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

Marieke A. Hillaert [a], Eef G. Lentjes [b], Hans Kemperman [b], Yolanda van der Graaf [c], Hendrik M. Nathoe [a], Farzin Beygui [e], Gilles Montalescot [e], Pieter A. Doevendans [a], Annemarie M. Wassink [d], Eric van Belle [f,*] and on behalf of the SMART Study Group [1]

[a] Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands
[b] Department of Clinical Chemistry and Haematology, University Medical Center Utrecht, The Netherlands
[c] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands
[d] Department of Vascular Medicine, University Medical Center Utrecht, The Netherlands
[e] Institute of Cardiology, CHU La Pitié-Salpêtrière, Paris, France
[f] Department of Cardiology, University Medical Center, EA 2693-Université Lille Nord de France and Faculté de Médecine Lille, France

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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

* Corresponding author at: Department of Cardiology, University Medical Center, EA 2693-Université Lille Nord de France and Faculté de Médecine Lille, France. Tel.: +33 6 82 47 65 84.
E-mail address: ericvanbelle@aol.com (E. van Belle).
[1] Members of the SMART Study Group are Ale Algra, MD, PhD, Pieter A. Doevendans, MD, PhD, Yolanda van der Graaf, MD, PhD, Diederick E. Grobbee, MD, PhD, L. Jaap Kappelle, MD, PhD, Willem P. Mali, MD, PhD, Frans L. Moll, MD, PhD, Guy E. Rutten, MD, PhD, and Frank L. Visseren, MD, PhD.

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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