Observational Study Mortality in Treated Primary Aldosteronism : The German Conn's Registry

Martin Reincke, Evelyn Fischer, Sabine Gerum, Katrin Merkle, Sebastian Schulz, Anna Pallauf, Marcus Quinkler, Gregor Hanslik, Katharina Lang, Stefanie Hahner, Bruno Allolio, Christa Meisinger, Rolf Holle, Felix Beuschlein, Martin Bidlingmaier and Stephan Endres

Hypertension. published online July 23, 2012;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

Observational Study Mortality in Treated Primary Aldosteronism

The German Conn's Registry

Martin Reincke, Evelyn Fischer, Sabine Gerum, Katrin Merkle, Sebastian Schulz, Anna Pallauf, Marcus Quinkler, Gregor Hanslik, Katharina Lang, Stefanie Hahner, Bruno Allolio, Christa Meisinger, Rolf Holle, Felix Beuschlein, Martin Bidlingmaier, Stephan Endres, for the Participants of the German Conn's Registry-Else Kröner-Fresenius-Hyperaldosteronism Registry

Abstract—In comparison with essential hypertension, primary aldosteronism (PA) is associated with an increased risk of cardiovascular morbidity. To date, no data on mortality have been published. We assessed mortality of patients treated for PA within the German Conn's registry and identified risk factors for adverse outcome in a case-control study. Patients with confirmed PA treated in 3 university centers in Germany since 1994 were included in the analysis. All of the patients were contacted in 2009 and 2010 to verify life status. Subjects from the population-based F3 survey of the Cooperative Health Research in the Region of Augsburg served as controls. Final analyses were based on 600 normotensive controls, 600 hypertensive controls, and 300 patients with PA. Kaplan-Meyer survival curves were calculated for both cohorts. Ten-year overall survival was 95% in normotensive controls, 90% in hypertensive controls, and 90% in patients with PA (*P* value not significant). In multivariate analysis, age (hazard ratio, 1.09 per year [95% CI, 1.03–1.14]), angina pectoris (hazard ratio, 3.6 [95% CI, 1.04–12.04]), and diabetes mellitus (hazard ratio, 2.55 [95% CI, 1.07–6.09]) were associated with an increase in all-cause mortality, whereas hypokalemia (hazard ratio, 0.41 per mmol/L [95% CI, 0.17–0.99]) was associated with reduced mortality. Cardiovascular mortality was the main cause of death in PA (50% versus 34% in hypertensive controls; $P<0.05$). These data indicate that cardiovascular mortality is increased in patients treated for PA, whereas all-cause mortality is not different from matched hypertensive controls. **(*Hypertension*. 2012;60:00.) • Online Data Supplement**

Key Words: Conn syndrome ■ aldosterone ■ renin ■ cardiovascular ■ morbidity ■ mortality

Aldosterone is a key regulator of fluid and electrolyte balance in human physiology. Aldosterone excess in the presence of a high-sodium diet raises blood pressure. High blood pressure, together with direct proinflammatory and profibrotic effects of aldosterone on the vessel wall, causes and sustains cardiovascular atherosclerosis.[1,2] In keeping with these findings, high aldosterone levels are associated with mortality in heart failure cohorts,[3] and blockade of the renin-angiotensin-aldosterone system by mineralocorticoid antagonists improves outcome in heart failure and after myocardial infarction.[4,5] The contribution of aldosterone to the development of arterial hypertension in the general population has been suggested by the Framingham Offspring Study, in which plasma aldosterone levels in normotensive subjects predicted subsequent increases in blood pressure and the development of hypertension.[6]

Recent evidence suggests that primary aldosteronism (PA) is more common than previously thought.[7] Several studies have provided evidence that patients with PA are especially prone to cardiovascular and renal complications. In a recent study by Catena et al,[8] aldosterone excess caused left ventricular hypertrophy and diastolic dysfunction independent of blood pressure. Several studies have indicated a higher prevalence of cardiovascular events and stroke in PA in comparison with essential hypertension.[9,10] Likewise, pronounced fibrosis of small resistance arteries was detected in a series of 13 patients with PA compared with blood pressure–matched patients with essential hypertension.[11] Overall, these

Received April 17, 2012; first decision May 6, 2012; revision accepted June 24, 2012.

From the Medizinische Klinik und Poliklinik IV (M.R., E.F., S.G., K.M., S.S., A.P., F.B., M.B., S.E.) and Klinik und Poliklinik für Strahlentherapie (S.G.), Klinikum der Ludwig-Maximilians-Universität München, München, Germany; Klinische Endokrinologie (S.G., M.Q., G.H.), Charité Campus Mitte, Charité Universitätsmedizin Berlin, Berlin, Germany; Medizinische Klinik und Poliklinik I (K.L., S.H., B.A.), Julius-Maximilians-Universität, Würzburg, Germany; Institute of Epidemiology II (C.M.), Helmholtz Zentrum München, Neuherberg, Germany; Institute of Health Economics and Health Care Management (R.H.), Helmholtz Zentrum München, Neuherberg, Germany.

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.112.197111/-/DC1.

Correspondence to Martin Reincke, Medizinische Klinik und Poliklinik IV, Campus Innnestadt, Klinikum der Universität München, Ziemssenstr 1, 80336 München, Germany. E-mail martin.reincke@med.uni-muenchen.de

examples provide evidence that PA needs to be detected early in the course of the disease and treated appropriately. Unilateral PA is generally treated by adrenalectomy, which provokes a major fall in blood pressure in >85% of patients and blood pressure normalization in 30% to 60%.[12] A similar effect is observed in patients with idiopathic bilateral adrenal hyperplasia treated with the mineralocorticoid antagonist spironolactone.[13] Recently, a study demonstrated that either treatment reduced excess renal and cardiovascular morbidity to a level similar to that of matched essential hypertensives.[14]

No study has so far investigated mortality in PA. Based on the blood pressure response to adrenalectomy or mineralocorticoid antagonist treatment, it is reasonable to assume that long-term mortality may be equal to or even lower than that of matched hypertensive controls. On the other hand, the lag period between first symptoms of PA (hypertension) and final diagnosis ranges from 9 to 12 years.[15,16] Therefore, aldosterone excess is typically long-standing, and the proinflammatory effects of aldosterone may have led to irreversible damage to the vascular wall, the myocardium, and the kidney, increasing long-term mortality despite initiation of specific treatment. The German Conn's Registry-Else Kröner-Fresenius Hyperaldosteronism Registry was founded in 2006 and investigates disease-specific effects of PA on a broad range of outcome variables using a multicenter approach. In this study we analyzed all-cause and cardiovascular mortality in a cohort of 337 patients with PA compared with a cohort of control subjects with and without hypertension.

Methods

Description of the Registry, Study Population

The German Conn's Registry (www.conn-register.de) is a multicenter database analyzing comorbidities and long-term outcomes of patients with PA.[16–18] Since the start of the prospective phase of the registry in 2008, all patients actively treated within the centers are entered in a common database.[19] For this study, the patients of the 3 largest German centers (Berlin, n=55; Würzburg, n=102; Munich, n=180) treated between 1994 and 2010 were included in the analysis. The ethics committees of the University of Munich and of the participating centers approved the protocol. Data protection laws were strictly adhered to.

Clinical data at time of diagnosis were extracted from patient charts, including laboratory test results, initiation of mineralocorticoid antagonist treatment, surgical treatment, cardiovascular comorbidities, body mass index (BMI), and metabolic conditions, such as diabetes mellitus and hyperlipidemia. In case of multiple determinations, the measurements of potassium, plasma renin activity or concentration, and aldosterone at first presentation were used for statistical calculations. Blood was generally drawn in the fasting state, although this was not standardized within centers.

The diagnostic criteria for PA in this study followed those of the Endocrine Society Practice guidelines.[20] All of the patients included had an elevated aldosterone:renin ratio and an abnormal confirmatory test (acute volume loading, furosemide test, fludrocortisone suppression test, or captopril test)[16,17] and/or had confirmation of PA by demonstration of elevated excretion of aldosterone and its metabolites in urine. Adjustment of medication before screening was performed as feasible, with β-blockers withdrawn for 1 week and mineralocorticoid antagonists for 4 weeks. The diagnosis of PA was centrally verified by review of all of the available data. A total of 337 patients with confirmed PA from the German Conn's Registry for whom sufficient data coverage was available were included in the final analysis. Subtype differentiation between aldosterone-producing adenoma and bilateral adrenal hyperplasia was based on adrenal imaging (computed tomography or MRI). In addition, adrenal vein sampling was performed in 36% (Berlin), 59% (Würzburg), and 21% (Munich) of patients, respectively, until 2007 and in 54%, 66%, and 87%, thereafter.[21] Unilateral adrenalectomy was performed in 157 of 337 patients (47%) for suspected unilateral aldosterone excess, mainly aldosterone-producing adenoma. The remaining patients were treated with mineralocorticoid receptor antagonists.

In 2009 and 2010, patients were contacted both by mail and telephone. In the case of nonresponse, the registration office, the health insurance, or the treating physician was contacted to retrieve information regarding the life status of the patient. In deceased patients, the cause of death was verified by death certificates and hospital records whenever possible using the International Classification of Diseases, 9th Revision.[22]

Control Population

The Cooperative Health Research in the Region of Augsburg (KORA) F3 survey[23] was performed in 2004 and represents a follow-up study of the population-based KORA S3 study. The S3 survey conducted in 1994/1995 was based on a random sampled of German residents of the Augsburg region aged 25 to 74 years identified through the public record office. For the purpose of the present study, 2835 normotensive and 2021 hypertensive subjects from the S3 survey were enrolled. Hypertension was defined as blood pressure ≥140/90 mm Hg and/or current use of antihypertensive drugs, given that the subjects were aware of being hypertensive.

More than 99.5% of the participants were white. The high standard of the World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease project applies to the survey. In 2004/2005, all of the study participants underwent a re-examination including a standardized interview, a physical examination, and nonfasting blood sampling by trained staff. Participants gave informed written consent on a form approved by the ethics committee of the Bavarian state board of physicians. The life status of all of the subjects was assessed in 2004/2005 and again in 2008/2009. Death certificates with exact date of death were obtained from local health departments and coded for the underlying cause of death by a single trained person.

Definitions

Diabetes mellitus was defined as a known history of diabetes mellitus at the time of first investigation of PA. Hypercholesterolemia was defined as total cholesterol >200 mg/dL and hypertriglyceridemia as total triglycerides >180 mg/dL. Overweight was defined as a BMI >25 kg/m^2. Cardiovascular events were classified according to the International Classification of Diseases, 9th Revision.

Statistics

Results are expressed as mean±1 SD for normally distributed data and as median plus range in nonnormally distributed data, if not stated otherwise. A P value <0.05 was considered as significant. Matching between patients with PA and subjects from the KORA F3 survey was performed in a 1:2 fashion using age, sex, and BMI as matching variables, leading to a match in 300 patients and 600 normotensive and 600 hypertensive controls. Patients <30 years of age were excluded from the PA group for lack of counterparts in KORA. In addition, we matched for age, sex, and blood pressure using best-fit matching. Maximum matching variability for age was 5 years and for BMI 2 kg/m^2. To increase the number of matches, a BMI mismatch of >2 kg/m^2 was accepted in <1% of cases. Significance of differences was analyzed by t test, Wilcoxon signed-rank test with continuity correction, Fisher exact test, and McNemar χ^2 test with continuity correction, as appropriate. Kaplan-Meier plots were calculated to estimate the survival curves of PA patients and hypertensive controls (time of diagnosis to last contact or death in PA; date of survey to life status assessment/death in controls). Analyzing survival curves we used Cox regression and, if appropriate, also log-rank test. Cox regression was also used for regression analysis with multiple parameters to identify risk factors associated

Table 1. Baseline Characteristics of Patients With PA and Hypertensive/Normotensive Controls After Matching for Age, Sex, and BMI

Parameters	Patients With PA	Hypertensive Controls	*P* Value	Normotensive Controls	*P* Value
N, 100%	300	600		600	
Women, n %	116 (39)	232 (39)	Match	232 (39)	Match
Age, y	50	50	Match	50	Match
BMI, kg/m^2	28	28	Match	27	Match
All-cause mortality, n (%)	22 (7)	74 (12)		47 (7)	
Coronary heart disease, n (%)	13 (4)	31 (5)	NS	34 (6)	NS
Diabetes mellitus, n (%)	41 (14)	40 (7)	<0.001	22 (4)	<0.001
Cholesterol, mg/dL	207 (108–333)	234 (88–415)*	<0.001	230 (120–419)*	<0.001
LDL cholesterol, mg/dL	126 (51.210)	142 (40–322)*	<0.001	143 (31–325)*	<0.001
HDL cholesterol, mg/dL	52 (20–123)	48 (10–121)*	<0.001	51 (24–119)*	<0.01
Triglycerides, mg/dL	127 (25–497)	163 (37–845)*	<0.001	152 (21–876)*	<0.001
Systolic and diastolic blood pressure at initial presentation, mm Hg	168 (25)/99 (16)	147 (16)/91 (11)	<0.001	122 (10)/77 (8)	<0.001

BMI indicates body mass index; PA, primary aldosteronism; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NS, not significant. *P* value was a test against PA patients.

*Data are for nonfasting.

with death at the time of diagnosis. Potential risk factors were identified by manual backward elimination. Age, sex, BMI, systolic and diastolic blood pressure at first presentation, prevalent diabetes mellitus, lipid and potassium concentrations, plasma aldosterone and renin concentrations, and adrenalectomy were used for the initial model. All of the statistical analyses were carried out using R version 2.6.2 software.[24]

Results

Clinical Characteristics of the Study Populations

Clinical characteristics of the study populations are summarized in Table S1, available in the online-only Data Supplement. As expected, the cohorts differed in multiple variables.

Mortality in the Case-Control Study

Using age, sex, and BMI as matching variables, a case-control study of 300 patients with PA and 600 normotensive and 600 hypertensive controls was performed (for clinical characteristics, see Table 1), and Kaplan-Meier survival plots were calculated. Controls had higher triglyceride and cholesterol concentrations (probably because of the nonfasting state), lower blood pressure levels, and less frequently diabetes mellitus. Plasma potassium, plasma aldosterone, and plasma renin levels were unavailable in the control cohort.

Despite clinical and metabolic differences, 5- and 10-year overall survival of patients with PA (96% and 90%, respectively) was similar to that of hypertensive controls (95% and 90%, log rank test, not significant) and not significantly different from normotensive control (98% and 95%, not significant; Figure 1). We also matched in a separate approach for systolic blood pressure (in addition to age and sex) to take blood pressure as one of the most important determinants of cardiovascular mortality into account. This decreased the number of matches to 288 (based on a 1:1 matching of patients with hypertensive controls) but did not change all-cause mortality, which remained comparable in the cohorts (Table S2 and Figure S1).

Table 2 provides causes of death for PA patients and controls according to International Classification of Diseases, 9th Revision, classification. Cardiovascular causes were the main cause of death in the cohorts but were more frequent in PA than in controls (50% versus 34% in hypertensive controls [$P<0.05\%$] versus 38% in normotensive controls).

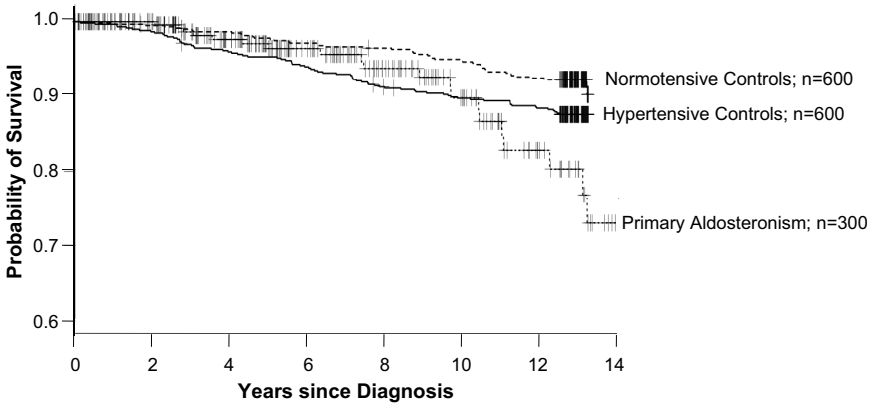

Figure 1. Kaplan-Meier survival plot of patients with primary aldosteronism (PA; n=300) vs normotensive (n=600) and hypertensive controls (n=600) matched for age, sex, and body mass index (BMI).

Table 2. Causes of Death in PA and Controls According to ICD-9 Classification

Parameters	Patients With PA (n=300)	Hypertensive Controls (n=600)	Normotensive Controls (n=600)
Cardiovascular disease (ICD-9 390–459, 798)	11 (50)	25 (34)*	18 (38)
Coronary heart disease (ICD-9 410–414, 798)	3 (14)	12 (16)	18 (38)
Neoplasm (ICD-9 140–208)	2 (9)	20 (27)	18 (38)*
Other	3 (14)	26 (35)	11 (23)
Unknown	6 (27)	3 (4)	0 (0)
Total mortality	22 (100)	74 (100)	47 (100)

PA indicates primary aldosteronism; ICD-9, International Classification of Diseases, 9th Revision. Data are n (%).

*$P<0.05$ vs PA.

Assuming that two thirds of the unknown causes of death are attributable to cardiovascular death, the differences to hypertensives and normotensives are highly significant ($P=0.004$ and 0.02, respectively).

Causes and Risk Factors Associated With Mortality in PA

Hazard ratios (HRs) for variables likely associated with adverse outcome in PA were calculated. In univariate analysis, age, diabetes mellitus, and angina pectoris were associated with increased all-cause mortality (Table 3). Conversely, adrenalectomy (as compared with medical treatment of PA) was associated with reduced all-cause mortality and proved to be protective. Initial plasma aldosterone, plasma renin levels, initial blood pressure, and lipid concentrations had no significant effect on all-cause mortality. In a multivariate model, age (HR, 1.09 per year [95% CI] 1.03–1.14), angina pectoris (HR, 3.6 [95% CI. 1.04–12.4), and diabetes mellitus (HR, 2.55 [95% CI, 1.07–6.09]) were associated with an increase in mortality, whereas the presence of hypokalemia (HR, 0.41 per mmol/L [95% CI, 0.17–0.99]) was associated with a reduced mortality (Figure S2). This latter finding might be explained by a higher likelihood of aldosterone-producing adenoma and, consequently, adrenalectomy in severely hypokalemic PA patients (odds ratio, 1.9 [Fisher exact test] $P<0.01$).

Table 3. Factors Associated With Increased or Reduced Mortality Rate From Any Cause in Patients With PA (Univariate Analysis)

Parameters	Hazard Ratio	*P* Value
Age, per y	1.09	0.0009
Male sex	2.8	0.06
BMI, per kg/m^2	0.99	0.75
Systolic blood pressure >164 mm Hg	1.19	0.69
Diastolic blood pressure >100 mm Hg	1.32	0.51
Serum potassium, per mmoL	2.01	0.08
Adrenalectomy	0.38	0.046
Aldosterone >265 pg/mL	0.67	0.34
Plasma renin concentration >0.19 ng/mL per h	0.51	0.16
Plasma renin concentrations >2.4	0.47	0.52
Angina pectoris	5.05	0.025
Diabetes mellitus	13.6	0.014
Coronary artery disease	1.52	0.71
Plasma potassium <3.2 mmol/L	0.64	0.3
Cholesterol >205 mg/dL	1.1	0.93
HDL cholesterol >51 mg/dL	1.46	0.62
LDL cholesterol >124 mg/dL	1.01	0.43
Triglycerides >126 mg/dL	1.97	0.32

PA indicates primary aldosteronism; BMI, body mass index; HDL, high density lipoprotein; LDL, low-density lipoprotein.

Using age >50 years. diabetes mellitus. and angina pectoris as risk parameters, we developed a model with a scoring system of 0 to 3 points. As given in Figure 2, patients with PA with a score of ≥2 had an increased mortality rate that becomes evident ≥6 years after diagnosis.

Discussion

Using data of the German Conn's Registry and a German control cohort of subjects from a population-based survey, we investigated long-term mortality of treated PA in Germany. By combining the data of 3 centers, we collected a total of 337 patients with confirmed PA. After matching for age, sex, BMI, or blood pressure, our data show that all-cause mortality in patients with PA is not significantly different from that of hypertensive controls. These data are in accordance with the hypothesis that treatment of PA by adrenalectomy or mineralocorticoid receptor antagonist medication reduces increased morbidity of untreated PA,[14] thereby reducing overall mortality. However, beyond 10 years of follow-up, mortality in PA patients appears to be higher than in hypertensive controls, but the number of patients is too low to reach statistical significance.

We matched the cohorts using confounders of mortality as matching variables, such as age, sex, BMI, or blood pressure. Nevertheless, the cohorts remained unbalanced for important variables, such as diabetes mellitus and plasma lipids (Tables 1 and S2). Patients with PA had initially a much higher diabetes mellitus prevalence than controls (14% versus 7%), a finding reported previously.[18] In contrast, control subjects had significantly higher total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels and lower high-density lipoprotein levels, which might be at least in part explained by the nonfasting status of the KORA F3 subjects.

Numerous studies have shown that patients with PA have an increased risk for cardiovascular morbidity. In comparison with blood pressure–matched hypertensive controls without aldosterone excess, patients with PA have increased left ventricular mass and more severely impaired diastolic relaxation.[8,25] This finding argues for aldosterone-specific effects on left ventricular function independent of blood pressure. Aldosterone excess results in glomerular hyperfiltration and microalbuminuria[26] and, after a prolonged period of time, in loss of glomerular function.[16] PA causes atherosclerotic changes in resistance arteries in fat biopsies.[11] Patients with PA have an increased risk of cerebrovascular events[10] and are more likely to experience atrial fibrillation and myocardial infarction.[10,14] Patients with PA have increased left ventric-

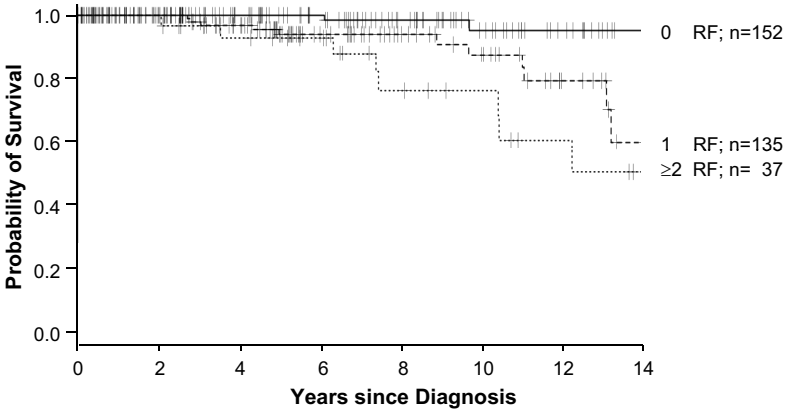

Figure 2. Kaplan-Meier survival plot of patients with primary aldosteronism (PA) according to the number of risk factors (age >50 years and presence of diabetes mellitus and angina pectoris). **Solid line**, score 0 (n=152); **dashed line**, score 1 (n=135); **dotted line**, score 2 and higher (n=37).

ular wall thicknesses and reduced diastolic function even in the absence of arterial hypertension, as shown by Stowasser et al[26] in familial hyperaldosteronism type 1. In summary, these data support the concept that aldosterone excess is detrimental not only through increased blood pressure and hypokalemia but also through blood pressure independent proinflammatory and profibrotic effects on the heart and vessel wall.

Longitudinal studies by Catena et al[14] and Sechi et al[27] have shown that unfavorable effects of aldosterone excess can be ameliorated by adrenalectomy and mineralocorticoid antagonist treatment, respectively. Microalbuminuria, although much more prevalent in PA, is reversed to a similar degree as in hypertensive controls treated conventionally with antihypertensive drugs. In addition, disease control by targeted treatment reduces the cardiovascular risk to a degree comparable to that of patients with primary hypertension. In this setting, magnetic resonance angiogram treatment seems to be similarly effective as adrenalectomy. Up to this point, no study had reported mortality data in PA. Our study shows that overall mortality after diagnosis of PA and initiation of specific treatment is similar to that of matched hypertensive controls. A detailed analysis of the causes of death indicates that 50% of all-cause mortality (and 69% of known mortality) is attributable to cardiovascular mortality.

As summarized in Table 3, a number of factors were associated with increased mortality in the presence of aldosterone excess. These include age, diabetes mellitus, and angina pectoris. It might be surprising that, in this context, a variable such as blood pressure is not associated with increased mortality. However, it is reasonable to assume that our study is underpowered to detect a significant effect of this variable. A separate analysis including all 4856 KORA F3 subjects shows that blood pressure is indeed a highly significant predictor ($P=0.003$) of all-cause mortality (data not shown). Protective factors identified in our cohort were intervention by adrenalectomy and the presence of hypokalemia at diagnosis. The latter might be seen as an unexpected finding. Severe hypokalemia is an indirect measure of the level of aldosterone excess. Therefore, one might assume that severe hypokalemia can be detrimental in PA, increasing long-term mortality. However, 3 reasons may explain a favorable outcome with hypokalemia. First, the improved survival associated with severe hypokalemia may reflect earlier case detection of PA leading to more rapid treatment. Second, pronounced hypokalemia is frequently found in aldosterone-producing adenoma. Evidently more patients with severe hypokalemia had aldosterone-producing adenoma leading to a higher rate of adrenalectomy and possibly a better long-term control of blood pressure. Although the former is supported by the improved survival in PA patients undergoing adrenalectomy, the latter remains speculative because we cannot provide sufficient data of interim blood pressure measurements after adrenalectomy or spironolactone treatment. Third, an additional reason might be the more rapid therapeutic effect of adrenalectomy, which was shown for cardiac hypertrophy in PA patients.[14] Along the same line, 2 studies showed that preoperative potassium levels are predictors of blood pressure control after adrenalectomy.[28,29]

Based on age, diabetes mellitus, and angina pectoris, which remained significant in a multivariate model, we calculated a sum score associated with an adverse outcome. As shown in Figure 2, patients with a score of ≥2 had an increased risk for death. The survival curves start to separate after 6 years of follow-up. These data suggest a lag period of several years until mortality increases in high-risk subjects, and long-term surveillance might be indicated accordingly. We believe that cardiovascular risk factors should be controlled tightly in patients who remain hypertensive after adrenalectomy or do not fully respond to mineralocorticoid antagonist therapy.

Limitations and Strengths of the Study

The strengths of our study are the large sample size of the PA cohort, the long period of follow-up, and the large hypertensive control cohort allowing a 2:1 matching. The limitations include the retrospective design of the analysis. For example, it is impossible to control for the intensity with which cardiovascular risk factors were managed in the PA subjects who were managed by hypertension specialists versus the matched subjects presumably managed by nonspecialists. Regression variables, such as blood pressure or diabetes mellitus, are entered into the model based on a single baseline measure but will have improved over time because of treatment effects. The magnitude of this effect could not be assessed in the present study. The control cohort was drawn from a population-based study and not from a patient cohort

collected under similar conditions. Although subjects with PA were not excluded from our control cohort, we have reported previously that the prevalence of an elevated aldosterone:renin ratio in population-based cohorts is <5.1%.[30] Furthermore, because of the high prevalence of essential hypertension, it is likely that, in a subgroup of our patients from our PA cohort, a component of essential hypertension was also present, indicating that a small overlap of diagnosis is virtually unavoidable in such an analysis.

In conclusion, our data show that all-cause mortality in patients with PA is similar to that of matched control hypertensives. PA patients at higher age and with coexisting conditions such as diabetes mellitus or angina pectoris are at higher risk and should be followed more closely in clinical practice.

Perspectives

PA is associated with increased cardiovascular and cerebrovascular morbidity in excess to what might be expected from elevated blood pressure. This has been attributed to additive direct effects of aldosterone on the endothelium and the myocardium. Our study provides for the first time long-term data on mortality in PA. Mortality rates of treated patients with PA proved to be not different from those of matched hypertensives. Depending on the perspective, one might see the glass half-full (at least similar mortality rate to matched hypertensives) or half empty (a lower mortality rate might have been expected because of the often well-controlled blood pressure levels after initiation of specific treatment for PA). In the future, earlier detection of PA and more intensive blood pressure management after diagnosis hold the promise of a better outcome than shown in our study.

Sources of Funding

M.R. is supported by grants of the Else Kröner-Fresenius Stiftung and the Deutsche Forschungsgemeinschaft (Re 752/17-1). The Cooperative Health Research in the Region of Augsburg research platform and the Monitoring Trends and Determinants in Cardiovascular Disease Augsburg studies were initiated and financed by the Helmholtz Zentrum München-National Research Center for Environment and Health, which is funded by the German Federal Ministry of Education, Science, Research, and Technology and by the State of Bavaria.

Disclosures

None.

References

1. Calhoun DA. Aldosterone and cardiovascular disease: smoke and fire. *Circulation*. 2006;114:2572–2574.
2. Funder JW, Reincke M. Aldosterone: a cardiovascular risk factor? *Biochim Biophys Acta*. 2010;1802:1188–1192.
3. Güder G, Bauersachs J, Frantz S, Weismann D, Allolio B, Ertl G, Angermann CE, Störk S. Complementary and incremental mortality risk prediction by cortisol and aldosterone in chronic heart failure. *Circulation*. 2007;115:1754–1761.
4. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J, for the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341:709–717.
5. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M, for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309–1321.
6. Vasan R, Evans JC, Larson MG, Wilson PW, Meigs JB, Rifai N, Benjamin EJ, Levy D. Serum aldosterone and the incidence of hypertension in nonhypertensive persons. *N Engl J Med*. 2004;351:333–341.
7. Rossi GP, Bernin G, Caliumi C, Desideri G, Fabris B, Ferri C, Ganzaroli C, Giacchetti G, Letizia C, Maccario M, Mallamaci F, Mannelli M, Mattarello MJ, Moretti A, Palumbo G, Parenti G, Porteri E, Semplicini A, Rizzoni D, Rossi E, Boscaro M, Pessina AC, Mantero F, for the PAPY Study Investigators. A prospective study of the prevalence of primary aldosteronism in 1125 hypertensive patients. *J Am Coll Cardiol*. 2006;48:2293–2300.
8. Catena C, Colussi G, Lapenna R, Nadalini E, Chiuch A, Gianfagna P, Sechi LA. Long-term cardiac effects of adrenalectomy or mineralocorticoid antagonists in patients with primary aldosteronism. *Hypertension*. 2007;50:911–918.
9. Suzuki T, Abe H, Nagata S, Saitoh F, Iwata S, Ashizawa A, Kuramochi M, Omae T. Left ventricular structural characteristics in unilateral renovascular hypertension and primary aldosteronism. *Am J Cardiol*. 1988;62:1224–1227.
10. Milliez P, Girerd X, Plouin PF, Blacher J, Safar ME, Mourad JJ. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. *J Am Coll Cardiol*. 2005;45:1243–1248.
11. Rizzoni D, Paiardi S, Rodella L, Porteri E, De Ciuceis C, Rezzani R, Boari GE, Zani F, Miclini M, Tiberio GA, Giulini SM, Rosei CA, Bianchi R, Rosei EA. Changes in extracellular matrix in subcutaneous small resistance arteries of patients with primary aldosteronism. *J Clin Endocrinol Metab*. 2006;91:2638–2642.
12. Amar L, Plouin PF, Steichen O. Aldosterone-producing adenoma and other surgically correctable forms of primary aldosteronism. *Orphanet J Rare Dis*. 2010;5:9–21.
13. Schirpenbach C, Reincke M. Primary aldosteronism: current knowledge and controversies in Conn's syndrome. *Nat Clin Pract Endocrinol Metab*. 2007;3:220–227.
14. Catena C, Colussi G, Nadalini E, Chiuch A, Baroselli S, Lapenna R, Sechi LA. Cardiovascular outcomes in patients with primary aldosteronism after treatment. *Arch Intern Med*. 2008;168:80–85.
15. Matrozova J, Steichen O, Amar L, Zacharieva S, Jeunemaitre X, Plouin PF. Fasting plasma glucose and serum lipids in patients with primary aldosteronism: a controlled cross-sectional study. *Hypertension*. 2009;53:605–610.
16. Born-Frontsberg E, Reincke M, Rump LC, Hahner S, Diederich S, Lorenz R, Allolio B, Seufert J, Schirpenbach C, Beuschlein F, Bidlingmaier M, Endres S, Quinkler M; Participants of the German Conn's Registry. Cardiovascular and cerebrovascular comorbidities of hypokalemic and normokalemic primary aldosteronism: results of the German Conn's Registry. *J Clin Endocrinol Metab*. 2009;94:1125–1130.
17. Reincke M, Rump LC, Quinkler M, Hahner S, Diederich S, Lorenz R, Seufert J, Schirpenbach C, Beuschlein F, Bidlingmaier M, Meisinger C, Holle R, Endres S, for the Participants of German Conn's Registry. Risk factors associated with a low glomerular filtration rate in primary aldosteronism. *J Clin Endocrinol Metab*. 2009;94:869–875.
18. Reincke M, Meisinger C, Holle R, Quinkler M, Hahner S, Beuschlein F, Bidlingmaier M, Seissler J, Endres S, for the Participants of the German Conn's Registry. Is primary aldosteronism associated with diabetes mellitus? Results of the German Conn's Registry. *Horm Metab Res*. 2010;42:435–439.
19. Fischer E, Beuschlein F, Bidlingmaier M, Reincke M. Commentary on the Endocrine Society Practice guidelines: consequences of adjustment of antihypertensive medication in screening of primary aldosteronism. *Rev Endocr Metab Disord*. 2011;12:43–48.
20. Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, Young WF Jr, Montori VM, for the Endocrine Society. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2008;93:3266–3281.
21. Vonend O, Ockenfels N, Gao X, Allolio B, Lang K, Mai K, Quack I, Saleh A, Degenhart C, Seufert J, Seiler L, Beuschlein F, Quinkler M, Podrabsky P, Bidlingmaier M, Lorenz R, Reincke M, Rump LC, for the German Conn's Registry. Adrenal venous sampling: evaluation of the German Conn's Registry. *Hypertension*. 2011;57:990–995.
22. Search the DIMDI Web site. http://www.dimdi.de/dynamic/de/suche.html. Accessed August 8, 2011.
23. Herder C, Lankisch M, Ziegler D, Rathmann W, Koenig W, Illig T, Döring A, Thorand B, Holle R, Giani G, Martin S, Meisinger C. Sub-

clinical inflammation and diabetic polyneuropathy: MONICA/KORA Survey F3 (Augsburg, Germany). *Diabetes Care*. 2009;32:680–682.
24. The Comprehensive R Archive Network. http://cran.r-project.org/. Accessed August 8, 2011.
25. Rossi GP, Sacchetto A, Visentin P, Canali C, Graniero GR, Palatini P, Pessina AC. Changes in left ventricular anatomy and function in hypertension and primary aldosteronism. *Hypertension*. 1996;27:1039–1045.
26. Stowasser M, Sharman J, Leano R, Gordon RD, Ward G, Cowley D, Marwick TH. Evidence for abnormal left ventricular structure and function in normotensive individuals with familial hyperaldosteronism type I. *J Clin Endocrinol Metab*. 2005;90:5070–5076.
27. Sechi LA, Novello M, Lapenna R, Gordon RD, Ward G, Cowley D, Marwick TH. Long-term renal outcomes in patients with primary aldosteronism. *JAMA*. 2006;295:2638–2645.
28. Zarnegar R, Young WF Jr, Lee J, Sweet MP, Kebebew E, Farley DR, Thompson GB, Grant CS, Clark OH, Duh QY. The aldosteronoma resolution score: predicting complete resolution of hypertension after adrenalectomy for aldosteronoma. *Ann Surg*. 2008;247:511–518.
29. Mourad JJ, Girerd X, Milliez P, Lopez-Sublet M, Lejeune S, Safar ME. Urinary aldosterone-to-active-renin ratio: a useful tool for predicting resolution of hypertension after adrenalectomy in patients with aldosterone-producing adenomas. *Am J Hypertens*. 2008;21:742–747.
30. Hannemann A, Bidlingmaier M, Friedrich N, Manolopoulou J, Spyroglou A, Völzke H, Beuschlein F, Seissler J, Rettig R, Felix SB, Biffar R, Döring A, Meisinger C, Peters A, Wichmann HE, Nauck M, Wallaschofski H, Reincke M. Screening for primary aldosteronism in hypertensive subjects: results from two German epidemiological studies. *Eur J Endocrinol*. 2012;167:7–15.

Novelty and Significance

What Is New?

- PA is a secondary form of hypertension associated with increases cardiovascular morbidity. This is the first study to report long-term mortality in treated PA compared with matched hypertensive controls.

What Is Relevant?

- Our data show that all-cause mortality in patients with PA is similar to that of matched control hypertensives.

Summary

PA patients at higher age and with coexisting conditions, such as diabetes mellitus or angina pectoris, are at higher risk and should be followed more closely in clinical practice.