Comparison of C-reactive Protein and Albumin Excretion as Prognostic Markers for 10-Year Mortality After Myocardial Infarction

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ABSTRACT

Background: C-reactive protein (CRP) is an established prognostic marker in the setting of acute coronary syndromes. Recently, albumin excretion rate also has been found to be associated with adverse outcomes in this clinical setting. Our aim was to compare the prognostic power of CRP and albumin excretion rate for long-term mortality following acute myocardial infarction (AMI).

Hypothesis: To determine whether albumin excretion rate is a better predictor of long-term outcome than CRP in post-AMI patients.

Methods: We prospectively studied 220 unselected patients with definite AMI (median [interquartile] age 67 [60–74] y, female 26%, heart failure 39%). CRP and albumin-to-creatinine ratio (ACR) were measured on day 1, day 3, and day 7 after admission in 24-hour urine samples. Follow-up duration was 10 years for all patients.

Results: At survival analysis, both CRP and ACR were associated with increased risk of 10-year all-cause mortality, also after adjusting for age, hypertension, diabetes mellitus, prehospital time delay, creatine kinase-MB isoenzyme peak, heart failure, and creatinine clearance. CRP and ACR were associated with nonsudden cardiovascular (non-SCV) mortality but not with sudden death (SD) or noncardiovascular (non-CV) death. CRP was not associated with long-term mortality, while ACR was independently associated with outcome both in short- and long-term analyses. At C-statistic analysis, CRP did not improve the baseline prediction model for all-cause mortality, while it did for short-term non-SCV mortality. ACR improved all-cause and non-SCV mortality prediction, both in the short and long term.

Conclusions: ACR was a better predictor of long-term mortality after AMI than CRP.

Introduction

C-reactive protein (CRP) and albumin excretion rate (AER) are well recognized predictors of adverse events and mortality in patients at high cardiovascular (CV) risk and even in apparently healthy subjects.[1,2] In the last few years, both CRP and AER have been identified as independent risk markers for mortality also in patients with acute myocardial infarction (AMI).[3–8] Recently, it has been shown that the increase in AER during AMI is independent from renal tubular function and that its prognostic power is independent from the presence of hypertension (HT), diabetes mellitus (DM), and renal dysfunction.[7,9,10] In a previous study, we showed that urinary albumin is a better predictor for long-term mortality in AMI than "traditional" risk markers.[11] In keeping with our results, Schiele et al recently showed that AER is strongly associated with mortality after AMI and that albuminuria can improve risk stratification based on the Global Registry of Acute Coronary Events (GRACE) score.[12] However, in spite of these results, AER has not gained much credit as a prognostic marker for mortality in AMI, whereas CRP is a well recognized predictor of mortality in this setting.[8,13]

The aim of the present study was to compare the prognostic power of CRP and AER for long-term mortality following AMI, adjusting for several risk factors and confounders. In addition, as virtually all previous studies examined CV modes of death as a composite outcome, we wanted to investigate whether CRP and AER have a different predictive value for sudden death (SD) and nonsudden CV (non-SCV) mortality.

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Methods

Patients

This is a prospective study including 244 consecutive unselected patients admitted with definite AMI to the intensive care units of 2 general hospitals in northeast Italy from October 3, 1996 to January 19, 1998. Fourteen patients with preexisting or acute inflammatory processes, or with concomitant clinical situations that could affect albumin excretion, were excluded: urinary tract infections (n = 5), chronic renal failure (glomerular filtration rate [GFR] <60 mL/min/1.73 m^2 for ≥3 months, with or without kidney damage; n = 2), nephrotic proteinuria (n = 2), dialytic treatment (n = 1), surgical treatment of bone fractures (n = 1), bronchial infection (n = 1), recent surgery (n = 1), and menstrual flow (n = 1). Additional patients were excluded due to neoplastic disease (n = 3), death within 3 days of admission (n = 2), and insufficient data collection (n = 5). The final analysis was performed in 220 patients. Written informed consent was obtained from all patients, and the study was approved by the hospitals' ethics committees.

Measurements

Baseline clinical and laboratory data were obtained during the first week of hospitalization. The criteria for AMI diagnosis were based on fulfillment of at least 2 of the following: central chest pain lasting >30 minutes, typical changes in total creatine kinase (CK) and creatine kinase-MB isoenzyme (CK-MB), and typical electrocardiographic (ECG) changes with occurrence of pathological Q waves, and/or localized ST-T segment changes in at least 2 contiguous leads.[14] In addition to baseline biochemical blood determinations, an estimated GFR (eGFR) at baseline was calculated with the use of the modified Modification of Diet in Renal Disease (MDRD) Study equation.[15] The presence and degree of heart failure were assessed according to the Killip classification.[16] Left ventricular ejection fraction (LVEF) was assessed by 2-dimensional ECG between day 3 and day 7 after enrollment according to Simpson's method. LVEF was missing for 26 patients who underwent ECG after discharge from the intensive care units or had technically unsatisfactory ECG images. The records were examined by 2 physicians who had no knowledge of patients' clinical data.

C-reactive Protein and Albumin Excretion Rate Measurement

Venous blood was drawn on days 1, 3, and 7 after admission for measurement of CRP. The samples were put in ice and centrifuged within 20 minutes at 4 °C, and the plasma was stored at −20 °C until assayed (storage time <1 mo). CRP was measured at the University of Padova by means of nephelometric method with particle-bound goat antihuman CRP (Beckman Instruments, Inc., Fullerton, CA) and expressed as mg/L.[17] On the same days, three 24-hour urine collections 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).[18–20] For each 24-hour urine sample, creatininuria was measured using the Jaffe method.[21] AER was expressed as the ratio of albumin to creatinine (ACR) as mg/g. Standard urinalysis was performed at the time of urinary sample collections.

Endpoints

For the patients who died during a hospital stay, the date and cause of death were obtained from public administration and hospital records (including postmortem reports when available). For those who did not die in hospital, data were obtained from the family doctor and the death certificate. None of the patients were lost to follow-up, the duration of which was exactly 10 years for all of the censored patients except for one who underwent heart transplantation within 1 year after AMI and was censored at that time.

The primary endpoint was all-cause mortality. Secondary endpoints were modes of death. They were classified as non-SCV, SD, and non-CV death. SD was defined as out-of-hospital, witnessed cardiac arrest or death within 1 hour of the onset of acute symptoms or unexpected, unwitnessed death (eg, during sleep) in patients who were known to have been well in the previous 24 hours.[22] All other CV deaths, including heart failure with progression of congestive symptoms or pulmonary edema or cardiogenic shock, were classified as non-SCV deaths. Modes of deaths were classified by 2 doctors blinded with regard to baseline information.

Statistical Analysis

Statistical analyses were made using software packages SYSTAT 12 (Systat Inc., Chicago, IL) and JMP 4.0 for Windows (SAS Institute, Inc. Cary, NC). For continuous variables, comparisons between groups were made by Student *t* test or by analysis of variance (ANOVA). CRP and ACR trends during the week of hospital stay were evaluated with repeated-measure ANOVA and the Tukey post-hoc test. Skewed variables were log-transformed before analysis. The Pearson 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. Survival curves were constructed by the Kaplan-Meier method and compared by log-rank test. The test on proportionality assumption was based on the scaled Schoenfeld residuals. As mortality distribution appeared to be bimodal with an early high mortality and a gradual long-term attrition, the proportional-hazards assumption of the Cox model for CRP and ACR was violated ($P = 0.01$ and $P = 0.03$ for CRP and ACR,

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respectively). The typical effect of this violation is to make statistical comparisons more conservative and confidence limits on the hazard ratios (HR) wider.[23] By dividing survival time at the median time to non-SCV death into 2 periods, short term (survival ≤515 d), and long term (survival >515 d), the proportional-hazards assumption was verified for both markers in both periods ($P < 0.30$ for all tests). The risk was quantified as odds ratio (OR) for logistic regression and as HR for Cox regression with 95% confidence interval (CI). First we ran several models including all variables of interest. In a second step, we ran a parsimonious model excluding all variables that did not show an independent association with outcome. The association between variables and modes of death was tested by means of multivariable polynomial logistic regression. To assess the predictive capability of multivariable model and the contribution of CRP and ACR, the C-statistic and Harrell's C-statistic analyses were used.[24] Analogous to the area under the receiver operating characteristic (ROC) curve, the C-statistic ranges from 0.5 (ie, no discrimination ability) to 1.0 (maximum discrimination ability).

Data are presented as median and interquartiles for continuous measures and as proportion for categorical variables. All P values are 2-tailed, and statistical significance was established as $P < 0.05$.

Results

CRP and ACR levels showed different trends during AMI, the former peaking on day 3 after admission and the latter declining from day 1 to day 7. However, log-transformed ACR and CRP values were correlated in all 3 days of measurement. Their correlation was weak soon after AMI, and tended to increase during subsequent days ($r = 0.15$, $P = 0.03$; $r = 0.19$, $P = 0.008$; and $r = 0.25$, $P < 0.0001$ on day 1, day 3, and day 7, respectively).

The baseline clinical characteristics of the AMI patients according to tertiles of ACR are reported in Table 1. Patients with ACR in the upper tertile were older, were more frequently women, were more likely to have a history of HT and DM, and were less frequently smokers. Furthermore, they more frequently had clinical signs of heart failure and had longer prehospital time delay. Blood pressure was higher among the patients of the top ACR tertile than among the patients of the other tertiles, whereas LVEF and creatinine clearance were lower in the former. During follow-up, use of antiplatelet medication was less frequent in the top tertile, while anticoagulants had similar prevalence. β-Blockers, angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin II receptor blockers (ARBs), and statins were less frequently used in the top tertile than in the lower ones.

After 10 years of follow-up, 115 (52%) patients had died. Sixty-six (30%) died of non-SCV causes (14 reinfarction, 19 heart failure–cardiogenic shock, 14 stroke, 19 other causes), 25 (11%) of SD, and 24 (11%) of non-CV causes (including 14 from neoplastic disease and 3 from traumatic causes). Follow-up time was exactly 10 years for all survivors except for 1 patient censored after 368 days (see Methods) (mean 3618 ± 321 d).

CRP and ACR levels were higher in the patients who died than in those who survived throughout the 7 days of the hospital stay (Table 2). However, in the analysis of modes of death, both CRP and ACR were elevated only in the patients who died from non-SCV causes (Table 2).

All-Cause Mortality and Modes of Death

Kaplan-Meier estimates of survival for 10-year all-cause mortality showed increasing mortality rate across tertiles of both CRP and ACR (Figure; A and B). However, when modes of death were considered, the trend remained significant only for non-SCV mortality (Figure C,D).

At survival analysis, both CRP and ACR were associated with increased risk of 10-year all-cause mortality even after adjustment for age, HT, DM, pre-hospital time delay, CK-MB peak, heart failure, creatinine clearance, and thrombolysis. No interactive effect of CRP and ACR on outcome was found. As both markers showed similar strength of association with mortality across the 3 days of measurement, only day-3 data are shown (Table 3). When modes of death were examined, both CRP and ACR were associated with non-SCV mortality, but not with SD or non-CV mortality (Table 3). In the fully adjusted model, CRP showed a marginal independent association with non-SCV mortality, while ACR still showed a significant independent association with this outcome variable (Table 3). Inclusion of LVEF in the multivariable model did not modify the relationship with outcome (results for all-cause mortality: HR: 1.3, 95% CI: 1.1–1.8, $P = 0.02$; and HR: 1.4, 95% CI: 1.1–1.9, $P = 0.007$ for increasing tertiles of CRP and ACR, respectively). Inclusion of β-blockers, ACEIs, ARBs, statins, coronary artery bypass graft surgery, and percutaneous coronary angioplasty during follow-up did not modify the association between CRP, ACR, and all-cause mortality (HR: 1.3, 95% CI: 1.1–1.7, $P = 0.01$; and HR: 1.4, 95% CI: 1.1–1.9, $P = 0.005$ for increasing tertiles of CRP and ACR, respectively).

Short- and Long-term Prognosis

As survival curves appeared to be bimodal with early higher mortality and a gradual long-term attrition, we divided the follow-up time into a short-term hazard and a long-term hazard. The discriminant cut-off between short- and long-term mortality was chosen at the median time to non-SCV death, in order to have half of the events in each of the 2 periods. Median time was 515 days. CRP showed a strong association with short-term mortality but failed to discriminate long-term mortality (Table 3). At variance, ACR was independently associated with outcome, both in the short-term and long-term analyses (Table 3). To verify

Table 1. Baseline Clinical Characteristics of Patients With AMI According to Tertiles of ACR Measured on Hospitalization Day 3

Patient Characteristics	Tertile 1(<6.8 mg/g) n = 74	Tertile 2 (6.9–20.5 mg/g) n = 73	Tertile 3 (>21.8 mg/g) n = 73	*P* Value
Age, y	64 (57–71)	65 (58–73)	73 (68–79)	<0.0001
F	15	22	41	0.001
BMI (kg/m^2)	25.7 (24.4–27.7)	26.9 (24.0–29.8)	25.9 (24.0–29.4)	0.35
Previous AMI	19	15	15	0.76
History of angina	16	11	14	0.65
Current smoker	53	37	22	0.001
HT	36	45	62	0.008
DM	13	23	41	0.001
Prehospital time delay, min[a]	177 (120–360)	165 (120–244)	270 (120–607)	0.04
Total cholesterol (mg/dL)	220 (182–245)	199 (175–245)	203 (170–227)	0.13
SBP (mm Hg)	120 (105–130)	120 (110–131)	125 (115–140)	0.006
DBP (mm Hg)	70 (65–80)	70 (70–80)	80 (70–85)	0.005
eGFR (ml/s × 1.73m^2)	76 (67–88)	78 (63–88)	60 (45–77)	<0.0001
CK-MB peak (IU/L)	160 (73–231)	135 (75–242)	155 (81–280)	0.35
NSTEMI	65	75	74	0.31
Killip class <I	22	37	59	<0.0001
AF	9	11	20	0.10
LVEF in percentage (n = 194)	53 (46–60)	51 (44–60)	44 (34–56)	0.08
Thrombolysis	50	55	38	0.12
Medications during follow-up				
Antiplatelet	90	89	71	0.002
Anticoagulant	13	22	15	0.35
β-Blocker	54	57	33	0.005
ACEI and/or ARB	59	75	62	0.09
Statin	58	45	26	<0.0001

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; AF, atrial fibrillation; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; BMI, body mass index; CK-MB, creatine kinase-MB isoenzyme; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; F, female; HT, hypertension; LVEF, left ventricular ejection fraction; n, number of patients; NSTEMI, non–ST-segment-elevation myocardial infarction; SBP, systolic blood pressure.
Data are presented as median and interquartile ranges for continuous measures and as percentage for categorical variables.
[a] Time from onset of symptoms to arrival at coronary care unit.

whether CRP and ACR are also associated with very-late mortality, a Cox analysis was made on the events occurring in the second half of the follow-up period (from year 6 to year 10 of follow-up). It showed that CRP is not associated with very-late mortality, whereas ACR still is (HR: 1.3, 95% CI: 0.8–2.1, $P = 0.23$; and HR: 1.7, 95% CI: 1.1–2.8, $P = 0.02$ for increasing tertiles of CRP and ACR, respectively).

Table 2. CRP and ACR Levels During Hospitalization Week 1 According to 10-Year Mortality and Modes of Death

	Day 1	Day 3	Day 7	Adjusted *P* (Sbjs)	Adjusted *P* (Trend)
CRP (mg/L)					
Survivors (n = 105)	5.0 (4.9–13.1)	24.0 (11.4–58.1)	6.9 (5.0–23.8)	NA	NA
All-cause mortality (n = 115)	8.8 (5.0–3.0)	49.6 (16.6–105.2)	17.9 (5.0–47.5)	0.004	0.001
Non-SCV mortality (n = 66)	14.0 (5.0–38.7)	71.4 (22.0–130.0)	32.7 (5.1–57.6)	0.001	<0.0001
SD (n = 25)	6.8 (5.0–24.2)	40.6 (7.0–76.7)	12.4 (5.0–20.3)	0.13	<0.0001
Non-CV mortality (n = 24)	8.0 (5.0–17.5)	40.0 (11.2–57.7)	13.4 (5.0–45.1)	0.17	<0.0001
ACR (mg/g)					
Survivors (n = 105)	21.6 (9.7–46.0)	7.4 (4.2–13.4)	5.4 (3.0–10.5)	NA	NA
All-cause mortality (n = 115)	39.7 (16.8–163.4)	19.0 (7.9–60.0)	9.7 (4.9–39.4)	0.01	0.002
Non-SCV mortality (n = 66)	67.2 (23.2–231.5)	42.1 (16.9–80.8)	21.8 (6.0–65.9)	<0.0001	0.01
SD (n = 25)	31.8 (8.2–64.4)	8.5 (5.3–19.0)	7.0 (4.4–15.4)	0.24	0.08
Non-CV mortality (n = 24)	23.2 (9.5–41.7)	9.0 (4.6–20.6)	6.6 (3.7–10.4)	0.93	0.04

Abbreviations: ACR, albumin-to-creatinine ratio; CRP, C-reactive protein; CV, cardiovascular; DM, diabetes mellitus; HT, hypertension; n, number of patients; NA, not applicable; non-CV, non-cardiovascular; non-SCV, non-sudden cardiovascular; *P* (sbjs), *P* value for between-subject difference; *P* (trend), *P* value for trend; SD, sudden death.
Data are median and interquartile range. *P* values are vs survivors. Data in patients who died during the follow-up and survivors were compared by repeated-measure analysis of covariance (ANCOVA) using log-CRP and log-ACR adjusted for age, gender, and presence of DM and/or HT.

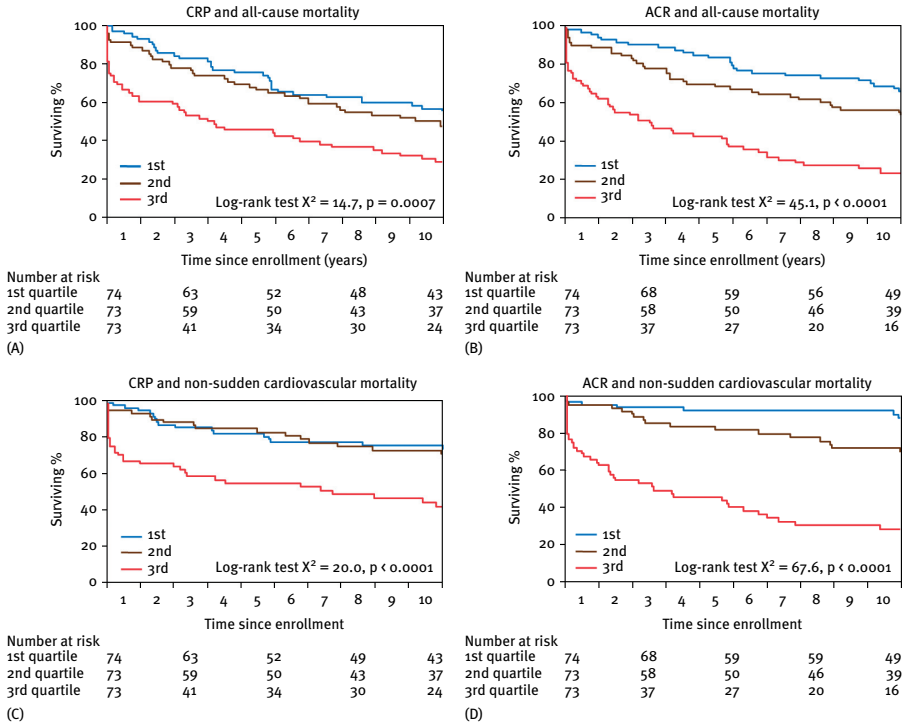

Figure 1. Kaplan-Meier estimates of the probability of all-cause and non-sudden cardiovascular mortality in the patients stratified by tertiles of C-reactive protein (CRP) and albumin-to-creatinine ratio (ACR).

Table 3. Mortality Risk by Tertiles of CRP and ACR on Hospitalization Day 3 for All-Cause Mortality, Main Modes of Death, and Short- and Long-term Mortality

Overall Mortality		OR (95% CI)	*P* Value
Bivariable			
CRP		1.5 (1.1–2.1)	0.03
ACR		2.4 (1.7–3.4)	<0.0001
Interaction CRP*ACR		1.1 (0.7–1.8)	0.60
Multivariable			
CRP		1.4 (1.1–1.8)	0.005
ACR		1.5 (1.2–2.0)	0.001
Main Modes of Death		**OR (95% CI)**	***P* Value**
Bivariable			
CRP	SD	1.4 (0.8–2.5)	0.20
	non-SCV	1.8 (1.2–2.9)	0.008
	non-CV	1.1 (0.6–1.8)	0.83
ACR	SD	1.4 (0.8–2.5)	0.22
	non-SCV	4.7 (2.8–7.8)	0.0001
	non-CV	1.2 (0.7–2.1)	0.58
Multivariable			
CRP	SD	1.3 (0.7–2.3)	0.41
	non-SCV	1.5 (0.9–2.4)	0.07
	non-CV	0.9 (0.5–1.7)	0.81
ACR	SD	1.1 (0.6–2.1)	0.73
	non-SCV	3.2 (1.8–5.8)	0.0001
	non-CV	0.9 (0.5–1.8)	0.83
Short-term Mortality		**HR (95% CI)**	***P* Value**
Bivariable			
CRP		2.7 (1.6–4.7)	0.0001
ACR		6.3 (3.2–14.6)	<0.0001
Multivariable			
CRP		2.8 (1.6–5.0)	0.0001
ACR		3.9 (2.0–9.0)	<0.0001

Table 3. (*continued*)

Long-term Mortality	HR (95% CI)	*P* Value
Bivariable		
CRP	1.3 (0.8–2.0)	0.26
ACR	2.8 (1.7–4.6)	<0.0001
Multivariable		
CRP	1.1 (0.7–1.8)	0.65
ACR	1.8 (1.1–3.1)	0.01

Abbreviations: ACR, albumin-to-creatinine ratio; CRP, C-reactive protein; CV, cardiovascular; HR, hazard ratio from Cox model; non-CV, non-cardiovascular; non-SCV, non-sudden cardiovascular; OR, odds ratio from logistic regression; SD, sudden death.

C-statistic Discriminant Analysis

At C-statistic analysis, CRP showed a smaller area under the ROC curve (ie, lower predictive ability) than ACR for both all-cause (0.64 vs 0.71) and non-SCV mortality (0.68 vs. 0.82). At multivariable level, CRP did not improve the model prediction based on the significant variables of the Cox model (age, HT, DM, prehospital time delay, CK-MB peak, heart failure, and creatinine clearance) for all-cause mortality, whereas it improved the model prediction for non-SCV mortality (Table 4). ACR was able to improve both all-cause and non-SCV mortality prediction models.

Discussion

The present study showed that ACR was a stronger and more consistent prognostic marker than CRP for mortality following AMI. CRP was independently associated with short-term mortality, whereas ACR was able to predict both

Table 4. Predictive Models Based on C-statistic Analysis

Mortality	Standard Model	Including CRP	Δ C-statistic	Including ACR	Δ C-statistic
All-cause	0.84	0.84	0.00	0.85	0.01
Non-SCV	0.86	0.87	0.01	0.89	0.03
Short-term non-SCV[a]	0.87	0.88	0.01	0.91	0.04
Long-term non-SCV[a]	0.82	0.82	0.00	0.83	0.01

Abbreviations: ACR, albumin-to-creatinine ratio; CRP, C-reactive protein; non-SCV, non-sudden cardiovascular.
[a] Harrell C-statistic (see Methods).

short-term and long-term mortality. Their predictive ability was chiefly related to non-SCV mortality.

Human CRP production is greatly increased after AMI. It affects the extent of myocardial damage produced by ischemic injury, and it is associated with early and late clinical outcomes.[25–28] The behavior and the clinical significance of the increase in AER during AMI has been much less investigated.[13] Only in the last decade did some groups of investigators show that AER acutely increases during AMI and that it is related to prognosis.[7,11,12,29] Microalbuminuria is a well-known marker of endothelial dysfunction and is considered to reflect increased "leakiness" of the endothelium throughout the body.[30]

In agreement with previous results, in the present study both CRP and ACR were independently associated with all-cause mortality after AMI.[12,31] However, CRP was predictive of outcome only in the short term, whereas ACR kept its prognostic power up to 10 years after AMI. The lack of association of CRP with long-term mortality cannot be attributed to the role of other variables included in the multivariable models, because CRP was not associated with long-term mortality also in the univariate model. It can be speculated that the inflammatory injury heralded by CRP during AMI is shorter lasting than the endothelium dysfunction reflected by increased ACR.[32,33] In addition, at C-statistic analysis, ACR but not CRP was able to improve the multivariable prediction model. The above findings indicate that ACR should be preferred to CRP for risk stratification after AMI.

Study Limitations

A limitation of the present study is the relatively small number of patients and events. However, small studies such as the present one can serve to create exploratory hypotheses that should be validated in future larger studies and/or with the use of meta-analyses. Thus, both significant and insignificant *P* values should be interpreted conservatively, especially for the short-term study results and for the subanalysis on modes of death. Another limitation is that, at the time of patient enrollment, percutaneous coronary angioplasty was not currently used in patients with AMI, and this procedure may affect CRP and albumin excretion levels.[6,34] However, recent studies in AMI patients, part of whom underwent percutaneous coronary intervention during hospitalization, showed associations of CRP and albumin excretion with mortality similar to those observed in the present study.[7,12]

Conclusion

The present results show that ACR is a stronger predictor of long-term mortality after AMI than CRP. For both markers, the predictive power was related to non-SCV mortality, whereas no association was found with SD or non-CV mortality.

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