	1.5 (1.1-2.2)	.03
CV mortality				
Age (y)	3.2 (2.6-4.0)	<.0001	2.0 (1.6-2.6)	<.0001
ACR (mg/mmol) *	2.4 (1.9-2.9)	<.0001	1.7 (1.4-2.0)	<.0001
Diabetes mellitus (yes/no)	2.5 (1.8-3.6)	<.0001	1.8 (1.3-2.6)	.001
Heart rate (beats/min)	1.5 (1.3-1.7)	<.0001	1.3 (1.1-1.5)	.002
Previous myocardial infarction (yes/no)	2.1 (1.5-3.0)	<.0001	1.6 (1.1-2.4)	.02
History of angina (yes/no)	2.0 (1.4-2.9)	.0002	1.6 (1.1-2.4)	.03
Patients with assessment of LVEF (n = 402)				
All-cause mortality				
Age (y)	3.2 (2.5-4.0)	<.0001	1.9 (1.5-2.5)	<.0001
ACR (mg/mmol) *	2.3 (1.9-2.8)	<.0001	1.5 (1.2-1.9)	<.0001
LVEF (%)	0.5 (0.4-0.6)	<.0001	0.7 (0.5-0.8)	.0002
Diabetes mellitus (yes/no)	2.5 (1.7-3.6)	<.0001	1.8 (1.2-2.6)	.003
CV mortality				
Age (y)	3.1 (2.4-4.0)	<.0001	2.0 (1.5-2.6)	<.0001
ACR (mg/mmol) *	2.5 (2.0-3.1)	<.0001	1.6 (1.3-1.9)	<.0001
LVEF (%)	0.5 (0.4-0.6)	<.0001	0.6 (0.5-0.8)	.0001
Diabetes mellitus (yes/no)	2.8 (1.9-4.1)	<.0001	1.8 (1.2-2.8)	.004

Patients who died inhospital (early mortality) were censored. Relative risks and 95% CIs were calculated as HRs from the multivariable Cox regression models. For continuous variables, the unit of increased risk of mortality is for 1-SD increase in the variable.
* *P* values were calculated on log-transformed data.

(Table II). Nonearly all-cause and CV mortality rates significantly rose from the first to the fourth quartile of ACR (Table I).

Predictors of mortality

Kaplan-Meier estimates of survival for nonearly all-cause mortality based on quartile of increasing values of ACR are shown in Figure 2.

In multivariable Cox analysis including all the variables of the baseline traditional risk factor model, listed in the statistical analysis section, ACR level was associated with nonearly all-cause and CV mortality in all 3 measurements. In contrast, no association was found between ACR and death from non-CV causes (data not shown).

In the final parsimonious multivariable model, third-day ACR showed an independent association with nonearly all-cause and CV mortality (in Table III, both the unadjusted and the adjusted HRs are reported). Other independent predictors of mortality were age, diabetes mellitus, heart rate, previous myocardial infarction, and history of angina, whereas creatinine clearance and the other variables were not. Thrombolytic therapy, coronary artery bypass graft surgery, and percutaneous coronary angioplasty were negatively, independently associated with all-cause mortality. Inclusion of β-blocker, ACE inhibitor, antiplatelet, anticoagulant, and statin treatments in the model did not modify the association between ACR and nonearly all-cause mortality (HR 1.6 [95% CL 1.3-1.9, $P < .0001$] per 1-SD increase of ACR).

No significant interactions were found between ACR and the variables used in the multivariable models.

Based on ROC curve analysis, optimal prognostic threshold value for third-day ACR approximated 0.97 mg/mmol, being 0.95 and 0.99 mg/mmol for nonearly all-cause and CV mortality, respectively. Hazard ratios for ACR ≥0.97 mg/mmol were 3.0 (95% CL 2.2-4.1), $P < .0001$, for nonearly all-cause mortality and 3.5 (95% CL 2.5-5.0), $P < .0001$, for CV mortality. Correspondent fully adjusted HRs were 1.9 (95% CI 1.4-2.6), $P < .0001$, and 2.2 (95% CI 1.5-3.2), $P < .0001$, respectively. Similar results were observed for first- and seventh-day measurements (data not shown).

Furthermore, in the subset of patients with left ventricular ejection fraction, ACR showed an independent association with nonearly all-cause and CV mortality at Cox analysis (Table III).

Table IV. Predictive models for nonearly 7-year mortality with and without ACR tested with likelihood ratio χ^2 and C-statistic analysis (n = 505)

Likelihood ratio χ^2 test		**Likelihood ratio χ^2**	**Likelihood ratio χ^2 including ACR**	**Δ χ^2**	***P***
Standard model	All-cause mortality	228	244	16	<.0001
Standard model	CV mortality	202	218	16	<.0001
C-statistic analysis		**C statistic**	**C-statistic including ACR**	**Δ C-statistic**	***P***
Standard model	All-cause mortality	0.81	0.82	0.01	<.0001
Standard model	CV mortality	0.84	0.85	0.01	.002

Patients who died inhospital (early mortality) were censored.

The ACR predictive power for mortality was significant in both men and women, nondiabetic and diabetic patients, and patients with ST elevation and non–ST-elevation AMI.

Predictive models

In Table IV, the results of the likelihood ratio χ^2 analysis are reported. By adding ACR as a continuous variable to the 18-variable baseline traditional risk marker model, ACR improved significantly the model fitting for nonearly all-cause and CV mortality. Furthermore, using C-statistic analysis, a more conservative test, ACR significantly improved the model prediction for nonearly all-cause and CV mortality (Table IV), irrespective of whether the analysis was made in the whole sample or the subset with left ventricular ejection fraction.

Discussion

This prospective study demonstrates that ACR measured during AMI is independently associated to long-term all-cause and CV mortality and provides prognostic information beyond that yielded by indicators of heart failure and myocyte necrosis, renal function, and presence of major CV risk factors. Indeed, adding ACR to the baseline traditional risk factor models improved the predictive power of the models both for all-cause mortality and CV mortality by using either a sensitive or a conservative statistical approach.

Albuminuria is an independent risk factor for CV morbidity and mortality in general populations, patients with diabetes or hypertension, and people at high risk for CV disease.[1-3] Only a few studies have dealt with albumin excretion in the setting of AMI.[6,8] The present study extends our research that first demonstrated the association between albumin excretion and early mortality after AMI, showing that ACR carries independent prognostic information also in very long term follow-up, and contributes to our ability to predict patient global mortality over and above traditional risk markers.[6]

Timing of ACR measurement in AMI

In the present study, blood sampling was performed on the first, third, and seventh days after admission. Although the predictive power of ACR for outcome was similar for the 3 samples, it should be noted that the level of ACR rapidly fell from the first to the seventh day because ACR varies with changes in hemodynamics and the inflammation process in the immediate post-AMI period.[6] Thus, the time point of making the ACR measurement is crucial; and the 0.97-mg/mmol threshold value identified by the ROC curve in the present study should be used only for ACR measured on the third day. This time point appears ideal for ACR assessment because third-day ACR showed a slightly better predictive value than ACR measured on the first day or the seventh day, it avoids the confounding effect of the acute hemodynamic response that may be present in the early phase of AMI, and it precedes dismission from hospital also for patients with uncomplicated AMI. The 0.97-mg/mmol ACR level is lower than the conventional screening threshold for a diagnosis of microalbuminuria (2.65 mg/mmol).[15] However, recent results suggest that the relationship between albumin excretion and mortality extends at far lower levels of urinary albumin.[16]

ACR and renal function

Indicators of renal function are considered to be independent predictors of mortality also in patients with AMI, and even mild renal failure should be considered a major risk factor for CV complications after AMI.[17-19] In keeping with the results of the Copenhagen City Heart Study, in the present study, ACR held a strong predicting power for mortality even when including creatinine clearance in the multivariable models, indicating that the ACR predictive power is independent of renal function assessment.[16]

Mechanism of the increased urinary albumin in myocardial infarction

The mechanisms underlying the adverse prognosis associated with microalbuminuria are not well known.

However, according to most authors, microalbuminuria represents an index of generalized vascular damage because it has been correlated with markers of endothelial dysfunction and inflammation that are directly involved in atherogenesis.[20,21] Acute myocardial infarction causes the activation of neurohormonal and inflammatory systems that increase the level of several humoral markers.[22-26] Many of these markers have shown independent prognostic information for mortality and have been used for optimal risk stratification in post–myocardial infarction patients.

Limitations of the study

At the time of patient enrollment, percutaneous coronary angioplasty was not currently used to reopen coronary artery. We have recently shown that thrombolytic therapy does not affect albumin excretion levels, but we do not know whether percutaneous transluminal coronary angioplasty does.[6] However, a recent study in 175 nondiabetic AMI patients, of whom more than half underwent percutaneous coronary intervention during hospitalization, showed similar associations between albumin excretion and 3-year mortality.[8]

Clinical implications

The present results show that an early increase of urinary albumin in AMI is a strong independent predictor of long-term adverse clinical outcome. The ACR improved clinical prediction over and above baseline traditional multivariable risk models. It follows that long-term stratification of patients into low- and high-risk groups can be facilitated by ACR measurement. On the basis of these results, we suggest that this measurement be included in the routine clinical workup of the patient with AMI.

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