Association of Aldosterone with Mortality in the General Population

Authors

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ABSTRACT

Introduction Aldosterone excess is linked to cardiovascular events and mortality as well as to low-grade inflammation in the context of metabolic diseases. Whether mildly elevated aldosterone levels in the general population promote cardiovascular risk is still under debate. We analyzed the association of plasma aldosterone concentrations with incident cardiovascular events, cardiovascular and all-cause mortality as well as with biomarkers of subclinical inflammation in the population-based KORA F4 study.

Methods Plasma aldosterone concentrations were measured with an in-house immunoflurometric assay. The analyses included 2935 participants (n = 1076 for selected biomarkers of subclinical inflammation) with a median follow-up of 8.7 (8.2; 9.1) years. The associations were estimated using Cox proportional hazard and linear regression models adjusted for renin, sex, age, body mass index, arterial hypertension, diabetes, estimated glomerular filtration rate, low- and high-density lipoprotein cholesterol, physical activity, smoking, use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics and calcium channel blockers.

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Results Aldosterone was significantly associated with all-cause mortality (hazard ratio per standard deviation increase: 1.20; 95 % confidence interval 1.04–1.37), but not with cardiovascular mortality, incident cardiovascular events, or with biomarkers of subclinical inflammation.

Conclusions Aldosterone was associated with all-cause mortality in the population-based KORA F4 study, but the previously described associations of excess aldosterone with cardiovascular complications and biomarkers of subclinical inflammation could not be shown.

Introduction

Primary aldosteronism is accompanied by an increase in cardiovascular risk [1, 2], which may not be fully balanced by treatment [3, 4]. For instance, the association of primary aldosteronism with adverse cardiovascular outcomes persisted after treatment with mineralocorticoid receptor antagonists despite normalization of the blood pressure, as long as renin remained suppressed [5], indicating that even moderately increased mineralocorticoid receptor activation results in cardiovascular alterations. The subsequent question whether plasma aldosterone levels are linked to cardiovascular risk beyond (diagnosed) primary aldosteronism has mainly been investigated in populations with a high risk of cardiovascular disease. For instance, plasma aldosterone was associated with adverse outcomes, including acute ischemic events and cardiovascular and all-cause mortality in patients submitted for coronary angiography [6], referred for elective coronary angioplasty [7], with stable coronary artery disease [8], after acute myocardial infarction [9] and with chronic heart failure [2]. In line, mineralocorticoid receptor blockade improved the cardiovascular adverse event rate and survival of patients after myocardial infarction despite plasma aldosterone levels in the normal range [10–14]. Preclinical studies elucidate possible mechanisms behind these observations. In mice, cardiomyocyte-specific mineralocorticoid receptor deficiency improved infarct healing and prevented adverse cardiac remodeling [15], whereas aldosterone infusion promoted atherosclerosis with an inflammatory plaque phenotype [16]. Pro-atherogenic aldosterone effects were mediated by elevated intercellular adhesion molecule 1 (ICAM-1) expression [17]. Further, aldosterone increased the expression of ICAM-1 and the adherence of monocytes on human coronary endothelial cells [18] and interleukin (IL)-6 production in human umbilical vein endothelial cells [19]. In primary aldosteronism, plasma IL-6 [19], as well as IL-6 and tumor necrosis factor-α (TNF-α) in perirenal adipose tissue, were elevated [20]. Thus, vascular adhesion, inflammation and fibrosis are possible connections between aldosterone and atherosclerosis [21].

Given the putative link of moderately elevated mineralocorticoid receptor activation with atherosclerosis, adverse cardiovascular outcomes and mortality, we investigated the association of aldosterone with cardiovascular events, cardiovascular and all-cause mortality in the population-based KORA F4 study. Considering the postulated proinflammatory effects of aldosterone on atherosclerosis, we further examined the association of aldosterone with selected markers of subclinical inflammation.

Methods

Study participants and definition of variables

The KORA (Cooperative Health Research in the Region of Augsburg) F4 (2006–2008) study included 3080 participants. The study was approved by the Ethics Committees of the Bavarian Medical Association (approval number 06068) in adherence to the declaration of Helsinki. All participants gave written informed consent. Recruitment and eligibility criteria, study design, standardized sampling methods and data collection (medical history, medication, anthropometric and blood pressure measurements) have been described in detail elsewhere [22].

The outcomes all-cause and cardiovascular mortality (ICD-9 codes 390–459 and 798) were ascertained by regularly checking the status of the participants through the population registries until 2016. Death certificates were obtained from the local health authorities. The median (1st quartile; 3rd quartile) follow-up time was 8.7 (8.2; 9.1) years. Myocardial infarction and stroke at baseline were self-reported diagnoses. Incident myocardial infarction occurring until the age of 74 years (for cases occurring before 2009) and until the age of 84 years (for cases occurring since 2009) was assessed by surveillance through the local myocardial infarction registry. Incident non-fatal myocardial infarction occurring in participants > 74 and > 84 years, respectively, depending on the year of occurrence, or residing outside the study area and non-fatal stroke were assessed by postal follow-up questionnaires. All self-reported incident stroke and myocardial infarction cases occurring outside the study area or in persons > 74 or 84 years and the date of diagnosis were validated using data from hospital records of participants and their attending physicians. Incidents of stroke and myocardial infarction were pooled to a combined endpoint, with only the first event taken into account in case of several events. Participants with prevalent stroke (n = 67) or prevalent myocardial infarction (n = 80), or missing data on incident stroke (n = 206) and myocardial infarction (n = 24) were excluded from the respective analyses. The follow-up time (median (1st quartile; 3rd quartile)) was 8.6 (8.1; 9.0) years for stroke and 8.6 (8.2; 9.1) years for myocardial infarction. Arterial hypertension was defined as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg and/or intake of anti-hypertensive medication, given that the participants were aware of being hypertensive. The definition of the covariables, diabetes mellitus, smoking and physical activity were described before [23].

Laboratory measurements

Measurements of high-sensitivity C-reactive protein (hsCRP) were available for 2931 participants; IL-6, TNF-α, IL-18, soluble intercellular adhesion molecule-1 (sICAM-1), myeloperoxidase (MPO),

IL-22 and IL-1 receptor antagonist (IL-1RA) were available for 1076 participants aged ≥ 62 years. Blood samples were collected after an overnight fast of at least eight hours in a sitting position after a rest of 10 min (sitting) and were kept at room temperature until centrifugation. Plasma was separated immediately and serum after 30 min. Samples were assayed immediately or stored at −80 °C. Plasma renin concentrations were measured using the Liaison active renin assay (Diasorin, Dietzenbach, Germany) using monoclonal antibodies to only detect active renin molecules without interference with pro-renin. Intra- and inter-assay coefficients of variation were less than 5.6 % and 12.2 %, respectively, and the functional sensitivity was < 2.0 µU/mL. Plasma aldosterone concentrations were measured within 2 years from the sampling date with an in-house immunoflurometric assay involving an extraction step before the measurements as described previously [24]. Inter- and intra-assay coefficients of variation were 15.2 % and 7.3 % in low, and 8.0 % and 4.4 % in high concentrations, respectively. Measurements procedures of serum creatinine, glucose, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), hsCRP, IL-6, TNF-α, IL-18, sICAM-1, MPO, IL-22, and Il-1RA are described elsewhere [23]. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (2009) based on serum creatinine.

Statistical analyses

Characteristics of the study participants were compared between survivors and non-survivors using t-tests in the case of approximately normally distributed variables. Mann-Whitney U-tests were performed for variables with skewed distributions. Binomial proportions were compared with Chi-square tests. The associations of aldosterone with cardiovascular events and mortality were examined using Cox proportional hazard models. The associations of aldosterone with biomarkers of subclinical inflammation were assessed with linear regression models. Continuous variables were transformed to approach Gaussian distribution by the probability integral transformation followed by an inverse transform sampling and were used in calculations per one standard deviation. The associations were adjusted for renin, sex, age, body mass index (BMI), arterial hypertension, diabetes, estimated glomerular filtration rate, low- and high-density lipoprotein cholesterol, physical activity, smoking, use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics and calcium channel blockers. For power calculation for Cox proportional hazards regression for nonbinary covariates, the formula derived by Hsieh and Lavori was used [25]. The level of statistical significance was set at 5 % (two-sided). The calculations were performed using the statistical environment R, version 3.6.0 (R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2019).

Results

▶ **Table 1** displays the baseline characteristics of the study population. There was no difference in renin and aldosterone levels in non-survivors compared to survivors.

In the fully adjusted model, aldosterone was not significantly associated with incident stroke, myocardial infarction, the combined endpoint including stroke and myocardial infarction, or with cardiovascular mortality (▶ **Table 2**). The power analysis revealed that given the observed event rate and hazard ratio of 1.18, 5216 participants should have been included to detect a significant association of aldosterone with the combined cardiovascular endpoint with a power of 0.8. With the available number of study participants (n = 2597 for the combined cardiovascular outcome), a hazard ratio of at least 1.27 would have been necessary for a power of 0.8.

There was a significant association between high aldosterone levels and all-cause mortality (HR (95 % CI) 1.20 (1.04–1.37); p = 0.0099) that was not substantially altered (HR (95 % CI) 1.21 (1.05–1.39); p = 0.0098) by the exclusion of participants with aldosterone levels > 160 ng/L (n = 59).

Renin and the aldosterone-to-renin ratio were not significantly associated with all-cause-mortality (HR (95 % CI) 0.97 (0.86–1.10) and 1.11 (0.98–1.26), respectively) or with cardiovascular events (**Table S1**).

We stratified the study cohort by factors possibly influencing the association of aldosterone with all-cause mortality (sex, age, BMI, diabetes mellitus and eGFR). The association of aldosterone with all-cause mortality was only significant in men (vs. women), participants ≥ 60 years (vs. < 60 years), with a BMI ≥ 30 kg/m² (vs. < 30 kg/m²), without diabetes (vs. type 2 diabetes) and with an eGFR ≥ 60 mL/min/1.73 m² (vs. < 60 mL/min/1.73). However, none of the interaction terms were statistically significant (**Table S2**).

Aldosterone was not significantly associated with any of the analyzed markers of subclinical inflammation (hsCRP, IL-6, TNF-α, IL-18, sICAM-1, MPO, IL-22 and IL-1RA; **Table S3**).

Discussion

Higher aldosterone levels were moderately associated with all-cause mortality in the KORA F4 study. There was a non-significant trend towards a positive association with stroke, the combined cardiovascular endpoint and cardiovascular mortality, but not with myocardial infarction. Aldosterone was not associated with any of the examined markers of subclinical inflammation.

In contrast to populations at high risk for cardiovascular diseases, previous studies investigating the association of aldosterone with cardiovascular events and mortality in the general population yielded inconsistent results. Aldosterone was associated with all-cause mortality in a population-based cohort from Olmsted County, MN (n = 1674), with an HR of 1.14 after adjustment for sex, age and BMI [26]. However, this association was no longer significant after the exclusion of participants with aldosterone levels above the normal range (n = 95). In contrast, the exclusion of participants with aldosterone levels above the normal range did not alter the association of aldosterone with all-cause mortality in the KORA F4 study. Interestingly, in a Japanese population-based study (n = 1310), the aldosterone-to-renin ratio was inversely associated with all-cause mortality [27], whereas plasma renin activity was positively associated with all-cause mortality [28]. However, in KORA F4, neither the aldosterone-to-renin ratio nor renin was significantly associated with cardiovascular events or mortality. The HR for the aldosterone-to-renin ratio showed a positive association

▶ **Table 1** Characteristics of the study participants; overall and stratified by survival status [1].

	Total study cohort (n = 2935)	Survivors (n = 2690)	All-cause death (n = 245)	p-value
Male sex n (%)	1420 (48)	1272 (47)	148 (60)	<0.001 [4]
Age (years)	56.2 ± 13.2	54.9 ± 12.7	70.8 ± 9.2	<0.001 [2]
BMI (kg/m²)	27.6 ± 4.8	27.5 ± 4.8	29.2 ± 5.0	<0.001 [2]
eGFR (mL/min/1.73 m²)	89.2 (77.6; 100.0)	90.4 (78.9; 100.8)	73.9 (61.2; 86.4)	<0.001 [3]
Arterial hypertension n (%)	1125 (38)	959 (36)	166 (68)	<0.001 [4]
Type 2 diabetes n (%)	334 (11)	256 (10)	78 (32)	<0.001 [4]
Low-density lipoprotein (mmol/L)	3.44 (2.88; 4.06)	3.44 (2.87; 4.06)	3.41 (2.82; 3.95)	0.372 [3]
High-density lipoprotein (mmol/L)	1.40 (1.16; 1.68)	1.40 (1.16; 1.68)	1.34 (1.11; 1.60)	0.074 [3]
Smoker n (%) (current/former)	523 (18)/1189 (41)	491 (18)/1074 (40)	32 (13)/115 (47)	0.051/0.040 [4]
Physically inactive	1331 (45)	1178 (44)	153 (62)	<0.001 [4]
Plasma renin (µU/mL)	6.84 (3.72; 12.06)	6.78 (3.78; 11.82)	7.68 (3.06; 16.44)	0.111 [3]
Plasma aldosterone (ng/L)	38 (26; 58)	38 (26; 58)	38 (22; 66)	0.717 [3]
Aldosterone-to-renin ratio	5.65 (2.93; 10.75)	5.71 (3.02; 10.74)	4.91 (2.26; 11.71)	0.130 [3]
Angiotensin-converting enzyme inhibitors n (%)	223 (8)	196 (7)	27 (11)	0.050 [4]
Angiotensin receptor blockers n (%)	385 (13)	301 (11)	84 (34)	<0.001 [4]
Beta blockers n (%)	554 (19)	454 (17)	100 (41)	<0.001 [4]
Diuretics n (%)	522 (18)	420 (16)	102 (42)	<0.001 [4]
Calcium channel blockers n (%)	230 (8)	178 (7)	52 (21)	<0.001 [4]

[1] mean ± standard deviation, median (1st quartile; 3rd quartile), or number of participants (proportion in %); [2] t-test; [3] Mann-Whitney U-test; [4] Chi-square test; the p-value is related to the null hypothesis of no difference between survivors and non-survivors.

▶ **Table 2** Hazard ratios (95 % confidence interval, CI) of the association between aldosterone (per standard deviation) and cardiovascular events, cardiovascular mortality, and all-cause mortality.

	Unadjusted analyses		Adjusted analyses [1]	
Outcome and numbers (total/events)	**HR (95 % CI)**	**p value**	**HR (95 % CI)**	**p-value**
Stroke n = 2662/104	1.03 (0.84–1.25)	0.810	1.15 (0.93–1.43)	0.188
Myocardial infarction n = 2831/90	0.92 (0.74–1.13)	0.422	0.99 (0.78–1.24)	0.937
Cardiovascular events (combined) n = 2597/159	1.03 (0.88–1.21)	0.685	1.18 (0.99–1.41)	0.061
Cardiovascular mortalityn = 2935/105	1.02 (0.84–1.24)	0.845	1.19 (0.97–1.47)	0.102
All-cause mortality n = 2935/245	1.04 (0.92–1.19)	0.540	**1.20 (1.04–1.37)**	**0.0099**

[1] The results are adjusted for sex, age, renin, body mass index, hypertension, diabetes, estimated glomerular filtration rate, low-density lipoprotein, high-density lipoprotein, smoking, physical activity, use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics and calcium channel blockers. The bold print indicates significance in the fully adjusted model after correction for multiple testing using the Bonferroni method (p < 0.01 (0.05 ÷ 5)).

with all-cause mortality, whereas the HR for renin was < 1.00. In 3866 participants of the Chronic Renal Insufficiency Cohort, aldosterone was not associated with atherosclerotic events and all-cause mortality [29], whereas in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study (including patients referred for coronary angiography), the association of aldosterone with cardiovascular mortality was only present in participants with an eGFR in the lowest tertile (mean eGFR 61.9 mL/min/1.73 m²), but not in tertile 2 and 3 [30]. In the current study, we found no significant interaction with the eGFR, although the association of aldosterone with mortality was only present in participants with an eGFR ≥ 60 mL/min/1.73 m² – contrary to that observed in the LURIC study, but in line with the Chronic Renal Insufficiency Cohort with no association of aldosterone with mortality in chronic kidney disease.

Since experimental data suggest a role of mineralocorticoid receptor activation in obesity-related endothelial dysfunction [31], Western diet-induced aortic stiffness, fibrosis and proinflammatory responses [32], and coronary vasoconstriction and atherosclerosis in metabolic syndrome [33], we further tested the interaction with BMI and diabetes mellitus. Both were not significant, although the association of aldosterone with mortality was stronger in participants with a BMI ≥ 30 kg/m² compared to participants with a BMI < 30 kg/m². However, the association of aldosterone with mortality was only significant in participants without diabetes as compared to participants with type 2 diabetes.

Our study included biomarkers reflecting diverse aspects of subclinical inflammation (hsCRP, IL-6, TNF-α, IL-18), vascular inflammation (sICAM-1), oxidative stress (MPO) and anti-inflammatory

biomarkers (IL-22 and IL-1RA). However, none of them showed a relevant association with aldosterone levels, so they may not represent mediators in the relationship between aldosterone and mortality.

Limitation

Although the present analysis is based on a large, well-characterized sample from the general adult population, the statistical analyses regarding the interaction terms as well as cardiovascular events and cardiovascular mortality, seem to be insufficiently powered to draw definitive conclusions. Plasma aldosterone concentrations were measured using an in-house immunoflurometric assay. Today, liquid chromatography-mass spectrometry is often preferred due to greater accuracy, but it requires larger sample volumes and was not available to us at the time of aldosterone measurements.

Conclusion

Aldosterone was associated with all-cause mortality in the population-based KORA F4 study but not clearly with cardiovascular events, cardiovascular mortality, or biomarkers of subclinical inflammation, suggesting that the latter associations are restricted to aldosterone excess and/or populations at high risk for cardiovascular diseases. Beneficial effects of mineralocorticoid receptor blockade in patients with heart failure and after myocardial infarction despite normal aldosterone levels [10–14] might, therefore, be explained by the elevated cardiovascular risk. Plasma measurements may poorly reflect increased aldosterone tissue levels and paracrine mineralocorticoid effects, as observed in isolated perfused rat hearts after myocardial infarction [34] and in human failing ventricles [35]. In this regard, the prognostic clinical significance of mildly elevated plasma aldosterone levels in the general population appears to be limited.

Author Contribution Statement

Conception and design of the study: M. Re, BT, CM, CH, MH, AP, WK and WR; collection of data: BT, M. Re, MB, CT, CM, CH, MH, AP, WK, WR and M. Ro; data analysis, interpretation of results and manuscript writing: CT, BT, CS, AP and M. Re; all authors revised the manuscript critically for important intellectual content and approved the final version.

Data Availability Statement

The data are subject to national data protection laws; restrictions were imposed by the Ethics Committee of the Bavarian Chamber of Physicians to ensure the data privacy of the study participants. Therefore, data cannot be made freely available in a public repository. However, data can be requested through an individual project agreement with KORA via the online portal KORA.passt (https://epi.helmholtz-muenchen.de/).

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Conflicts of Interest

The authors declare that they have no conflict of interest associated with this manuscript.

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