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Aldosterone, atherosclerosis and vascular events in patients with stable coronary artery disease

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ABSTRACT

Background and aims: Plasma aldosterone has been associated with all-cause and cardiovascular mortality in high-risk cardiovascular populations, including patients with heart failure, myocardial infarction and high-risk coronary artery disease (CAD) patients. In the present study, we evaluated the association of plasma aldosterone levels with vascular events in a large prospective cohort of stable CAD patients recruited in an outpatient setting. Moreover, we investigated the relationship between aldosterone and atherosclerotic burden.
Methods and results: Baseline plasma aldosterone levels were measured in 2699 subjects with CAD (mean age 60 ± 10 years, 82% male). During a median follow-up of 4.7 years, 308 (11%) patients died, of which 203 were from a vascular cause. Vascular endpoints of myocardial infarction, ischemic stroke or vascular death occurred in 355 (13%) patients. Multivariable Cox regression analysis was performed, adjusting for multiple confounders. Aldosterone (median 96 pg/mL, interquartile range 70–138 pg/mL, normal range 58–362 pg/mL) was independently associated with major vascular events (hazard ratio (HR) 1.56, 95% confidence interval (CI) 1.13–2.15) and vascular mortality (HR 1.95, 95% CI 1.27–3.00). By multivariable regression analysis, aldosterone was also associated with the presence of atherosclerosis in additional vascular territories (cerebrovascular disease and/or peripheral artery disease) ($p = 0.026$).
Conclusions: In patients with stable coronary artery disease, plasma aldosterone is independently associated with the risk of major vascular events and vascular mortality and with atherosclerotic burden.

1. Introduction

Renin-angiotensin-aldosterone system (RAAS) activation is an important factor in the pathophysiology of cardiovascular disease. Aldosterone is a hormone with mineralocorticoid activity that is synthesized by the adrenal glands. As a component of the RAAS, aldosterone is classically known to play a regulatory role in body fluid and electrolyte homeostasis, thus contributing to the development of hypertension. Recent findings from experimental and clinical studies have indicated that aldosterone might be involved in cardiovascular disease through a mechanism distinct from its contribution to hypertension [1–3]. Under controlled experimental conditions, RAAS activation and administration of aldosterone resulted in myocardial and vascular fibrosis, inflammation, and endothelial dysfunction; such physiologic perturbations are known to complicate the atherosclerotic process [4–8].

The experimental associations between aldosterone and end-organ damage have been supported by clinical data showing benefit of aldosterone blockade in patients with heart failure or left ventricular dysfunction after acute myocardial infarction (MI) [9–11]. Likewise, in patients with hypertension, aldosterone blockade induced beneficial vascular wall changes, on top of blood pressure effects [12].

Several observational studies of patients with heart failure have revealed a strong association of aldosterone levels with increased mortality and with an increased risk of a combined endpoint comprising cardiovascular mortality, development of severe heart failure or

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recurrent MI [13–16]. In addition, aldosterone levels in patients presenting with an acute MI were found to be associated with increased cardiovascular risk during follow-up, even in the absence of heart failure or marked left ventricular dysfunction [17–19]. Clinically relevant associations between aldosterone levels and patient outcome have recently been demonstrated in individuals with coronary artery disease (CAD) admitted for coronary angiography and including a large proportion (40%) with an acute coronary syndrome (ACS) [20]. Likewise, we demonstrated aldosterone levels to be associated with an increased risk of cardiovascular and all-cause mortality in a group of 807 patients undergoing elective percutaneous coronary intervention, of whom 26% with a very recent history (2–7 days) of an ACS [21].

However, both studies did not specifically investigate the association between aldosterone and clinical outcome in the non-ACS population and the prognostic value of aldosterone in patients with stable CAD remains unknown. Similarly, the potential link between aldosterone and the process of atherosclerosis has yet to be reported in the literature.

Therefore, the primary objective of this study was to investigate the association between plasma aldosterone levels and future vascular events in patients with stable CAD recruited for the Secondary Manifestations of ARTerial disease (SMART) outpatient cohort study [22]. In addition, we aimed to define the relationships between baseline aldosterone levels and fatal vascular events or atherosclerosis burden.

2. Methods

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.1. Study population

This study was approved by the Ethics Committee of the University Medical Centre Utrecht (UMCU), The Netherlands, and all patients provided written informed consent.

Patients were derived from the SMART study, an ongoing, prospective outpatient cohort study at the UMCU [22]. SMART was originally designed to determine the prevalence of concomitant arterial diseases and risk factors for atherosclerosis in a patient population characterized by a high cardiovascular risk profile. Study patients were newly referred to the UMCU with symptomatic arterial disease (coronary heart disease, cerebrovascular disease, abdominal aortic aneurysm or peripheral arterial disease) or with traditional cardiovascular risk factors (hypertension, hyperlipidemia, or diabetes mellitus). Enrolees were non-invasively screened to ascertain manifestations of atherosclerotic diseases and risk factors other than the qualifying diagnosis, as previously described; briefly, at baseline patients underwent a standardized vascular screening programme, including laboratory tests, ultrasonography and completion of a health questionnaire (described below).

For the current study, we extracted the data of 2862 consecutive patients enrolled between September 1996 and March 2008 and having established coronary artery disease. Plasma aldosterone levels were available for 2810 (98%) of the patients. Fifty-two patients were excluded based on reported administration of aldosterone-blocking agents, leaving a total of 2758 patients for analysis.

2.2. Definitions

CAD was defined as a history of myocardial infarction or coronary revascularization (coronary bypass surgery or coronary angioplasty).

Cerebrovascular disease was defined as a history of transient ischemic attack, cerebral infarction, amaurosis fugax, retinal infarction or carotid surgery.

Peripheral artery disease was defined as a symptomatic and documented obstruction of distal arteries of the leg or surgery of the leg (percutaneous transluminal angioplasty, bypass or amputation).

Markers of atherosclerotic burden were identified as involvement of multiple vascular territories (CAD plus at least one other manifestation of atherosclerotic vascular disease), presence of carotid artery stenosis (>50%), ankle-brachial index (ABI) and carotid intima-media thickness.

Diabetes mellitus at baseline was defined as a documented history of diabetes or use of glucose-lowering agents. In addition, subjects without a history of diabetes but with a fasting plasma glucose level of ≥7.0 mmol/L at baseline and record of having received treatment with glucose-lowering agents within 1 year after baseline attainment were considered as having diabetes at baseline.

Hypertension and hyperlipidemia were defined as previously described [22].

2.3. Data collection

At enrolment, patients were asked to complete a standardized questionnaire on medical history, symptoms of and risk factors for cardiovascular disease, presence of vascular disease in first-degree relatives and current medication use. Furthermore, a standardized diagnostic protocol was performed, including physical examination (height, weight, waist circumference, systolic and diastolic blood pressure) and laboratory tests to determine fasting plasma lipid, glucose and insulin levels. For the purpose of this study, aldosterone, B-type natriuretic peptide (BNP) and high-sensitivity C-reactive protein (hsCRP) were measured (blinded to clinical data) in EDTA-plasma. Aldosterone was measured by manual radioimmunoassay (Diagnostic Systems Laboratories, Beckman Coulter, Sinsheim, Germany). The inter-assay coefficient of variation ranged from 6 to 9% at 160 and 350–1100 pmol/L, respectively. hsCRP was measured on a DxC 800 routine chemistry system and BNP was analysed on a Dxl 800 immunochemistry system (both from Beckman Coulter, Brea, California, USA).

To obtain reference values, measurements were repeated in 70 healthy volunteers.

2.4. Follow-up

During follow-up, patients were asked to complete a biannual questionnaire on hospitalizations and outpatient clinic visits.

The primary outcome of interest for this study was the occurrence of vascular events defined as non-fatal MI, non-fatal stroke or vascular death (Table 1). Secondary outcome of interest was vascular mortality. When a possible event was reported, hospital discharge letters and results of relevant laboratory and radiology examinations were collected. Death was reported by relatives of the participant, the general practitioner or the vascular specialist treating the patient. Based on the information from the questionnaire and/or the family, all events were audited by three members of the SMART study Endpoint Committee, comprising physicians from the Departments of Cardiology, Neurology and Vascular Surgery. Follow-up duration (years) was defined as the period between study enrolment and first cardiovascular event or death from any cause, date of loss to follow-up or the preselected censoring date of 1 March 2009.

2.5. Data analysis

Since plasma aldosterone was not normally distributed, aldosterone levels were categorized into quartiles, segregated by sex. Next, the corresponding male and female quartiles were merged to generate quartiles with equal proportions of men vs. women in each (sex-pooled analysis). This was done to ensure comparable percentages of both sexes in all quartiles, since aldosterone levels tend to be higher in women as compared to men. The lowest quartile served as the reference group.

Cox proportional hazard analysis was performed to estimate hazard ratios (HR) and corresponding 95% confidence intervals (CI) for the occurrence of major vascular events and for the occurrence of vascular death associated with plasma aldosterone levels. If a patient had multiple events, the first recorded event was used in the analyses. Patients were censored if they were lost to follow-up. HRs were calculated both across aldosterone quartiles, with quartile 1 as reference, and per quartile increment.

Cox proportional hazard analysis was also performed with aldosterone levels log-transformed. For presentation purposes, results are displayed for quartile-based analyses.

Four models were constructed, the first model being a crude model, including only aldosterone. In the second model adjustments were made for age and gender. In the third model additional adjustments were made for systolic blood pressure, diabetes mellitus,

Table 1
Definitions of major vascular events.

Myocardial infarction	At least two of the following criteria: – Chest pain for at least 20 min, not disappearing after administration of nitrates – ST segment-elevation > 1 mm in two following leads or a new left bundle branch block on electrocardiogram – Creatine kinase (CK)-elevation of at least two times the normal value of CK and a MB-fraction > 5% of the total CK
Ischemic stroke	– Definite ischemic stroke: relevant clinical features that have caused an increase in impairment of at least one grade on the modified Rankin scale, accompanied by a fresh ischemic infarction on brain-scan – Definite stroke, probably non-haemorrhagic: relevant clinical features that have caused an increase in impairment of at least one grade on the modified Rankin scale, without new (haemorrhagic) infarction on brain-scan and without signs of recovering bleeding
Vascular death	– Death from myocardial infarction – Sudden death: unexpected cardiac death within 1 h after onset of symptoms, or within 24 h given convincing circumstantial evidence – Death from ischemic stroke – Death from intracerebral hemorrhage – Death from decompensated heart failure – Death from rupture of abdominal aortic aneurysm – Vascular death from other cause

history of MI, body mass index (BMI), creatinine clearance, plasma BNP-levels and the use of beta-blockers, diuretics, angiotensin converting enzyme (ACE)-inhibitors and angiotensin II-receptor blockers (ARBs), all considered as potentially confounding factors in the relationship between plasma aldosterone and vascular events. In the fourth model we additionally explored the effects of low-density lipoprotein (LDL)-cholesterol, smoking and hsCRP, in order to assess the effect of plasma aldosterone levels on cardiovascular risk while taking into account other established cardiovascular risk factors that could not be considered as obvious confounders in the relationship between aldosterone and vascular events.

To investigate whether the relation between plasma aldosterone and vascular events was modified by the duration of CAD at baseline or by the presence of vascular disease at other locations (brain, legs, abdominal aorta) we included these interaction terms in the Cox models. If the p-value of the interaction term was ≤ 0.05, then effect-modification was considered to be present.

The association of aldosterone levels with atherosclerotic burden was analyzed with univariable and multivariable linear or logistic regression analysis, as appropriate. For this purpose, markers of atherosclerotic burden (described above) were considered. Again, aldosterone levels were entered into the models as sex-pooled quartiles. In multivariable regression analysis age, gender, systolic blood pressure, diabetes mellitus, BMI, creatinine clearance, LDL-cholesterol, hsCRP and current smoking were included in the models as possible confounders.

3. Results

3.1. Baseline characteristics

The baseline characteristics of the study population according to aldosterone quartiles are displayed in Table 2.

The mean age of the 2699 subjects was 60 ± 10 years and 497 patients (18%) were female. A history of myocardial infarction was present in 53% ($n = 1426$) of the patients. Diabetes mellitus was present in 460 (17%) patients. The median plasma aldosterone level was 96 pg/mL with an interquartile range of 70–138 pg/mL. Median aldosterone levels were higher in females (102, IQR 74–146 pg/mL) than in males (94, IQR 68–137 pg/mL).

The aldosterone values measured are within the 95% reference range as obtained by repeating the same measurements in 70 local healthy control subjects (aged 40–65 years): 58–362 pg/mL.

3.2. Follow-up

The median follow-up period was 4.7 years (interquartile range 2.7–7.5), for a total follow-up of 13,396 person years. Sixty-eight of the 2699 participants (2.5%) were lost to follow-up before the censoring date, due to migration or withdrawal from the study. Median follow-up duration in these 68 participants was 3.3 years (1.7–5.6).

3.3. Aldosterone levels, vascular events and vascular death

During follow-up 308 (11%) patients died, 203 (7.5%) from a vascular cause. Additional vascular events were recorded in 148 patients (5.5%) having a myocardial infarction and 69 patients (2.6%) who suffered from an ischemic stroke. The vascular endpoint of MI, ischemic stroke or vascular death occurred in 355 (13%) patients. The cumulative five-year risk for the vascular events was 9.0% (95%CI 7.6–10.3%) and 4.7% (3.7–5.6%) for vascular death.

Table 2
Baseline characteristics of the study population according to plasma aldosterone concentration quartiles.

Total population ($n = 2699$)	Quartile 1	Quartile 2	Quartile 3	Quartile 4
	$n = 673$	$n = 677$	$n = 679$	$n = 670$
Aldosterone range (pg/mL)	<=74	68–102	94–146	>=137
Aldosterone median (pg/mL)	53 (43–61)	83 (76–89)	114 (104–126)	178 (154–223)
Age (years)	60 ± 10	60 ± 10	60 ± 10	60 ± 10
Female, *n* (%)	123 (18%)	125 (19%)	135 (18%)	124 (19%)
Current smoking, *n* (%)	169 (25)	170 (25)	186 (27)	188 (28)
Body mass index (kg/m^2)	27 ± 4	27 ± 4	27 ± 4	27 ± 4
Diabetes mellitus, *n* (%)	115 (17)	110 (16)	106 (16)	129 (19)
Family history of CAD, *n* (%)	158 (24)	141 (21)	151 (22)	109 (16)
History of myocardial infarction, *n* (%)	336 (50)	360 (53)	357 (53)	381 (57)
Time since first manifestation of CAD (years)	1.0 (0.5–5.0)	1.0 (0.5–6.0)	1.0 (0.5–6.0)	1.0 (0.5–8.0)
First manifestation of CAD ≥1 year, *n* (%)	339 (51)	378 (57)	380 (57)	396 (61)
Systolic blood pressure (mmHg)	138 ± 20	139 ± 21	140 ± 21	142 ± 22
Diastolic blood pressure (mmHg)	80 ± 11	81 ± 11	81 ± 11	82 ± 11
Total cholesterol (mmol/L)	4.5 (3.8–5.2)	4.6 (4.0–5.4)	4.7 (4.0–5.4)	5.0 (4.2–5.8)
Triglycerides (mmol/L)	1.3 (1.0–1.9)	1.5 (1.1–2.1)	1.5 (1.1–2.0)	1.6 (1.1–2.4)
HDL-cholesterol (mmol/L)	1.1 (1.0–1.4)	1.2 (1.0–1.4)	1.1 (0.9–1.4)	1.2 (0.9–1.4)
LDL-cholesterol (mmol/L)	2.6 (2.0–3.3)	2.7 (2.1–3.3)	2.7 (2.1–3.3)	2.9 (2.2–3.7)
BNP (pmol/L)	13 (7.0–24)	11 (5.0–23)	11 (5.0–21)	10 (5.0–21)
hsCRP (mg/L)	1.7 (0.8–3.4)	2.0 (0.9–3.8)	2.2 (1.1–4.4)	2.3 (1.1–4.5)
Creatinine clearance (Cockroft mL/min)	79 (67–91)	77 (65–90)	75 (63–90)	74 (59–88)
ABI at rest	1.18 (1.09–1.25)	1.18 (1.09–1.25)	1.17 (1.08–1.25)	1.15 (1.02–1.24)
Medication use				
Use of beta-blockers, *n* (%)	527 (78)	510 (75)	475 (70)	439 (66)
Use of antiplatelet medication, *n* (%)	558 (83)	574 (84)	569 (84)	531 (79)
Use of lipid lowering medication, *n* (%)	507 (75)	516 (76)	522 (77)	452 (68)
Use of ACE-inhibitors, *n* (%)	218 (32)	206 (30)	197 (29)	173 (26)
Use of ARBs, *n* (%)	64 (9.5)	50 (7.4)	56 (8.2)	47 (7.0)
Use of diuretics, *n* (%)	84 (13)	90 (13)	117 (17)	178 (27)
Territories affected by atherosclerosis				
Coronary artery disease, *n* (%)	673 (100)	677 (100)	679 (100)	670 (100)
Cerebrovascular disease, *n* (%)	51 (8)	52 (8)	67 (10)	83 (12)
Peripheral artery disease, *n* (%)	59 (9)	55 (8)	58 (9)	99 (15)
No. of vascular territories affected				
1	571 (85)	578 (85)	562 (83)	508 (76)
2	94 (14)	91 (13)	109 (16)	142 (21)
3	8 (1.2)	8 (1.2)	8 (1.2)	20 (3.0)

HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, BNP: B-type natriuretic peptide, hsCRP: high-sensitivity C-reactive protein, ABI: ankle-brachial index, ACE: angiotensin converting enzyme, ARB: angiotensin II receptor blocker.
Data are mean ± standard deviation (SD) or median (interquartile range) unless otherwise stated.
Categories of vascular territories affected are not mutually exclusive.

Table 3
Hazard ratios of plasma aldosterone quartiles on the occurrence of vascular death and the composite endpoint of myocardial infarction, stroke or vascular death.

	Quartile 1 n=673	Quartile 2 n=677	Quartile 3 n=679	Quartile 4 n=670
Aldosterone range (pg/mL)	<=74	68-102	94-146	>=137
	MAJOR VASCULAR EVENTS			
No. of events	64	80	81	126
Model I	Reference	1.12 (0.81-1.56)	1.14 (0.82-1.58)	1.72 (1.27-2.33)
Model II	Reference	1.12 (0.81-1.56)	1.12 (0.80-1.56)	1.70 (1.26-2.30)
Model III	Reference	1.13 (0.81-1.59)	1.11 (0.79-1.56)	1.56 (1.13-2.15)
Model IV	Reference	1.16 (0.82-1.63)	1.13 (0.80-1.60)	1.51 (1.08-2.11)
	VASCULAR MORTALITY			
No. of events	33	42	42	86
Model I	Reference	1.11 (0.70-1.75)	1.12 (0.71-1.76)	2.18 (1.45-3.26)
Model II	Reference	1.15 (0.73-1.81)	1.09 (0.69-1.72)	2.09 (1.40-3.13)
Model III	Reference	1.10 (0.69-0.74)	1.08 (0.67-1.72)	1.95 (1.27-3.00)
Model IV	Reference	1.12 (0.69-1.83)	1.14 (0.70-1.85)	1.99 (1.26-3.13)

Model I: Aldosterone. Model II: Model I with adjustment for age and sex. Model III: Model II with additional adjustment for systolic blood pressure, diabetes mellitus, history of myocardial infarction, body mass index, creatinine clearance, plasma B-type natriuretic peptide levels and use of betablockers, diuretics, ACE-inhibition and angiotensin II-receptor blockers. Model IV: Model III with additional adjustment for LDL-cholesterol, current smoking and plasma high-sensitivity C-reactive protein levels.
Hazard ratios are reported with corresponding 95% confidence intervals.

As shown in Table 3, the risk of vascular events and vascular death increased across aldosterone quartiles. Compared with the lowest aldosterone quartile (<74 pg/mL), patients in the highest quartile (≥137 pg/mL) had a 60% higher risk (HR 1.60 (1.16–2.21)) for the combined vascular endpoint and a two times (HR 2.00 (1.30–3.07)) higher risk for vascular death, after adjustment for possible confounders (model III). For each quartile increment in plasma aldosterone levels the risk of the combined vascular endpoint increased by 16% (HR 1.16 (1.05–1.29)) while the risk of vascular death increased by 28% (HR 1.28 (1.11–1.47)) (model III) (Table 4). The associations were only slightly altered after additional adjustment for other established cardiovascular risk factors and hsCRP (model IV).

Cox proportional hazard analysis with aldosterone log-transformed yielded comparable results. For presentation purposes, results are displayed for quartile-based analyses.

Fig. 1 displays Cox proportional hazard survival curves according to quartiles of aldosterone. The incidence of vascular events (Fig. 1A) and vascular death (Fig. 1B) was highest in the upper aldosterone quartile, as compared to the lowest. The associations between plasma aldosterone levels and vascular events and between plasma aldosterone levels and vascular mortality were not modified by the duration of clinically manifest CAD at baseline (p-values for interaction 0.699 for vascular events and 0.756 for vascular mortality) nor by presence of manifest atherosclerotic disease at other locations ($p = 0.402$ for vascular events and $p = 0.427$ for vascular mortality).

3.4. Aldosterone levels and atherosclerotic burden

Univariable linear regression or logistic regression analysis, as appropriate, showed baseline aldosterone (expressed in sex-pooled quartiles) to be positively associated with both involvement of multiple vascular territories and presence of carotid artery stenosis and negatively associated with ankle-brachial index (Table 5).

After correction for possible confounders (age, gender, systolic blood pressure, diabetes mellitus, BMI, creatinine clearance, LDL-cholesterol, hsCRP, current smoking) in multivariable regression analysis, the associations were attenuated. However, aldosterone was still positively associated with involvement of multiple vascular territories.

Table 4
Hazard ratios for vascular death and the composite endpoint of myocardial infarction, stroke or vascular death per quartile increase in plasma aldosterone concentration.

	MAJOR VASCULAR EVENTS		VASCULAR MORTALITY	
	HR	95% CI	HR	95% CI
Model I	1.20	1.09-1.32	1.32	1.16-1.50
Model II	1.19	1.08-1.31	1.29	1.13-1.47
Model III	1.15	1.04-1.28	1.26	1.10-1.45
Model IV	1.14	1.02-1.26	1.27	1.10-1.47

Model I: Aldosterone. Model II: Model I with adjustment for age and sex. Model III: Model II with additional adjustment for systolic blood pressure, diabetes mellitus, history of myocardial infarction, body mass index, creatinine clearance, plasma B-type natriuretic peptide levels and use of betablockers, diuretics, ACE-inhibition and angiotensin II-receptor blockers. Model IV: Model III with additional adjustment for LDL-cholesterol, current smoking and plasma high-sensitivity C-reactive protein levels.
Hazard ratios are reported with corresponding 95% confidence intervals.

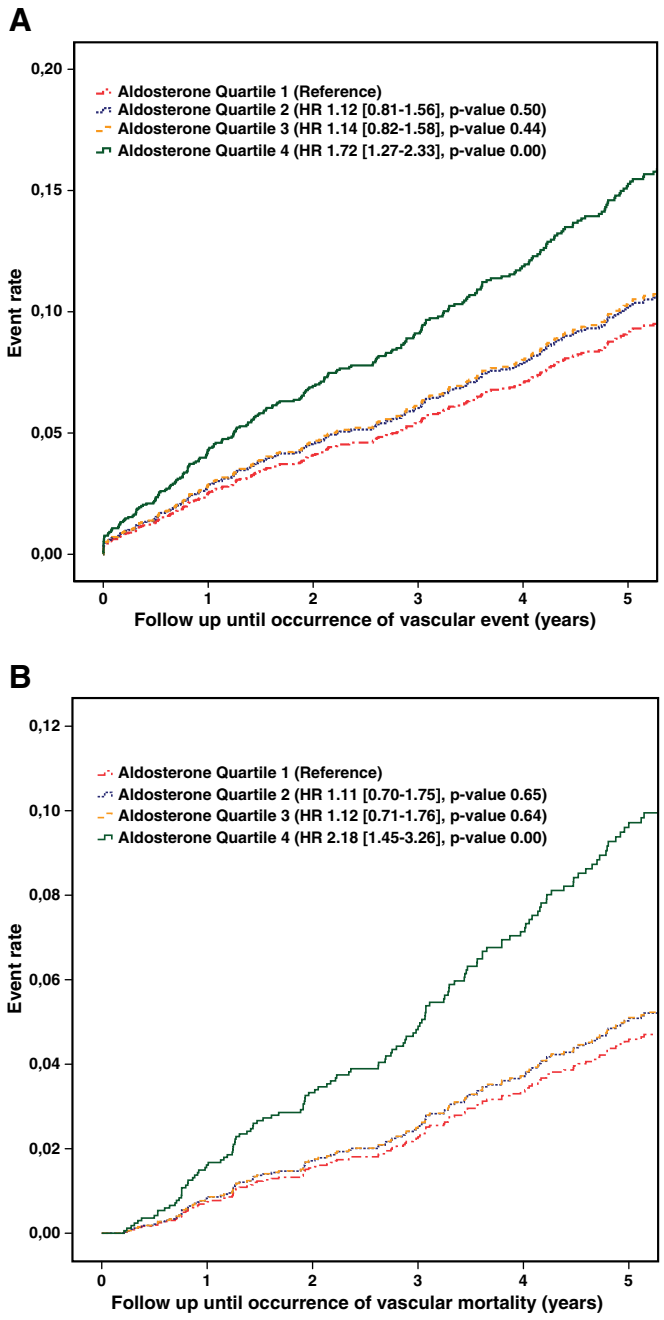

Fig. 1. Cox proportional hazard (survival) curves according to quartiles of aldosterone.

Table 5
Aldosterone in relation to several indicators of atherosclerotic burden.

Model	OR	95%CI	*p*-value
Multiple vascular territories affected			
Model A	1.79	1.36 to 2.35	0.000
Model B	1.79	1.35 to 2.36	0.000
Model C	1.41	1.04 to 1.91	0.026
Carotid stenosis (>50%)			
Model A	1.46	1.03 to 2.06	0.033
Model B	1.42	1.00 to 2.02	0.052
Model C	1.11	0.75 to 1.63	0.600
	β	95%CI	*p*-value
ABI			
Model A	−0.040	−0.061 to −0.019	0.000
Model B	−0.040	−0.060 to −0.019	0.000
Model C	−0.013	−0.034 to +0.008	0.223
IMT (mm)			
Model A	0.020	−0.010 to +0.050	0.196
Model B	0.018	−0.010 to +0.047	0.202
Model C	0.001	−0.029 to +0.030	0.960

Model A: Aldosterone. Model B: Model A with adjustment for age and sex. Model C: Model B with additional adjustment for systolic blood pressure, diabetes mellitus, body mass index, creatinine clearance, LDL, hsCRP and current smoking.
For logistic regression odd ratios (OR) are reported. For linear regression beta regression coefficients (β) are reported. Values for OR and β are reported for aldosterone Quartile 4 vs. Quartile 1.
ABI: ankle-brachial index, IMT: carotid intima-media thickness.

4. Discussion

Aldosterone is known to be associated with mortality in high-risk subgroups of patients with CAD. The present study is the first to confirm this finding in a stable and low risk population of CAD patients recruited in an outpatient clinic. In addition, this study further demonstrates that aldosterone levels are associated with the risk of future vascular events and with the degree of atherosclerotic burden. Ultimately, these observations suggest a link between the aldosterone pathway and the atherosclerotic process.

4.1. Aldosterone levels and vascular mortality in low risk and chronic CAD patients

Although several previous studies have shown an association between aldosterone and vascular mortality in CAD patients [17–19], those studies were performed in ACS patients and no information was reported about the effect of aldosterone levels on cardiovascular risk in stable CAD patients. Recently, Tomaschitz et al. reported associations of aldosterone with long-term mortality in 3153 patients scheduled for coronary angiography; however, in that heterogeneous population 23% did not have significant CAD, while in the remaining patients 40% presented with an ACS [20]. Similarly, the population that we recently studied and where we found an association of aldosterone levels with increased mortality risk, was a population of 807 patients undergoing an elective percutaneous coronary intervention, of whom 26% had a very recent history of (2–7 days) of an ACS [21]. No separate analysis of patients with CAD but without ACS is currently available. By contrast, our analyses presented herein uniquely focused on stable CAD patients recruited in an outpatient setting.

The low risk profile of the present population, as compared to patients with an ACS, is reflected by the low level of CRP (2.0 mg/L) and BNP (11 pmol/L) and by the low mortality rate: 23 per 1000 person years. Thus, the present study confirms that the previously established increased vascular mortality risk associated with plasma aldosterone levels is also present in a stable population of patients with CAD.

While previous studies have demonstrated that an acute aldosterone increase is associated with an increased (vascular) mortality [13–19,23], the present study demonstrates that vascular mortality is also related to aldosterone in the chronic phase.

Furthermore, the levels of aldosterone found in the present study were within the normal range, as confirmed by the same measurements in healthy control subjects. This contrasts to the levels found in heart failure patients, which are generally elevated as compared to normal [14,15].

In conclusion, the link between aldosterone and vascular mortality is time-independent of the first clinical manifestation of CAD and is associated with variations of aldosterone within the normal range. This finding suggests that besides acute neuro-hormonal activation, more subtle activation of the aldosterone pathway may be associated with increased vascular mortality.

4.2. Aldosterone, vascular events and atherosclerosis

Even though preclinical evidence has already linked aldosterone to essential processes involved in atherosclerosis, such as vascular inflammation, smooth muscle cell proliferation, endothelial dysfunction and intimal hyperplasia [8,24–28], clinical data confirming these findings have been lacking. In that regard, a particular strength of the present study is that the association between aldosterone and the risk for major vascular events, including MI and ischemic stroke, was investigated. This relationship has never been established before. In fact, to the best of our knowledge, this is the first study to demonstrate that plasma aldosterone levels are not only associated with an increased risk of fatal vascular events but also with an increased risk of major vascular events, including MI and ischemic stroke. The relationship between aldosterone levels and atherosclerotic burden found in the present study supports this etiologic association. Taken together, these results strongly suggest a relationship between the aldosterone pathway and the atherosclerotic process.

4.3. Limitations

We acknowledge some limitations of the study. First, due to the observational, though prospective, character of the study, the associations found do not necessarily reflect causality. Although we corrected for a substantial number of potential confounders, there may be residual confounding factors not taken into account. Second, results in this specific study population of stable CAD patients in an outpatient clinic setting may not be completely generalizable to other populations. Nevertheless, our results are in line with similar findings in other cohorts, suggesting the associations identified are not merely a coincidental finding specific to this one study population. Third, it would have been interesting to study aldosterone levels relative to renin levels. We would then have had an impression of the level of relative RAAS activation. However, since renin levels were not available, such analyses were not possible. Finally, although aldosterone is known to be higher in patients with heart failure, left ventricular ejection fraction and New York Heart Association functional class were not recorded in our patients. However, BNP was measured and BNP-levels were within normal ranges and, thus, argue against substantial numbers of heart failure patients. Moreover, BNP was included as a confounder in the multivariable models.

5. Conclusion

In conclusion, the present study is the first to confirm that the etiologic relationship between plasma aldosterone levels and the risk of major vascular events exists in a stable and low risk population of CAD patients recruited in an outpatient clinic setting. This study further demonstrates that aldosterone levels are associated with atherosclerotic burden, suggesting involvement of the aldosterone pathway in the atherosclerotic process.

The ability to identify those patients at highest risk of major vascular events from among stable and chronic coronary patients who otherwise present at low risk will facilitate more effective monitoring and may identify those patients who will most benefit from more aggressive treatment using existing therapeutic strategies. Hence, if future research indicates clinical benefit of aldosterone blockers in patients with stable CAD, this therapy can be readily applied.

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Conflict of interest

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