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Aldosterone, mortality, and acute ischaemic events in coronary artery disease patients outside the setting of acute myocardial infarction or heart failure

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Background Recent studies have demonstrated that aldosterone levels measured in patients with heart failure or acute myocardial infarction (MI) are associated with long-term mortality, but the association with aldosterone levels in patients with coronary artery disease (CAD) outside these specific settings remains unknown. In addition, no clear mechanism has been elucidated to explain these observations. The present study was designed to evaluate the relationship between the level of aldosterone and the risk of death and acute ischaemic events in CAD patients with a preserved left ventricular (LV) function and no acute MI.

Methods and results In 799 consecutive CAD patients referred for elective coronary angioplasty measurements were obtained before the procedure for: aldosterone (median = 25 pg/mL), brain natriuretic peptide (BNP) (median = 35 pg/mL), hsC-reactive protein (median = 4.17 mg/L), and left ventricular ejection fraction (mean = 58%). Patients with acute MI or coronary syndrome (ACS) who required urgent revascularization were not included in the study. The primary endpoint, cardiovascular death, occurred in 41 patients during a median follow-up period of 14.9 months. Secondary endpoints—total mortality, acute ischaemic events (acute MI or ischaemic stroke), and the composite of death and acute ischaemic events—were observed in 52, 54, and 94 patients, respectively. Plasma aldosterone was found to be related to BMI, hypertension and NYHA class, and inversely related to age, creatinine clearance, and use of beta-blockers. Multivariate Cox model analysis demonstrated that aldosterone was independently associated with cardiovascular mortality ($P = 0.001$), total mortality ($P = 0.001$), acute ischaemic events ($P = 0.01$), and the composite of death and acute ischaemic events ($P = 0.004$). Reclassification analysis, using integrated discrimination improvement (IDI) and net reclassification improvement (NRI), demonstrated incremental predictive value of aldosterone ($P < 0.0001$).

Conclusion Our results demonstrate that, in patients with CAD but without heart failure or acute MI, the level of aldosterone is strongly and independently associated with mortality and the occurrence of acute ischaemic events.

Keywords Coronary artery disease • Angioplasty • Aldosterone • BNP • Clinical outcome

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Introduction

Aldosterone is an important mineralocorticoid hormone involved in the regulation of water, electrolyte, and blood pressure homeostasis.[1] Increasing evidence has suggested its involvement in physiological and pathophysiological processes in the cardiovascular system. Experimental data suggest that aldosterone could have toxic effects on the myocardium[1,2] and could be implicated in a range of deleterious aspects of coronary artery disease (CAD), including endothelial dysfunction, macrophage oxidative stress, vascular inflammation, atherosclerosis, and myocardial ischaemia.[3–6]

The association between plasma aldosterone and long-term mortality has been demonstrated in patients with congestive heart failure[7–10] and, more recently, in patients with acute myocardial infarction (AMI). Beygui *et al.*[11] found that aldosterone levels in plasma at time of admission were associated with cardiovascular morbidity and mortality at the 6-month follow-up in their study cohort of 356 patients admitted with acute ST-segment-elevation myocardial infarction. Subsequently, two other studies[12,13] of 471 and 583 patients, respectively, showed that aldosterone levels in plasma measured within hours of AMI were associated with mortality at the 1-year and 5-year follow-up points.

The benefit of aldosterone-receptor blockade in high-risk patients after AMI was demonstrated in the Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS), which reported a reduction in morbidity and mortality among patients with AMI complicated by left ventricular (LV) dysfunction and heart failure when the selective aldosterone-blocker eplerenone was used to supplement optimal medical therapy.[14] Although another study recently demonstrated the relationship between aldosterone and mortality in a mixed population, including 67% of patients with CAD, no detailed information on the characteristics of the CAD population was available.[15] Therefore, to date the association between aldosterone and long-term mortality in patients with CAD outside the setting of heart failure or AMI remains unknown. In addition, although some preclinical studies have suggested that aldosterone could interact with the atherosclerosis process,[3–6] this issue has never been investigated in patients.

To this end, we investigated the relationship between the baseline level of plasma aldosterone and the subsequent risk of death or acute ischaemic event in a consecutive series of 799 patients with CAD and preserved LV function who had been referred for an elective percutaneous coronary intervention (PCI) procedure. The incremental predictive value of aldosterone was further investigated using reclassification analysis as developed by Pencina *et al.*[16,17] Patients with AMI or acute coronary syndrome (ACS) requiring emergent PCI were not included in the study. We also examined the clinical and biological covariates of baseline levels of aldosterone in plasma in this population.

Methods

Patients

From June 2000 to September 2001, 1209 patients underwent PCI in our institution. Consecutive patients scheduled for PCI during the daytime (between 8 a.m. and 4 p.m.) were enrolled in a bio-clinical cardiovascular registry ($n = 799$). The Ethics Committee of the Centre Hospitalier Régional Universitaire de Lille approved the study, and each subject gave informed written consent the day before PCI. As a result, patients with AMI or ACS who required invasive strategy, such as patients who required PCI within 24 h of symptoms or who were assessed for emergent or rescue PCI, were not included in this registry ($n = 402$). Eight patients who were taking a mineralocorticoid receptor (MR) blocker were also excluded, leaving 799 patients eligible for the analysis.

Hypertension was defined as a known blood pressure >140/90 mmHg or use of antihypertensive drugs. Smoking was defined as acknowledged ceased/unceased smoking. Diabetes mellitus was defined as a fasting glucose ≥126 mg/dL, use of hypoglycaemic agents, or a history of physician-diagnosed diabetes mellitus. Obesity was defined as body mass index >30 kg/m^2. Family history of premature CAD was defined as CAD in a male first-degree relative <55 years old or CAD in a female first-degree relative <65 years old. Peripheral arterial obstructive disease (PAOD) was defined as the presence of a cerebrovascular disease and/or a lower extremity peripheral arterial disease (PAD). Cerebrovascular disease was defined as a history of transient ischaemic attack or ischaemic stroke confirmed by a medical report and/or by a known carotid stenosis >70% confirmed by imaging and/or by a history of carotid surgery. A lower extremity PAD was defined as current intermittent claudication with an ankle brachial index < 0.75 and/or by a known lower extremity arterial stenosis >70% confirmed by imaging and/or by a history of previous lower extremity revascularization procedure.

Angiography and angioplasty procedure

This procedure is described in the Supplementary material.

Clinical follow-up

All patients were part of a registry. Long-term clinical follow-up started at the time of the index procedure and was completed for all patients. The clinical follow-up was intended to be performed after 12 months, and was accomplished through questionnaires completed by the patient and the referring physician, a copy of the last ECG and, if necessary, additional telephone contacts, review of hospital records and contact with the referring physician. The time of follow-up was recorded for every patient; the median follow-up period of the population was 14.9 months (inter-quartile: 12.0–18.5).

Total mortality and cardiovascular mortality were recorded. Sudden cardiac deaths, fatal MIs, deaths due to congestive heart failure, deaths immediately secondary to intervention to treat CAD or PAD, other causes of deaths secondary to cardiac diseases, fatal strokes, and death from unknown causes were classified as cardiovascular deaths. Deaths from other causes were classified as non-cardiovascular.

Acute ischaemic events, including acute MIs and acute ischaemic strokes, were recorded. In the peri-procedural period, AMI was defined as the development of new pathological Q-waves or creatine kinase-MB isoenzyme (or total CK, if CK-MB not available) more than three times normal. During the follow-up period, AMI was defined as the occurrence of new pathological Q-waves, or onset of ischaemic symptoms, or ischaemic ECG changes with total CK-MB (or total CK if CK-MB not available) more than two times normal.[18] A diagnosis of ischaemic stroke was made when patients presented with the abrupt onset of focal neurological deficit persisting for >24 h[19] without evidence of primary intracranial haemorrhage on imaging.

Classification of the cause of death (cardiovascular or non-cardiovascular), validation of the diagnosis of acute MI, and of ischaemic stroke were adjudicated by an independent committee of three experienced physicians who had access to all available documents describing the event in question, but not the baseline clinical and biological data for the patient.

The primary endpoint of our study was cardiovascular mortality. Three additional secondary endpoints were investigated: total mortality, acute ischaemic events defined as the composite of acute MI and ischaemic stroke, and the composite of death and acute ischaemic events.

Analysis of biological markers

For at least 12 h before PCI, patients were fasted and no hypoglycaemic drugs were administered. At the time of angioplasty, with the patients having been in a supine position for >1 h and immediately after puncture under sterile conditions, blood samples were drawn from the arterial sheath and collected into various Vacutainer tubes (Becton Dickinson France, Le Pont de Claix, France). Tubes with no additive were used for lipid and hsC-reactive protein measurements by nephelometry (Dade-Behring, Paris, France). Tubes containing heparin were used for glucose and creatinine measurements. Tubes with EDTA were used to measure HbA1c, brain natriuretic peptide (BNP), and aldosterone. BNP levels were determined using an automated chemiluminescent system (Advia Centaur, Siemens Healthcare Diagnostics, Cergy Pontoise, France), and aldosterone was measured by radioimmunoassay (Immunotech, Beckman Coulter, Villepinte France). For each parameter, all samples were analysed in duplicate in the same run on the same day. Inter-assay and intra-assay variations for C-reactive protein were 7.28 and 2.65% at low levels and 3.77 and 2% at high levels, respectively. Inter-assay and intra-assay variations for BNP were 5.1 and 4.3% at low levels and 4.9 and 2.0% at high levels, respectively. Inter-assay and intra-assay variations for aldosterone were 9.25 and 8.55%, respectively. All these variations were within the limits given by the manufacturer. Repeated aldosterone measurements in a subset of 103 patients demonstrated no significant change over time (see Supplementary data section).

Statistical analysis

Continuous variables with little-to-mild skew are presented as mean ± SD, and continuous variables with skewed distribution are presented as median values (inter-quartile range). Discrete variables are presented as absolute numbers and percentages.

The association between aldosterone and continuous variables was assessed using Spearman's correlation coefficient; for discrete variables, the association was assessed with a logistic regression analysis using the discrete variable as the dependent variable and aldosterone as the independent variable. A multiple regression analysis was performed to study the relationship between aldosterone and multiple categorical and continuous determinants. Categorical independent variables were encoded as 0 (absent) or 1 (present), and continuous independent variables were incorporated without any change.

Four types of events were investigated: cardiovascular mortality (primary end point), total mortality, acute ischaemic events, and the composite of death and acute ischaemic events. The relationships between aldosterone and these events were tested using aldosterone as a continuous variable. Event-free survival was estimated with the Kaplan–Meier method, and differences were tested with a log rank test. Hazard ratios were calculated using simple (univariate) and multiple (multivariable) Cox models. A Cox regression model was established to test the relationship between each type of event and aldosterone levels with adjustments for age, gender, hypertension, smoking, diabetes mellitus, BMI, family history of CAD, clinical status (post-ACS, NYHA class), PAOD, severity of CAD, left ventricular ejection fraction (LVEF), total cholesterol, creatinine clearance, haemoglobin, hsC-reactive protein, and BNP levels, and treatment with beta-blockers, diuretics, statins, and ACE inhibitors. Because of skewness, log transformations of aldosterone, BNP, and C-reactive protein were used. The contribution of aldosterone in the model was tested by the log-likelihood test comparing nested models without and with aldosterone. The incremental prognosis value of aldosterone on top of variables included in the model was assessed using the integrated discrimination improvement (IDI) and the net reclassification improvement (NRI) with a category free option as recently developed by Pencina *et al.*[16,17]

All hypotheses were two-tailed with a 0.05 type I error rate. Analyses were conducted using SPSS 17.0 (Chicago, IL, USA) and the SAS system (SAS v8; SAS Institute, Cary, NC, USA). Additional statistical information is provided in the Supplementary data section.

Results

Characteristics of the study population

The characteristics of the study population are presented in *Table 1*. Most of the population (78%) was male, the mean age was 61 years, and 32% suffered from diabetes.

All patients included in the study underwent an elective PCI procedure. Only patients who had a scheduled PCI and had provided informed consent the day before the procedure were included. The study excluded patients with AMI or ACS, which requires an urgent invasive strategy; specifically, no patients who required coronary angiography within 24 h of symptoms or patients assessed for emergent or rescue PCI, whatever the time between the acute symptom and coronary angiography, were enrolled or assessed. In 26% of the study population, the elective PCI procedure was performed in 'post-ACS' patients. These patients represented those whose ACS indicated a conservative medical treatment of medical stabilization and who had subsequently undergone an angiography leading to elective PCI. In this group, the median time between acute symptoms and PCI was 4 (3–6) days.

Most patients (93%) had NYHA class ≤II and a preserved LV function (mean LVEF = 58%). During the angioplasty procedure, stent implantation was performed in 93% of patients.

β-Blockers were used in 71% of patients, ACE inhibitors in 61% of patients, diuretics in 22%, and statins in 68%. Oral antiplatelet agents were prescribed for 96% of patients.

The median C-reactive protein level was 4.17 mg/L (1.52–11.70), while the median BNP level was 35 pg/mL (13–91), and the median aldosterone level was 25 pg/mL (13–45).

Aldosterone levels and cardiovascular risk factors

Correlates of aldosterone levels by univariate analysis as a function of baseline patient characteristics are presented in *Table 1*.

Multivariable analysis (*Table 2*) showed that a higher aldosterone level was associated with a higher NYHA class ($P = 0.0001$), a higher BMI (0.0006), the presence of hypertension ($P = 0.003$), and post-ACS ($P = 0.003$), but was inversely correlated with age

Table 1 Baseline characteristics of the study population and covariates of aldosterone levels by univariate analysis

	Total $n = 799$	Aldosterone		*P*-value
		<25 pg/mL n (%) = 397 (50)	≥25 pg/mL n (%) = 402 (50)	
Age	61 ± 12	62 ± 12	60 ± 12	0.0001
Men, *n* (%)	629 (78)	315 (79)	314 (78)	0.82
Risk factors, *n* (%)				
Hypertension	418 (52)	183 (46)	235 (58)	0.0005
Smoking	566 (71)	266 (67)	300 (75)	0.01
Diabetes mellitus	251 (31)	118 (30)	133 (33)	0.31
Obesity	193 (24)	79 (20)	114 (28)	0.006
BMI	27.5 ± 4.5	26.9 ± 4.4	28.1 ± 4.6	0.0001
Family history of CAD	313 (39)	136 (34)	177 (44)	0.005
Clinical condition, *n* (%)				
Post-ACS	207 (26)	87 (22)	120 (30)	0.01
No post-ACS	592 (74)	310 (78)	282 (70)	
Peripheral arterial obstructive disease	119 (15)	50 (13)	69 (17)	0.07
Cerebrovascular disease	39 (5)	19 (5)	20 (5)	0.90
Lower extremity PAD	92 (11)	38 (9)	54 (13)	0.08
NYHA class, *n* (%)				
I	515 (64)	280 (71)	235 (58)	
II	231 (29)	108 (27)	123 (31)	0.0001
III	47 (6)	8 (2)	39 (10)	
IV	6 (1)	1(0)	5 (1)	
Angiographic data and revascularization procedure				
LVEF, %	58 ± 15	58 ± 14	57 ± 15	0.43
No. of vessels with >50% stenosis	1.77 ± 0.79	1.75 ± 0.78	1.80 ± 0.80	0.52
Stent implantation	748 (93)	367 (92)	381 (95)	0.22
Medication at baseline, *n* (%)				
β-Blockers	568 (71)	306 (77)	263 (65)	0. 0004
ACE inhibitors	485 (61)	242 (61)	243 (60)	0.88
Diuretics	176 (22)	73 (18)	103 (26)	0.01
Statins	546 (68)	282 (71)	264 (66)	0.12
Oral antiplatelet agents	768 (96)	383 (96)	385 (96)	0.874
Total cholesterol, mg/dL	202 ± 46	201 ± 45	204 ± 48	0.25
LDL cholesterol, mg/dL	132 ± 42	132 ± 42	133 ± 42	0.49
HDL cholesterol, mg/dL	39 ± 12	39 ± 12	39 ± 12	0.73
Triglycerides, mg/dL	157 ± 118	156 ± 135	159 ± 99	0.09
Glycaemia, mmol/L (range)	5.4 (4.8–6.7)	5.2 (4.7–6.3)	5.6 (4.9–7.1)	0.01
HbA1c, % (range)	5.6 (5.3–6.5)	5.6 (5.2–6.4)	5.7 (5.3–6.5)	0.86
hsC-reactive protein, mg/L (range)	4.17 (1.52–11.7)	3.32 (1.32–8.99)	5.62 (1.86–14.60)	0.0002
Creatinine, mg/L	11.0 ± 6.0	10.4 ± 2.4	11.7 ± 8.2	0.004
Creatinine clearance, mL/min/1.73 m^2	85.63 ± 22.27	87.27 ± 20.57	84.00 ± 23.77	0.04
Haemoglobin, g/dL	13.8 ± 1.7	13.9 ± 1.8	13.7 ± 1.6	0.31
BNP, pg/mL (range)	35 (13–91)	35 (14–86)	37 (12–96)	0.27

Data are mean ± SD or median (inter-quartile range) unless otherwise stated. LVEF, left ventricular ejection fraction.

($P = 0.0001$), the use of β-blockers ($P = 0.0002$), and higher creatinine clearance ($P = 0.001$). BNP levels were significantly and inversely related to the LVEF ($R = 0.43$, $P = 0.0001$).

Aldosterone levels and mortality

Clinical follow-up was completed for all patients, with a median interval of 14.9 (12.0–18.6) months after enrolment in the study.

Table 2 Multivariable correlates of aldosterone levels (log)

Independent variable	β coefficient	95% CI	SE	*P*-value
Age (10 years increase)	(−)0.11	(−)0.15−(−)0.08	0.02	0.0001
Hypertension	+0.09	+0.03−+0.16	0.03	0.003
Body mass index	+0.02	+0.01−+0.02	0.01	0.0004
Post-ACS	+0.11	+0.04−+0.19	0.04	0.003
NYHA class	+0.12	+0.07−+0.18	0.03	0.0001
Use of β-blockers	(−)0.13	(−)0.20−(−)0.06	0.03	0.0002
Creatinine clearance (10 mL/min/1.73 m^2 increase)	(−)0.02	(−)0.04−(−)0.01	0.01	0.0009

SE, standard error; CI, confidence interval. Other data in the model are gender, smoking, family history of CAD, glycaemia, LVEF and treatment with statins and ACE inhibitors.

During the follow-up period, 52 of the patients died, including 41 from cardiovascular death.

A higher aldosterone level was associated with a higher risk of cardiovascular death during the follow-up period ($\chi^2 = 11.36$, HR = 3.11 for one log increase, 95% CI = 1.69−5.80, $P = 0.0005$; *Table 3*) and with a higher risk of death from any cause during the follow-up period ($\chi^2 = 5.95$, HR = 2.16 for one log increase, 95% CI = 1.28−3.76, $P = 0.005$; see Supplementary material online, *Table S1*). Other baseline characteristics associated with cardiovascular and all-cause mortality are presented in *Table 3* and in the see Supplementary material online, *Table S1*.

Multivariable analysis showed that aldosterone was independently associated with cardiovascular death ($\chi^2 = 9.64$, HR = 4.18 for one log increase, 95% CI = 1.70−10.30; $P = 0.001$). Five other parameters were also associated with cardiovascular death: PAOD ($P = 0.001$), BNP levels ($P = 0.0009$), post-ACS ($P = 0.03$), diabetes mellitus ($P = 0.02$), and a low LVEF ($P = 0.04$, *Table 5*). The contribution of aldosterone to the model, as evaluated by the log-likelihoods test, was highly significant ($\chi^2 = 12.29$; $P < 0.0005$). To estimate the incremental prognostic value of aldosterone to predict cardiovascular death, we compared the probabilities of events and non-events of the model with and without aldosterone. The IDI of adding aldosterone to the model was 3.1% (95% CI = 2.2−4.0), $P < 0.0001$. The consequence on reclassification of subjects was estimated with the NRI (category free option): 31.7% of the event subjects and 29.0% of the non-event subjects were correctly reclassified after addition of aldosterone to the model, resulting in an overall NRI of 60.7% (37.5−85.1%), $P < 0.0001$ (*Table 4*).

After exclusion of post-ACS patients, aldosterone remained independently associated with cardiovascular death ($\chi^2 = 7.98$, HR = 5.71 for one log increase, 95% CI = 1.49−22.74; $P = 0.005$). Similarly, after exclusion of patients with a NYHA >II, aldosterone remained independently associated with cardiovascular death ($\chi^2 = 8.07$, HR = 4.82 for one log increase, 95% CI = 1.63−14.26; $P = 0.004$). *Figure 1A* illustrates the occurrence of cardiovascular death according to the median aldosterone level. *Figure 2* illustrates the prognostic value of aldosterone stratified according to diabetic status (*A*), median BNP level (*B*), recent angina status (post-ACS vs. no post-ACS) (*C*), and median LVEF (*D*). Multivariable analysis showed that aldosterone was also independently associated with the risk of death from any cause ($\chi^2 = 10.2$, HR = 3.45 for one log increase, 95% CI = 1.64−7.40; $P = 0.001$). Five other parameters were associated with the risk of death from any cause: PAOD ($P = 0.001$), BNP level ($P = 0.009$), age ($P = 0.01$), C-reactive protein level ($P = 0.03$), and haemoglobin level ($P = 0.03$, *Table 5*).

Aldosterone and acute ischaemic events

During the follow-up period, 54 patients suffered from an acute ischaemic event; of which 41 had an acute MI and 16 had an ischaemic stroke. The composite of death and/or acute ischaemic event was observed in 94 patients.

A higher aldosterone level was associated with a higher risk of acute ischaemic event during the follow-up period ($\chi^2 = 6.75$, HR = 2.09 for one log increase, 95% CI = 1.19−3.50, $P = 0.009$; *Figure 1B* and *Table 3*) and with a higher risk of the composite of death and acute ischaemic event during the follow-up period ($\chi^2 = 11.14$, HR = 2.11 for one log increase, 95% CI = 1.40−3.33, $P = 0.0006$; *Figure 1C*, see Supplementary material online, *Figure S1* and see Supplementary material online, *Table S1*).

Other baseline characteristics associated with the occurrence of acute ischaemic events and of the composite of death and acute ischaemic events are presented in *Table 3* and in the Supplementary material online, *Table S1*.

Multivariable analysis showed that aldosterone was independently associated with the risk of acute ischaemic event ($\chi^2 = 6.21$, HR = 2.06 for one log increase, 95% CI = 1.17−3.63, $P = 0.01$; *Table 5*). In addition to aldosterone, PAOD ($P = 0.004$) and diabetes mellitus were associated with the risk of acute ischaemic event ($P = 0.03$; *Table 5*).

Multivariable analysis showed that aldosterone was also independently associated with the risk of the composite of death and acute ischaemic event ($\chi^2 = 8.05$, HR = 2.02 for one log increase, 95% CI = 1.34−3.28, $P = 0.004$). In addition to aldosterone, four other parameters were associated with the risk of death from any cause: PAOD ($P = 0.0006$), LVEF ($P = 0.01$), BNP level ($P = 0.03$), and C-reactive protein level ($P = 0.04$, *Table 5*). The results of this multivariate analysis were not significantly modified when post-ACS patients were excluded ($\chi^2 = 5.75$, HR = 2.10 for one log increase, 95% CI = 1.17−4.46, $P = 0.01$).

Table 3 Univariate relationship between baseline characteristics of the study population and the risk of cardiovascular death or the risk of acute ischaemic event (Cox model)

	Cardiovascular mortality			Acute ischaemic events		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P* value
Age (10 years increase)	1.57[a]	1.19–2.09	0.001	1.05[a]	0.83–1.31	0.70
Men, *n* (%)	0.85	0.42–1.74	0.66	1.23	0.66–2.29	0.54
Risk factors, *n* (%)						
Hypertension	1.99	1.03–3.85	0.04	1.24	0.94–2.89	0.08
Smoking	0.73	0.39–1.38	0.33	1.05	0.59–1.90	0.86
Diabetes mellitus	2.71	1.46–5.03	0.001	1.75	1.03–3.00	0.01
Obesity	1.08	0.54–2.16	0.83	1.13	0.60–2.16	0.70
BMI	0.98	0.91–1.04	0.52	0.97	0.91–1.03	0.38
Family history of CAD	0.60	0.33–1.29	0.22	1.25	0.78–2.15	0.42
Clinical condition, *n* (%)						
Post-ACS	1.80	0.97–3.36	0.06	1.53	0.78–2.96	0.21
No recent ACS						
History of peripheral obstructive disease	3.77	2.07–6.90	0.0001	2.60	1.38–4.90	0.003
Carotid	4.63	2.14–10.0	0.0001	3.07	1.30–7.30	0.01
Lower extremity	2.89	1.52–5.55	0.001	2.41	1.22–4.76	0.01
NYHA class, *n* (%)						
I						
II	2.93	2.09–4.11	0.0001	0.93	0.60–1.44	0.73
III						
IV						
Angiographic data and revascularization procedure						
LVEF, % (10% decrease)	1.98[b]	1.58–2.49	0.0001	1.17[b]	0.96–1.43	0.12
No. of vessels with >50% stenosis	1.71	1.17–2.50	0.005	1.55	1.11–2.16	0.009
Stent implantation, *n* (%)	0.85	0.26–2.75	0.78	0.88	0.32–2.46	0.82
Medication at baseline, *n* (%)						
β-Blockers	0.63	0.33–1.20	0.16	0.80	0.44–1.42	0.44
ACE inhibitors	2.00	1.07–3.77	0.03	2.43	1.24–4.73	0.01
Diuretics	2.73	1.29–5.33	0.01	1.50	0.83–2.72	0.19
Statins	0.87	0.43–1.75	0.69	0.48	0.21–1.09	0.08
Oral antiplatelet agents	1.56	0.21–11.36	0.66	0.53	0.13–2.16	0.37
Total cholesterol, mg/dL	1.01	1.00–1.01	0.13	1.00	0.99–1.01	0.70
LDL cholesterol, mg/dL	1.01	1.00–1.01	0.18	1.00	0.99–1.01	0.98
HDL cholesterol, mg/dL	0.98	0.96–1.01	0.26	0.97	0.95–1.00	0.05
Triglycerides, mg/dL	0.99	0.99–1.00	0.13	1.00	0.99–1.01	0.47
Fasting glycaemia, mmol/L	13.07[c]	2.29–74.56	0.004	0.88[c]	0.13–6.01	0.99
HbA1c, %	38.47[c]	2.51–590.36	0.008	2.13[c]	0.13–36.01	0.60
hsC-reactive protein, mg/L	3.37[c]	2.07–5.50	0.0001	1.63[c]	1.01–2.65	0.04
Creatinine, mg/L	1.03	1.01–1.05	0.004	1.01	0.95–1.06	0.85
Creatinine clearance, mL/min/1.73 m^2	0.73[a]	0.63–0.85	0.0001	1.02[a]	0.92–1.12	0.78
Haemoglobin, g/dL	1.33[d]	1.04–1.69	0.02	1.20[d]	1.02–2.01	0.03
BNP, pg/mL	7.03[c]	3.91–12.65	0.0001	1.68[c]	1.07–2.65	0.02
Aldosterone, pg/mL	3.11[c]	1.69–5.80	0.0005	2.09[c]	1.19–3.50	0.009
Aldosterone >25 pg/mL	3.45	1.15–6.39	0.002	2.42	1.18–5.01	0.01

Data are presented as mean ± SD or median (inter-quartile range), unless otherwise stated.
[a]Hazard ratio is provided for an increase in 10 unit of the variable.
[b]Hazard ratio is provided for a decrease in 10 unit of the variable.
[c]Hazard ratio is provided for 1 log increase in the variable unit.
[d]Hazard ratio is provided for a decrease in 1 unit of the variable.

Table 4 Aldosterone and reclassification 'without category' of the risk of cardiovascular death

	All	Reclassification upwards	Reclassification downwards		NRI (%)
Rate of cardiovascular death	0.051	0.0912	0.0278		
Expected number of subjects with cardiovascular death	41	27	14	Among subjects with CV death	31.7
Expected number of subjects without cardiovascular death	758	269	489	Among subjects without CV death	29.0
Overall					60.7 (37.5–85.1%)

NRI, net reclassification improvement.

Discussion

Previous studies have reported that high aldosterone levels are associated with long-term mortality in patients with congestive heart failure or AMI. The present study demonstrates for the first time that, outside of these very specific and high-risk populations, plasma aldosterone is independently associated with long-term mortality in patients with CAD and that aldosterone is associated with the risk of acute ischaemic event. In addition, reclassification analysis further demonstrates that aldosterone can provide complementary and incremental prognostic information to the most recently validated clinical and biological risk factors, including BNP and C-reactive protein, and that variations of aldosterone levels among patients with relatively low plasma concentrations of aldosterone can be predictive of clinical outcome.

Clinical and biological correlates of aldosterone levels

In a recent study, Palmer *et al.*[13] reported on the relationship between medications and aldosterone levels in patients with acute MI, but the present study represents the first systematic investigation into the clinical and biological correlates of aldosterone in patients with CAD. This study's observations that aldosterone levels are inversely related to age and creatinine clearance are consistent with those of previous reports that have shown that, in healthy subjects, aldosterone secretion, and concentration both decline with age[20] and that renal failure leads to an increase in aldosterone levels.[21] The relationship between renal failure and aldosterone levels could also partly reflect the deleterious effect of aldosterone on renal function.[22]

Among the risk factors, we found that aldosterone levels were positively correlated with obesity and hypertension, a finding that is consistent with previous epidemiological studies performed in different populations[23] and with preclinical studies that have suggested that adipocytes play a key role in stimulating mineralocorticoid secretion.[23,24] This relationship, combined with the increased mortality associated with higher aldosterone levels also reported in the present study, could explain part of the increased risk of mortality observed in patients with a metabolic syndrome.

The relationships between aldosterone and the clinical and biological parameters related to LV function are complex. While aldosterone levels were higher in patients with a high NYHA class, no significant relationship was found between aldosterone levels and LVEF or BNP, suggesting that the activation of the aldosterone system is a complex phenomenon in which the LVEF does not play a major part. In that regard, aldosterone is different from BNP, which is closely related to LVEF, as demonstrated in the present study and elsewhere. This information is also useful in the context of assessing the prognostic value of aldosterone in our population because it suggests that the information provided by aldosterone is not redundant to that provided by the coupled 'LVEF/BNP'.

The observation of a higher aldosterone level in post-ACS patients is consistent and extends the observation of a higher aldosterone level in patients with an acute or recent MI (*Table 6*) and could suggest that acute ischaemia can stimulate the aldosterone pathway. The lower level of aldosterone associated with the use of β-blockers confirms and extends the previous observation by Blumenfeld *et al.*,[25] in which the use of β-blockers was found to alter the renin–angiotensin–aldosterone system and decrease aldosterone production.

Finally, although some studies have reported a lower level of aldosterone in patients treated with ACE inhibitors,[13] this was not the case in the present study or in similar studies by others.[10,26,27] Several reasons can be proposed to explain this lack of association. First, longitudinal pharmacological studies have reported a gradual 'aldosterone escape' without significant effect on aldosterone levels in ~40% of patients, despite an adequate ACE inhibition.[28,29] It has also been demonstrated that the timing of blood sampling relative to drug intake is critical. In particular, studies in which patients were fasting at the time of blood sampling found no significant impact of treatment with ACE inhibitors on aldosterone level.[26,27] This is notable since in the present study blood sampling was also performed in fasting patients. Finally, imbalances in characteristics between those patients who were using and those who were not using ACE inhibitors may have influenced the findings. For instance, while patients with hypertension had higher levels of aldosterone (*Table 1*) they were also those who more frequently used ACE inhibitors (58 vs. 42%, $P = 0.0004$). Similarly, aldosterone was higher in patients using diuretics (*Table 1*), but these individuals also used ACE inhibitors more frequently (81 vs. 55%, $P = 0.0001$).

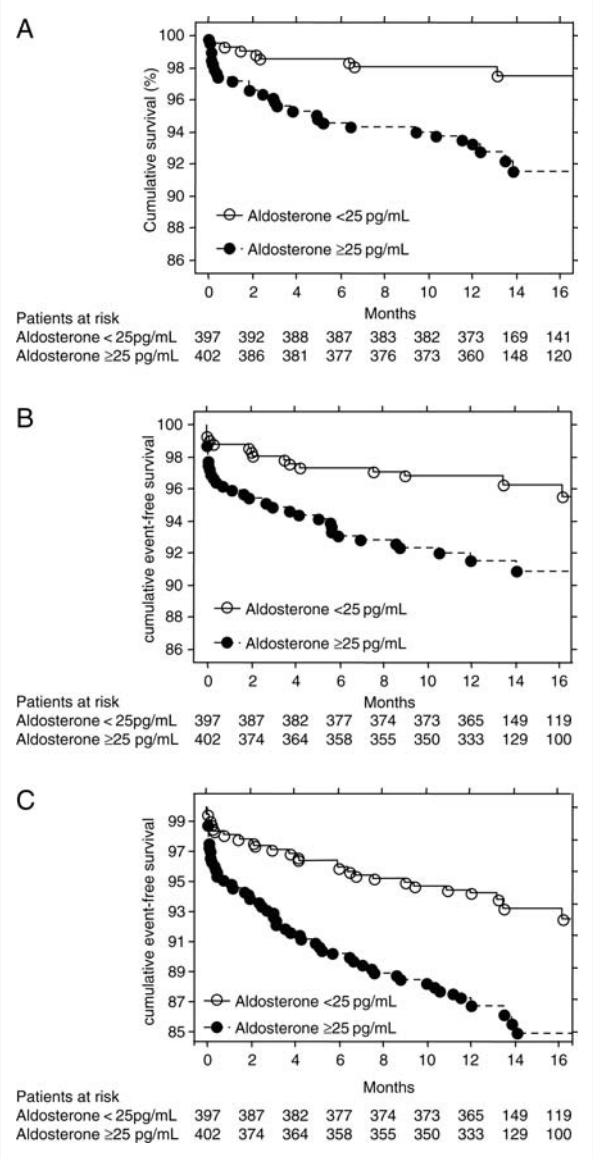

Figure 1 Occurrence of cardiovascular death (*A*, HR = 3.45, *P* = 0.002), acute ischaemic events (*B*, HR = 2.42, *P* = 0.01) and the composite of death and acute ischaemic events (*C*, HR = 2.40, *P* = 0.001) according to the median level of aldosterone (25 pg/mL).

Predictive value of aldosterone levels in patients with coronary artery disease

Because preclinical studies have suggested that aldosterone can have deleterious effects on the cardiac[1,2,30] and vascular injury/repair processes,[3–6,31] it has been suggested that the levels of aldosterone in plasma could predict clinical outcomes in patients with coronary atherosclerosis. However, the present study is the first to demonstrate that aldosterone is strongly and independently associated with the risk of cardiovascular and total mortality in patients with coronary atherosclerosis outside the setting of heart failure or AMI.[7–13,15] By design, no patient with an AMI or an ACS requiring an emergent angiography was included in the present study. All participants underwent an elective PCI, and only 26% of those were post-ACS patients for whom conservative medical treatment of medical stabilization had been indicated and who subsequently had undergone angiography leading to PCI. Furthermore, after exclusion of that subset of patients aldosterone remained independently associated with the risk of cardiovascular mortality and the risk of the composite of death and acute ischaemic events. The population we investigated was clearly not experiencing 'heart failure', as evidenced by the mean LVEF (58%) and by the very small proportion of patients having a NYHA class >II (7%). Even so, after exclusion of those patients, aldosterone remained independently associated with cardiovascular mortality and the risk of the composite of death and acute ischaemic events.

The comparative analysis of the median value of the three key risk factors (LVEF, BNP, or C-reactive protein; *Table 6*) also clearly demonstrated that the population investigated in the present study was at much lower risk than the CAD populations investigated previously.[7–13] Indeed, while in the present study LVEF was much higher and BNP and C-reactive protein were much lower than in those levels found in previous studies,[7–13] the value of these three key risk factors was typical for patients with stable CAD.[32]

Importantly, our study demonstrated that variations of aldosterone levels within the normal range can be associated with clinical outcome. While, to date, this association has been limited to populations with a high median aldosterone level (≥40 pg/mL, *Table 6*), analysis of the association between tertiles of aldosterone and the risk of death and ischaemic events (see Supplementary material online, *Figure S1*) demonstrates that variations of aldosterone in patients with an aldosterone level ≤35 pg/mL can impact the clinical outcome (see Supplementary material online, *Figure S1*).

Stimulation of the atherothrombotic process as a potential mechanism of the increased mortality associated with high aldosterone levels

One of the major findings of the present study is that baseline aldosterone levels are associated with the risk of an acute ischaemic event. This finding suggests that the increased cardiovascular mortality rate associated with a high aldosterone level could be, at least partly, related to an increased risk of experiencing an ischaemic event.

This finding confirms and extends previous preclinical observations which have suggested that aldosterone has the potential to interfere with the athero-thrombotic process in humans. Aldosterone may indeed promote endothelial dysfunction in animals[33] and in humans,[34] an effect that can occur either directly or indirectly via angiotensin II signalling.[33] Aldosterone is also known to induce the proliferation of inflammatory cells surrounding the coronary arteries, to stimulate macrophage infiltration within the vessel wall and to up-regulate inflammatory events in rat and human vascular cells.[3,35] In addition, aldosterone has been shown to stimulate smooth muscle cell proliferation and extracellular matrix synthesis and to accelerate neointimal hyperplasia in a rabbit model of vascular injury.[6] Stimulation of the

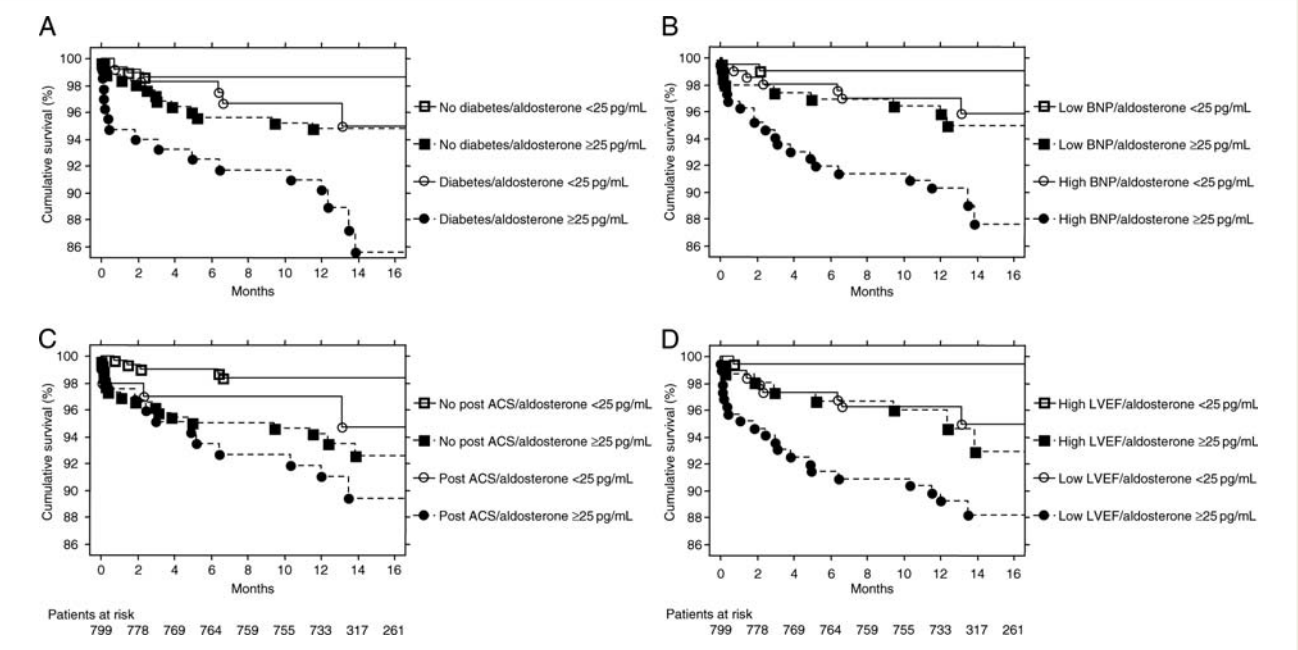

Figure 2 Occurrence of cardiovascular death according to the median level of aldosterone levels (25 pg/mL) adjusted to diabetic status (*A*, $P = 0.0008$), median BNP level (*B*, $P = 0.0006$), angina status (*C*, $P = 0.0007$), or median left ventricular ejection fraction (*D*, $P = 0.0006$). No significant interaction was found between aldosterone level cut at the median and diabetic status ($P = 0.32$), median BNP level ($P = 0.30$), angina status ($P = 0.75$), or median left ventricular ejection fraction ($P = 0.15$) on the related risk of cardiovascular death.

Table 5 Correlates of cardiovascular mortality, all causes mortality, acute ischaemic events, and the composite of death and acute ischaemic events by Cox model analysis

Independent variable	Hazard ratio	95% CI	*P*-value	β coefficient	SE	χ^2
Cardiovascular mortality						
Aldosterone (1 log increase)	4.18	1.70–10.30	0.001	1.43	0.46	9.64
PAOD	3.73	1.70–8.20	0.001	1.32	0.40	10.74
BNP (1 log increase)	4.19	1.50–11.66	0.006	1.44	0.52	7.46
Post-ACS	2.83	1.11–7.91	0.02	1.12	0.51	5.01
LVEF (10% decrease)	1.29	1.01–1.68	0.04	0.26	0.13	4.12
Diabetes mellitus	2.23	1.05–5.00	0.04	0.80	0.40	4.11
All causes mortality						
Aldosterone (1 log increase)	3.45	1.64–7.40	0.001	1.25	0.38	10.2
PAOD	2.84	1.50–5.38	0.001	1.05	0.32	10.1
BNP (1 log increase)	2.70	1.25–6.40	0.01	1.06	0.42	5.80
Age (10 years increase)	1.44	1.06–1.95	0.01	0.37	0.16	5.58
hsC-reactive protein (1 log increase)	1.88	1.04–3.41	0.03	0.64	0.30	4.47
Haemoglobin (1g/dL decrease)	1.55	1.03–3.11	0.03	0.53	0.30	4.40
Acute ischaemic events (MI and ischaemic stroke)						
PAOD	2.52	1.33–4.80	0.004	0.93	0.32	8.03
Aldosterone (1 log increase)	2.06	1.17–3.63	0.01	0.72	0.29	6.21
Diabetes mellitus	1.70	1.01–2.94	0.03	0.53	0.29	4.15
Death and acute ischaemic events						
PAOD	2.60	1.51–4.52	0.0006	0.96	0.28	11.82
Aldosterone (1 log increase)	2.02	1.34–3.28	0.004	0.70	0.25	8.05
LVEF (10% decrease)	1.23	1.04–1.46	0.01	0.21	0.09	5.72
BNP (1 log increase)	1.66	1.03–2.70	0.03	0.51	0.25	4.30
hsC-reactive protein (1 log increase)	1.46	1.01–2.12	0.04	0.38	0.19	3.92

Table 6 Previous studies investigating the relationship between plasma aldosterone levels and clinical events

Clinical setting	Authors	Total population (*n*)	Patients with CAD (%)	LVEF, % (mean)	Aldosterone level, pg/mL (median)	BNP level, pg/mL (median)	hsC-reactive protein, mg/L (median)	Main clinical endpoint	Non-fatal endpoint evaluated separately
Congestive heart failure	Swedberg *et al.* (CONSENSUS)[7]	239	73	NA[a]	399 (mean)	NA	NA	Mortality	No
	Vantrimpont *et al.*[8]	534	100	<40%	270 (mean)	NA	NA	Mortality	Heart failure
	Latini *et al.* (Val-HeFT)[9]	4300	57	26	101	97	3.23	Mortality	No
	Güder *et al.*[10]	294	44	NA	100	NA	6.6	Mortality	No
Acute MI	Beygui *et al.*[11]	356	100	NA	66	NA	NA	Total/CV mortality	No
	Palmer *et al.*[13]	583	100	47	40	90	NA	Total mortality	Heart failure
	Beygui *et al.*[12]	471	100	NA	42	207	19.9	Combined endpoint	No
Mixed (including CAD and MI)	Tomaschitz *et al.*[15]	3153	67	64[b]	79	NA	3.9	Total/CV mortality	No
CAD including MI	Tomaschitz *et al.*[15]	2140	100	NA	NA	NA	NA	Total/CV mortality	No
CAD without AMI or heart failure	Present study	799	100	58	25	35	4.1	Total/CV mortality	Ischaemic events

NA, not available.
[a]Major inclusion criteria was a NYHA class = IV without prespecified LVEF threshold.
[b]Available in 43% of the population.

atherosclerosis process has been confirmed in other animal models, including in non-human primates.[3,36] All of these vascular effects are independent of variations in blood pressure and can be inhibited by MR blockers.[6,36–38]

Value of the prognostic information associated with aldosterone levels

The present study has demonstrated the association between aldosterone levels and clinical events in a comparatively large population ($n = 800$) of consecutive patients—to date, one of the largest studies to investigate the prognostic value of aldosterone (*Table 6*). It is the first study to investigate the association between aldosterone and clinical outcome while being adjusted simultaneously on the three major validated risk factors of LVEF, BNP, and C-reactive protein (*Table 6*). Importantly, it is also the first to perform reclassification analysis and to demonstrate that aldosterone can provide complementary and incremental prognostic information on factors such as age, gender, diabetes, LVEF, C-reactive protein and BNP (*Table 4*).

The prognostic information provided by aldosterone is very high—in the same magnitude as the value provided by BNP, the other major risk factor identified by this study. In that regard, the observation that BNP is a major risk factor in patients with stable CAD is consistent with those of previously published studies.[32]

Study limitations

This was a single-centre study and, as such, patient referral, PCI technique, and medical management may have influenced the results. However, the consecutive nature of the population and the exclusion of patients with acute MI ensured useful insights into the analysis of the clinical and biological correlates of aldosterone in patients with CAD. These characteristics, in conjunction with the high rate of clinical follow-up (100%), ensured that the study assessed accurately the prognostic value of aldosterone in CAD patients with preserved LV function referred for elective PCI.

Clinical implications

The present study provides important information on the clinical significance of baseline levels of aldosterone in patients with established CAD by demonstrating that the level of aldosterone in the plasma of these patients is associated with the risk of death following elective PCI. These results extend previous findings in patients with heart failure or AMI and suggest that aldosterone levels may provide incremental prognostic information beyond that from classical markers like age, gender, diabetes, and LVEF, C-reactive protein and BNP levels. In addition, the demonstrated association of aldosterone and the risk of acute ischaemic event indicates a potential mechanism for the observed increased mortality rate by suggesting that aldosterone can interact with the atherosclerotic process.

However, some caution should be applied before generalizing the use of 'aldosterone level' as a risk factor for clinical management; further studies are needed. The data from this study strongly support the need for a randomized controlled trial to assess the hypothesis that an aldosterone-receptor blockade can improve the prognosis of patients with CAD, whether complicated by LV dysfunction or not.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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