Research Article

Long-Term Use of Aldosterone-Receptor Antagonists in Uncontrolled Hypertension: A Retrospective Analysis

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Background. The long-term efficacy of aldosterone-receptor antagonists (ARAs) as add-on treatment in uncontrolled hypertension has not yet been reported. *Methods*. Data from 123 patients (21 with primary aldosteronism, 102 with essential hypertension) with difficult-to-treat hypertension who received an ARA between May 2005 and September 2009 were analyzed retrospectively for their blood pressure (BP) and biochemical response at first followup after start with ARA and the last follow-up available. *Results*. Systolic BP decreased by 22 ± 20 and diastolic BP by 9.4 ± 12 mmHg after a median treatment duration of 25 months. In patients that received treatment >5 years, SBP was 33 ± 20 and DBP was 16 ± 13 mmHg lower than at baseline. Multivariate analysis revealed that baseline BP and follow-up duration were positively correlated with BP response. *Conclusion*. Add-on ARA treatment in difficult-to-treat hypertension results in a profound and sustained BP reduction.

1. Introduction

Aldosterone-receptor antagonists (ARAs) have been shown to be effective in blood pressure (BP) reduction [1–11], but until recently their use was mainly limited to certain conditions such as liver cirrhosis, heart failure, and primary aldosteronism (PA). With the recognition of PA as a common cause of resistant hypertension [12], a renewed interest in the use of ARAs in hypertension has emerged. However, aldosterone has also shown to be an important factor in other forms of resistant hypertension. In patients with elevated aldosterone-to-renin ratios (ARRs) and plasma aldosterone levels, but without genuine PA based on suppression testing, BP control was harder to achieve than in essential hypertensives (EHs) [13]. Furthermore, a proportion of patients treated with angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) show aldosterone breakthrough [14–16], contributing to therapy resistance by partly counteracting the intended blockade of the renin-angiotensin-aldosteron-system (RAAS).

The use of ARAs in resistant hypertension, therefore, seems rational, and several publications have pointed out the potential of aldosterone blockade in difficult-to-treat or resistant hypertension [17–24]. In many of these studies, the addition of spironolactone resulted in an impressive drop in systolic BP (SBP) of up to 25 mmHg and 12 mmHg in diastolic BP (DBP). However, most of these studies were either open label [17, 18, 20, 22], or retrospective [19, 21, 23] in design. One randomized, placebo-controlled, double-blind trial was performed comparing spironolactone with amiloride, the combination of both drugs, and placebo in black hypertensive patients with uncontrolled hypertension despite treatment with at least a diuretic and a calcium-channel-blocker [24]. Interestingly, the BP response was considerably smaller than in the aforementioned studies (-7.3 in SBP and -3.3 mmHg in DBP for spironolactone versus placebo). De Souza et al. recently performed an open-label, prospective study on the BP-lowering benefits of spironolactone in patients with resistant hypertension. By using 24-hour ambulatory BP measurements, at least part of the potential white coat and placebo effect could be

accounted for. Twenty-four-hour SBP and DBP decreased by 16 and 9 mmHg, respectively, after a median treatment duration of 7 months, and in a subgroup, the persistence of this effect was confirmed up to 15 months [22]. So far, longer followup periods have not been reported and although a persistence of the effect in the long run is expected, this remains to be confirmed.

Predicting factors for the BP response to ARA treatment have been identified in several studies. Lower serum potassium levels were pointed out by several groups to be associated with a larger decrease in BP [19, 21, 22, 25]. Most studies found no relation between plasma renin concentration or activity and the BP lowering response to ARAs [5, 9, 17, 26]. Also neither plasma aldosterone levels nor ARR levels seem to predict the BP-lowering effect [22, 26], although this could have been caused by the interfering effects of multidrug antihypertensive regimens on the ARR in these patients [25]. Other factors possibly associated with a better response are the absence of diabetes [23], higher waist circumference, lower aortic pulse wave velocity [22], and a lower baseline high-density lipoprotein (HDL) cholesterol [21].

ARAs have been prescribed in our clinic to patients with difficult-to-treat hypertension for a long time now, often with good results even after many years. This study aims to retrospectively characterize the long-term response to ARA treatment in patients with difficult-to-treat hypertension and to identify factors associated with this response.

2. Methods

2.1. Patients.

All patients who visited the outpatient hypertension clinic of the Erasmus Medical Center in Rotterdam and the TweeSteden Hospital in Waalwijk, the Netherlands, between May 2005 and September 2009 were screened for their eligibility for the study. Patients were selected when they had uncontrolled hypertension (BP > 140/90 mmHg, or >130/80 mmHg for patients with diabetes mellitus (DM) or manifest cardiovascular disease) despite the use of at least two antihypertensive drugs and were put on spironolactone or eplerenone during the study period. Patients who were already using an ARA when referred to our clinic were excluded. Patients of whom insufficient data was available to meet the primary objective (for instance insufficient data on medication use or the absence of a BP measurement at the start of treatment or last followup) or patients who were prescribed an ARA for another indication than hypertension were also excluded from the analysis.

2.2. Clinical Data.

At baseline, patients' sex, height, weight, the time of diagnosis of hypertension, their antihypertensive medication, their family history, and the presence or absence of diabetes at the start of ARA treatment were collected from patient files. Their electrocardiograms (ECGs), when not taken longer than one year before start of treatment, were scored for the presence of left ventricular hypertrophy (LVH) according to the Sokolow-Lyon criteria. The presence or absence of PA was based on the clinical judgement by their physician.

At baseline, at first followup (i.e., the first followup visit that BP was measured after start of ARA treatment), and at the end of followup (i.e., the date that ARA treatment was permanently discontinued or the last visit before the end of data collection), the following parameters were recorded: BP, serum sodium, potassium, urea, creatinine, uric acid, glucose, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and hemoglobin and hematocrit, and plasma renin and aldosterone levels, where available.

BP measurements were taken in triplicate at an interval of five minutes with a semiautomatic BP measuring device after a rest of five minutes in sitting position. The mean of these measurements was used in the analysis.

Biochemical measurements were taken on the visit day or the nearest previous moment.

Plasma renin concentrations (PRCs) were assessed using an immunoradiometric assay (Renin III, Cisbio, Gif-sur-Yvette, France). Plasma aldosterone concentrations (PACs) were measured with a radioimmunoassay (Coat-a Count, Diagnostics Product Corporation, LA, CA, USA). Hyperkalemia was defined as serum potassium levels exceeding 5.5 mmol/L.

2.3. Data Analysis.

Statistical analyses were performed in SPSS 17.0 for Windows.

Main effects at first followup and end of followup were calculated. Furthermore, to assess the long-term efficacy of treatment, patients were stratified based on the duration of followup into the following categories: <1 year, 1–5 years, and >5 years followup.

Values are expressed as mean ± SD, or as median and range when not normally distributed. Medication use was quantified by adding up the total number of different drugs, as well as by assessing the defined daily doses (DDDs) per drug and for total drug use according to the World Health Organization Anatomical Therapeutic Chemical (ATC) index [27]. Differences within subjects were tested using paired Student's t-tests for two groups and one-way analysis of variance (ANOVA) for repeated measurements for more groups. Between-subjects differences were tested with unpaired t-tests for two groups and one-way ANOVA for more groups. For values that were abnormally distributed, nonparametric tests were used (Mann-Whitney U test and Wilcoxon Signed Ranks test). Differences in proportions were tested with a chi-square test.

Patients with PA were excluded for regression analysis. A univariate linear regression analysis was performed to identify potential determinants of the BP response. Significant parameters were subsequently tested in a multivariate linear regression analysis. This model was further adjusted for age and sex.

3. Results

3.1. Study Population.

A total of 175 patients were prescribed an ARA during the study period. Fifty-two patients were excluded: 39 because of insufficient data, 5 because our

TABLE 1: Baseline characteristics of the study population.

	Total	EH	PA	P-value
Number	123	102	21	
Age (years)	56.6 ± 10.7	56.7 ± 11.2	56.5 ± 8.2	.959
Male (%)	60.1	56.9	76.2	.099
BMI (kg/m^2)	29.4 ± 5.0	29.3 ± 5.0	30.1 ± 5.2	.537
SBP (mmHg)	159.7 ± 19.1	158.4 ± 18.3	166.0 ± 21.7	.094
DBP (mmHg)	93.3 ± 12.2	92.7 ± 12.5	96.0 ± 10.8	.268
Time since diagnosis (years)	10.0 (0–50)	10.0 (0–50)	7.5 (1.0–34)	.319
Age at diagnosis (years)	42.0 ± 13.0	41.5 ± 13.3	44.7 ± 11.4	.335
Nr. of antihypertensives	3 (2–6)	3 (2–6)	3 (2–5)	.071
DDD	5.0 (1.25–13.0)	5.0 (1.25–13.0)	3.7 (1.5–10.0)	.117
DM (%)	22.8	23.2	21.1	.842
LVH (%)	28.5	26.5	38.1	.125
Family history of HT	52.0	53.9	42.9	.355
Serum sodium (mmol/L)	141.5 ± 2.7	141.2 ± 2.8	143.0 ± 2.14	.008
Serum potassium (mmol/L)	3.9 ± 0.6	4.0 ± 0.6	3.4 ± 0.5	<.001
Serum creatinine (μmol/L)	83.8 ± 20.1	83.8 ± 21.1	84.1 ± 14.4	.959
Serum uric acid (mmol/L)	0.36 ± 0.08	0.37 ± 0.08	0.34 ± 0.08	.134
Hemoglobin (mmol/L)	8.9 ± 0.82	8.8 ± 0.8	9.5 ± 0.6	.001
Hematocrit (%)	0.42 ± 0.04	41.3 ± 3.6	45.3 ± 2.1	.003
Cholesterol (mmol/L)	5.31 ± 0.96	5.27 ± 0.97	5.55 ± 0.90	.345
HDL (mmol/L)	1.35 ± 0.42	1.37 ± 0.41	1.26 ± 0.44	.347
LDL (mmol/L)	3.37 ± 1.02	3.41 ± 1.02	3.16 ± 1.03	.407
Glucose (mmol/L)	5.5 ± 1.6	5.5 ± 1.6	5.5 ± 1.8	.943
ACR (g/mol)	2.19 (0.95–12.4)	2.19 (0.15–453.8)	1.96 (0.37–592.0)	.518
PAC (pmol/L)	282.5 (2.8–4172)	224.4 (2.8–4172)	548.5 (199–2282)	$P < .001$
PRC (mU/L)	13.9 (1.0–4374)	19.8 (1.0–4374)	5.8 (1.8–18.9)	$P < .001$
ARR (pmol/mU)	19.4 (0.3–1087)	9.5 (0.3–781)	82.7 (17.4–1087)	$P < .001$

(EH: essential hypertension; PA: primary aldosteronism; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; DDD: defined daily dose; DM: diabetes mellitus; LVH: left ventricular hypertrophy; HT: hypertension; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ACR: urinary albumin-to-creatinine ratio; PAC: plasma aldosterone concentration; PRC: plasma renin concentration; ARR: aldosterone-to-renin ratio).

criteria for difficult-to-treat hypertension were not met, 3 because of questionable treatment adherence, 2 because of a followup duration less than a month, 1 because baseline BP measurement was not performed with a semi-automatic BP measuring device, and 1 because an ARA was prescribed because of another indication than hypertension. In total, 123 patients were included in the analysis with a mean age of 56.6 ± 10.7 years. The median duration between diagnosis and start of ARA treatment was 10 years (range 0–50 years). The median number of different antihypertensive agents was 3 (total DDD 5.0). Twenty-three percent of patients had DM, and 29 percent had LVH. Twenty-one patients were diagnosed as having PA by their physician. The baseline characteristics of all patients and of the EH and PA subgroups are shown in Table 1. Serum potassium levels were lower in patients with PA than with EH (3.4 mmol/L versus 4.0 mmol/L in EH, $P < .001$). Serum sodium levels were higher in patients with PA than with EH (143 versus 141 mmol/L, $P < .001$).

As expected, PRC was lower in PA than in EH patients (5.8 versus 19.8 mU/L, $P < .001$). PAC and ARR were higher in PA patients (548.5 versus 224.4 pmol/L ($P < .001$) for PAC, and 82.7 versus 9.5 pmol/mU ($P < .001$) for ARR).

Values of haemoglobin and hematocrit were also higher in PA than in EH patients.

3.2. Treatment. Ninety-four patients started on spironolactone treatment with a median dose of 50 mg daily (range 12.5–100 mg). Twenty-nine patients started on eplerenone with a median dose of 50 mg (range 25–50 mg). Total starting DDD of ARA was 0.67 (range 0.17–1.33). At the end of followup 91 patients were on spironolactone with a median dose of 25 mg (range 12.5–100 mg) and 32 patients on eplerenone (median dose 50 mg, range 25–100 mg). Median ARA DDD at end of followup was 0.67 (range 0.17–2.00). Median treatment duration at first followup was 8 weeks (range 1–66 weeks). The median treatment duration at end of followup was 25 months (range 1–144 months).
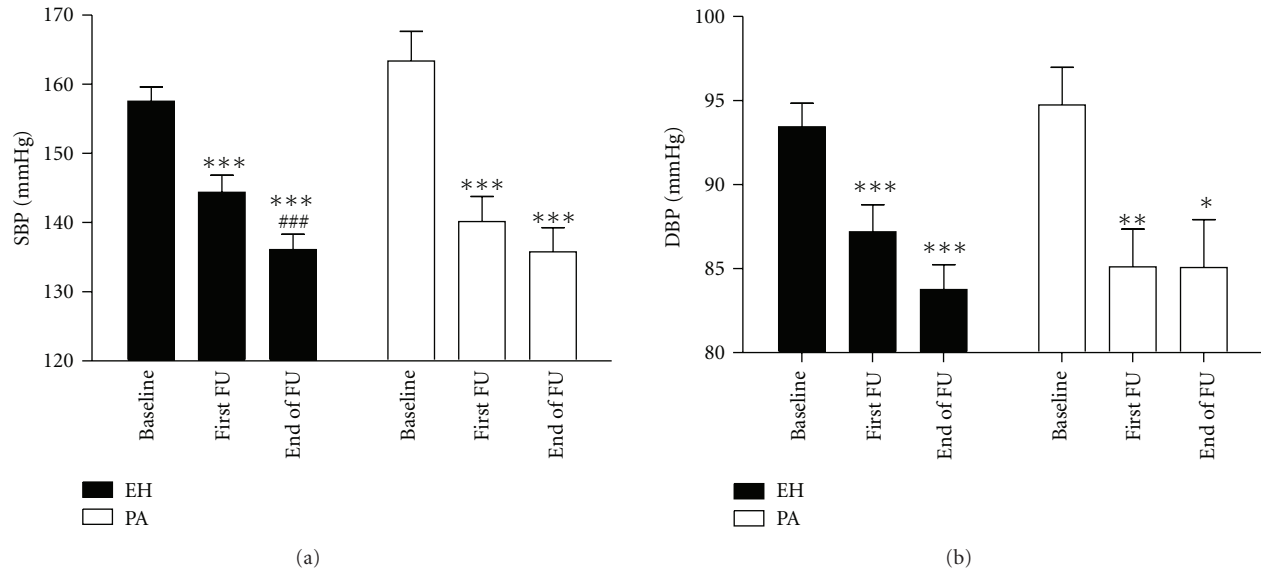
(a)

(b)

FIGURE 1: Systolic (SBP) and diastolic (DBP) blood pressure before start with an aldosterone-receptor antagonist (baseline), at first followup (FU), and at the end of FU in patients with essential hypertension (EH) and primary aldosteronism (PA). Overall trend was tested with one-way ANOVA for repeated measurements ($P < .001$ for all groups, except for DBP in the PA group ($P = .001$)). Indicated significance levels are for differences between groups after adjustment for multiple comparisons (* compared to baseline; # compared to first FU).

TABLE 2: Changes in biochemical parameters at first followup and end of followup after start of treatment with an aldosterone-receptor antagonist for patients with essential hypertension (EH) and primary aldosteronism (PA). (Values were tested with one-way ANOVA for repeated measurements. Indicated P values are for differences between baseline and first followup (a), first and last followup (b), and baseline and last followup (c) after Bonferroni adjustment; n represents the number of patients with measurements at all three time points).

		n	Baseline	P value[a]	First FU	P value[b]	End of FU	P value[c]
EH	Serum sodium (mmol/L)	66	141.2 ± 2.7	1.000	140.9 ± 3.0	.927	141.3 ± 3.2	1.000
	Serum potassium (mmol/L)	80	4.0 ± 0.6	<.001	4.4 ± 0.6	1.000	4.4 ± 0.5	<.001
	Serum creatinine (μmol/L)	78	84.6 ± 20.8	<.001	90.8 ± 24.7	.355	93.6 ± 26.2	<.001
PA	Serum sodium (mmol/L)	17	142.9 ± 2.1	.015	141.0 ± 3.4	.103	142.7 ± 3.4	1.000
	Serum potassium (mmol/L)	19	3.4 ± 0.5	<.001	4.3 ± 0.5	1.000	4.3 ± 0.5	<.001
	Serum creatinine (μmol/L)	18	85.7 ± 14.1	.011	96.1 ± 22.6	1.000	95.7 ± 19.6	.169

3.3. *Main Effects of ARA Treatment.* The BP levels at first followup and at the end of followup are shown in Figure 1. In EH patients, BP decreased by 13 ± 1.8 mmHg systolically and 6.2 ± 1.0 mmHg diastolically at first followup, and by 21 ± 2.1 and 9.7 ± 1.4 mmHg at the end of followup. In PA patients, SBP had decreased by 23 ± 4.8 mmHg and DBP by 9.6 ± 2.5 mmHg at first followup and by 28 ± 4.9 and 9.7 ± 3.1 mmHg at the end of followup. Changes in BP were not significantly different for EH and PA patients at both time points, although a trend existed towards a larger SBP decrease at first followup in the PA group ($P = .063$).

Serum potassium and creatinine levels increased significantly after start of ARA treatment for both EH and PA patients. Furthermore, in PA patients, serum sodium was significantly lower at first followup compared to baseline (Table 2).

At baseline, PA and EH patients used a median number of 3 antihypertensive drugs (range 2–6). At the end of

followup, the number of drugs had increased to 4 (range 1 to 7, $P < .001$). However, when expressed in DDD, the total amount of antihypertensive drugs remained unchanged (5 DDD at baseline versus 4.5 at end of followup, $P = .459$). Also in the EH subgroup, the number of antihypertensive drugs increased from 3 to 4 ($P < .001$), with a nonsignificant decrease in DDD (5 DDD at baseline against 4.6 at end of followup, $P = .663$). In PA patients, there was no significant change in number of antihypertensive drugs (3 versus 3, $P = .317$) or DDD (3.66 versus 3.83, $P = .407$).

3.4. *Stratification to Followup Duration.* Because of the wide variation in followup duration and to better assess the long-term efficacy of ARA treatment, patients were stratified according to their treatment followup. The following categories were formed: 0-1 year, 1–5 years, and >5 years. Number of patients in these categories were 33, 49, and
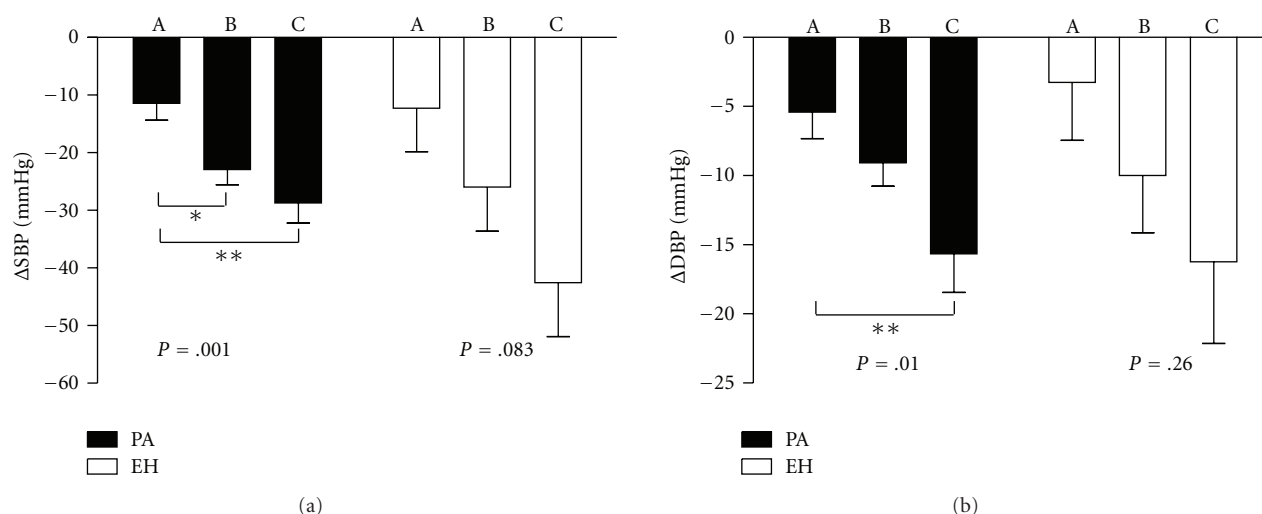
(a)

(b)

FIGURE 2: Changes in systolic (SBP) and diastolic (DBP) blood pressure at the end of followup compared to baseline for three categories of followup duration (A < 1 year; B 1–5 years; C > 5 years). *P* values are for trend tested with one-way ANOVA; indicated significance levels are for differences between groups after adjustment for multiple comparisons. (EH: essential hypertension; PA: primary aldosteronism).

20, respectively, for EH patients, and 5, 8, and 8 for PA patients. In Figure 2, blood pressure reduction is shown for the three categories of followup duration. In EH patients larger responses were seen with longer followup duration ($P = .001$ for ΔSBP and $P = .01$ for ΔDBP with one-way ANOVA). In PA patients, a similar trend was seen. The overall trends were not different for EH and PA patients ($P = .467$ for ΔSBP and $P = .907$ for ΔDBP at two-way ANOVA).

To investigate whether the reduction in BP was merely a result of a greater number of antihypertensive drugs than a specific effect of ARA treatment, baseline and end-of-followup BP is shown in relation to medication use for EH (Figure 3) and PA (Figure 4). The proportion of total DDD that consisted of ARA treatment is separately indicated. These figures show that at longer followup, BP further decreased, while the total DDD remained unchanged. In EH patients, the percentage of total DDD consisting of an ARA significantly increased from 9.1% to 14.2% ($P < .001$) in the 1–5-year followup group. In PA patients, the relative contribution of ARA to total DDD increased from 14.9% to 22.4% in the 1–5-year followup group ($P = .050$) and from 14.9% to 31.9% in the >5 years followup group ($P = .018$).

3.5. Predictors for the Blood Pressure Response. The main clinical parameters were tested for their potential association with SBP as well as DBP response at first and last followup by univariate regression analysis (with the change in BP being negative). Table 3 shows the beta coefficients of all parameters that were significantly associated with BP change in any of the four groups, as well as those considered relevant based on earlier reports. At first followup, the sodium/potassium ratio as well as followup duration were significantly associated with ΔSBP. The ARR was significantly associated with ΔDBP, yet with a very small and probably

irrelevant regression coefficient considering the range in ARR. Interestingly, haemoglobin and hematocrit levels, total cholesterol, and LDL levels were negatively associated with blood pressure change at univariate analysis for ΔSBP, and the latter two also for ΔDBP.

At last followup, the change in BP was significantly correlated with baseline BP, urinary albumin-to-creatinine ratio (ACR), LVH, followup duration, and, for DBP, the ARR.

To identify independent predictors for BP response, the variables significantly associated in the univariate analyses were included in a multivariate linear regression analysis. In addition, the model was adjusted for age and sex. The regression coefficients and significance levels are shown in Table 4. Unfortunately, hemoglobin, hematocrit, total cholesterol, LDL, LVH, and the ARR could not be included in the analysis because numbers were too small to maintain sufficient statistical power.

At first followup, only baseline SBP seemed to be an independent predictor (borderline significant) for ΔSBP. For ΔDBP, there were no independent predictors for the response. At the end of followup, higher baseline BP and longer FU duration were independently associated with the change in BP.

3.6. Adverse Events. ARA treatment was in general well tolerated. In total, 13 adverse events were reported. Five cases of gynaecomastia were reported with spironolactone use resulting in a switch to eplerenone in 1 patient. Two cases of hyperkalemia were seen, and in two patients, a clinically relevant decrease in renal function was observed. Two patients (one on eplerenone and one on spironolactone) reported general discomfort and headache, and one patient experienced gastrointestinal discomfort, although this was probably already present before start of spironolactone. In 1 patient, the nature of the adverse event was not further specified.
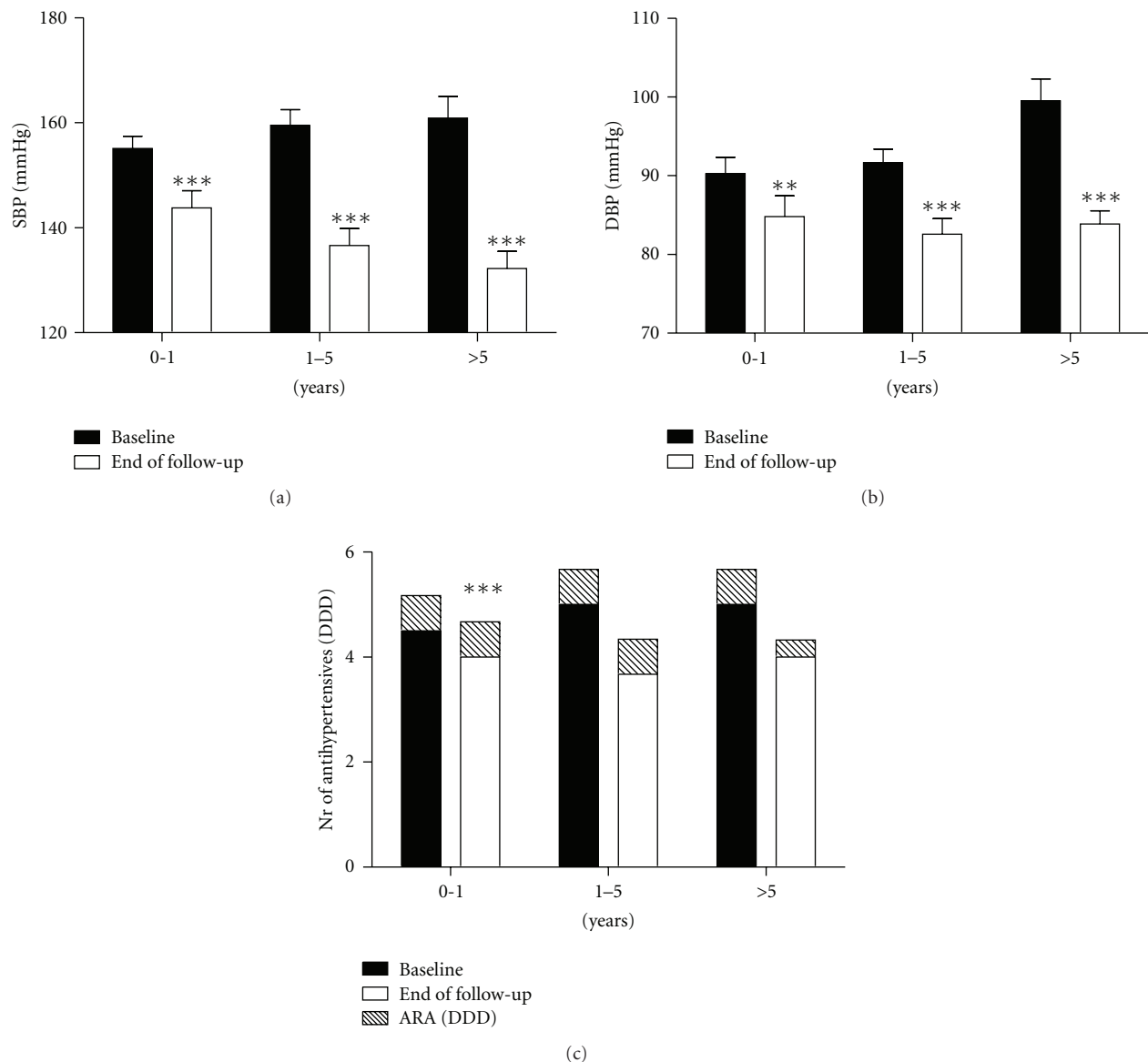
(a)

(b)

(c)

FIGURE 3: Systolic (SBP) (a), diastolic (DBP) (b) blood pressure and medication use (defined daily dose, DDD) (c) at baseline and end of followup after stratification for followup duration for patients with essential hypertension (Figure 3) and primary aldosteronism (Figure 4). Indicated in (c) is the DDD for the aldosterone-receptor antagonist (ARA). For baseline, this is added up to total DDD; at the end of followup, this is part of the total DDD since ARA was started at baseline. Differences were tested with paired t-test for SBP and DBP and Wilcoxon Signed Ranks test for DDD (DDD without ARA at baseline versus DDD including ARA at the end of followup).

4. Discussion

This study shows that the addition of aldosterone-receptor antagonists (ARAs) in patients with difficult-to-treat hypertension was highly effective in reducing SBP as well as DBP. This effect was already present at short-term followup (median followup 8 weeks) and persisted in the long run with a median followup of 25 months. The BP reduction in EH and PA patients was comparable, and in both groups ARA treatment resulted in a small rise in serum potassium and creatinine levels.

To assess whether the BP-lowering effect was still present after prolonged treatment, patients were stratified according to their duration of followup. We observed larger BP reductions with increasing followup, which was highly significant in EH patients. In the subgroup that had a followup of more than 5 years, SBP was 29 mmHg and DBP 16 mmHg lower than at baseline. In PA, a similar trend was seen although this failed to reach statistical significance, probably because of the small number of patients in each subgroup. Also in the multivariate regression analysis we observed a strong correlation between treatment duration and decrease in BP. Although it is appealing to conclude that a longer treatment duration leads to better BP control for instance by reversing target organ damage, a more likely explanation is some form of effect-bias implicating that patients with a better response
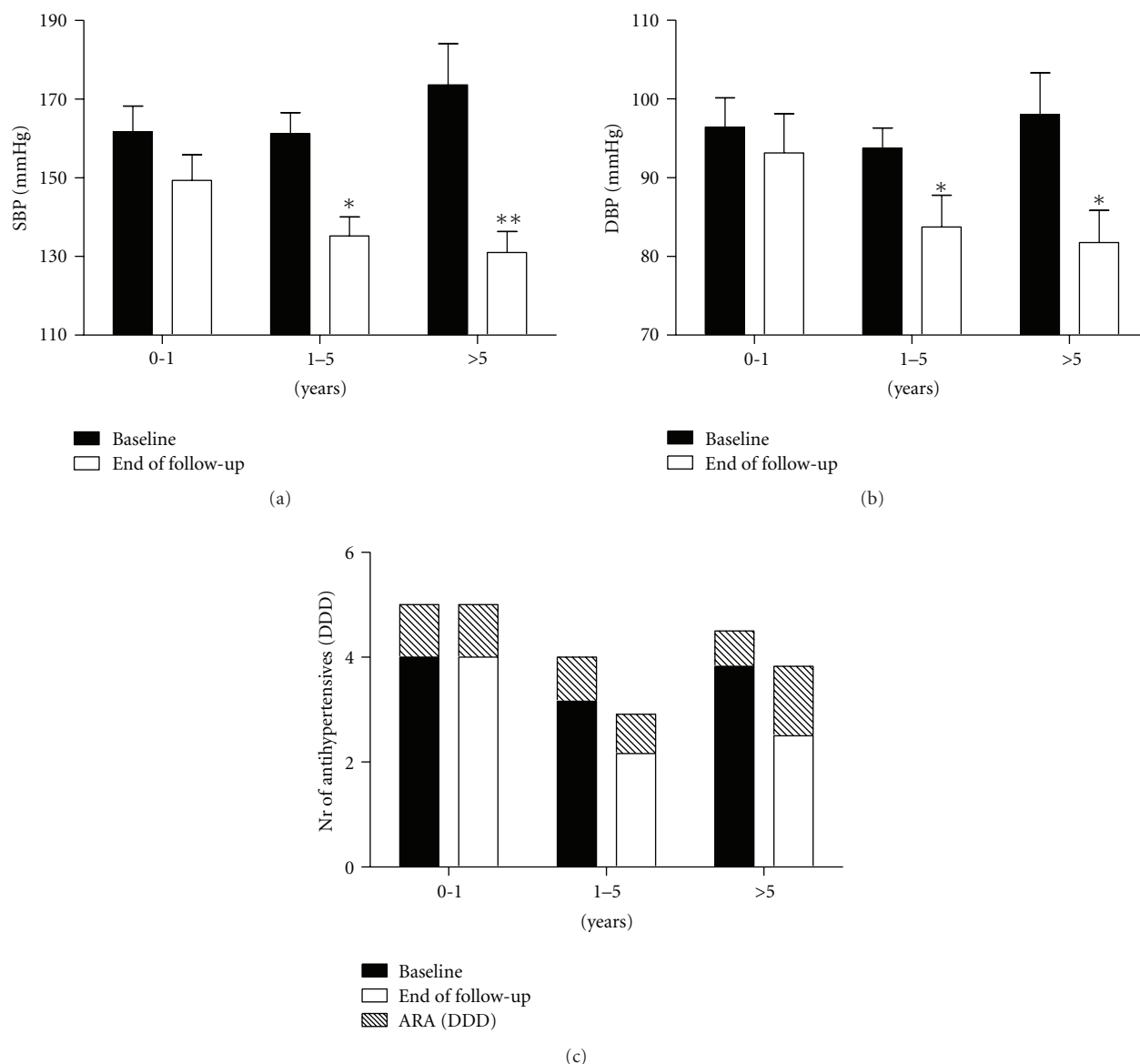
(a)

(b)

(c)

FIGURE 4: Systolic (SBP) (a), diastolic (DBP) (b) blood pressure and medication use (defined daily dose, DDD) (c) at baseline and end of followup after stratification for followup duration for patients with essential hypertension (Figure 3) and primary aldosteronism (Figure 4). Indicated in (c) is the DDD for the aldosterone-receptor antagonist (ARA). For baseline, this is added up to total DDD; at the end of followup, this is part of the total DDD since ARA was started at baseline. Differences were tested with paired t-test for SBP and DBP and Wilcoxon Signed Ranks test for DDD (DDD without ARA at baseline versus DDD including ARA at the end of followup).

are more likely to receive ARA treatment for a longer period. Whether prolonged treatment leads to a better BP control requires a long-term prospective study.

Another explanation for the favourable long-term BP response could be an optimalisation of the antihypertensive medication or merely the fact that the total amount of medication increased over time. To investigate this further, BP values at baseline and at end of followup were shown in relation to total medication use. Although BP decreased considerably over the study period, the total amount of DDD remained virtually the same. The relative contribution of ARA treatment to total DDD increased over time. The possibility that the improved BP reduction during long-

term followup is due to an increase in total amount of antihypertensive medication can therefore be excluded.

The BP responses in this study were of similar magnitude as those observed in other retrospective or open-label studies concerning add-on ARA treatment [17–21, 23]. Interestingly, in two prospective trials, BP reductions were considerably smaller than in the aforementioned studies. Saha et al. [24] studied the effect of spironolactone in black hypertensive patients with uncontrolled BP despite the use of at least a diuretic and a calcium-channel-blocker in a randomized, placebo-controlled manner and reported a reduction of 7.3 mmHg in SBP and 3.3 mmHg in DBP. In a recent study, De Souza et al. [22] assessed the effect of open-label

TABLE 3: Outcomes of a univariate linear regression analysis with the changes in systolic and diastolic blood pressure at first and last followup compared to baseline (ΔSBP1, ΔDBP1, ΔSBP2, and ΔDBP2, resp.) as dependent variables. Included in the table are all independent variables with a significant β-coefficient in one of the ΔBP categories or those assumed to be relevant based on the literature. Also shown are the numbers (n) available for the individual analyses.

Independent variable	ΔSBP1			ΔDBP1			ΔSBP2			ΔDBP2		
	β	n	P value	β	n	P value	β	n	P value	β	n	P value
Age (years)	−0.750	83	.660	0.030	83	.758	−0.013	102	.937	0.043	102	.689
Sex (1 = female, 2 = male)	4.199	83	.260	3.477	83	.101	−4.737	102	.207	−2.789	102	.251
DM	−5.684	78	.202	−0.746	78	.770	−5.896	95	.181	−0.206	95	.943
LVH	2.948	63	.526	2.875	63	.276	−9.461	76	**.031**	−2.897	76	.343
SBP$_0$ (mmHg)	0.170	83	.083	0.000	83	.994	−0.388	102	**<.001**	−0.034	102	.608
DBP$_0$ (mmHg)	0.080	83	.572	−0.118	83	.143	−0.378	102	**.010**	−0.407	102	**<.001**
Na$^+$ (mmol/L)	−0.742	78	.280	−0.825	78	**.032**	0.600	95	.393	−0.028	95	.951
K$^+$ (mmol/L)	4.206	83	.162	0.341	83	.844	0.017	102	.996	−0.344	102	.867
Na$^+$/K$^+$	−0.663	78	**.038**	−0.174	78	.343	−0.123	95	.723	0.035	95	.876
Hb (mmol/L)	6.79	52	**.023**	2.632	52	.125	−1.837	59	.576	−1.329	59	.529
Ht (%)	162.2	30	.084	56.75	30	.259	−19.98	35	.831	−23.75	35	.707
TC (mmol/L)	5.374	61	**.025**	2.609	61	**.044**	−1.555	79	.480	−1.136	79	.424
HDL (mmol/L)	4.880	64	.311	3.639	64	.162	0.283	81	.956	2.826	81	.387
LDL (mmol/L)	5.127	60	**.004**	2.111	60	**.031**	0.585	78	.784	−0.291	78	.832
ACR (g/mol)	0.031	40	.518	0.041	40	.170	0.078	45	**.036**	0.049	45	**.028**
FU duration (weeks)	−0.371	83	**.018**	−0.150	83	.098	−0.039	102	**.001**	−0.028	102	**<.001**
Total DDD	0.503	83	.539	0.348	83	.458	−0.649	102	.435	−0.250	102	.642
DDD ARA	5.446	83	.360	6.501	83	.054	−1.130	102	.847	1.799	102	.634
PAC (pmol/L)	0.001	46	.788	0.003	46	.149	0.002	55	.621	0.004	55	.117
PRC (mU/L)	0.002	47	.553	0.002	47	.325	0.004	56	.392	0.003	56	.225
ARR (pmol/mU)	−0.034	46	.094	0.027	46	**.020**	−0.027	55	.289	0.033	55	**.029**

(DM: diabetes mellitus; LVH: left ventricular hypertrophy; Na$^+$: sodium; K$^+$: potassium; Hb: hemoglobin; Ht: hematocrit; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ACR: urinary albumin-to-creatinine ratio; FU: followup; DDD: defined daily dose; ARA: aldosterone-receptor antagonist; PAC: plasma aldosterone concentration; PRC: plasma renin concentration; ARR: aldosterone-to-renin ratio).

TABLE 4: Multivariate linear regression analysis for the change in systolic and diastolic blood pressure at first and last followup (ΔSBP1, ΔDBP1, ΔSBP2, and ΔDBP2).

	ΔSBP1			ΔDBP1			ΔSBP2			ΔDBP2		
	β	SEM	P value	β	SEM	P value	β	SEM	P value	β	SEM	P value
Age (years)	0.015	0.203	.941	−0.026	0.117	.824	0.070	0.191	.716	−0.200	0.122	.104
Sex (1=female, 2 = male)	2.669	3.990	.506	3.387	2.291	.144	−5.776	3.799	.132	−1.125	2.429	.644
SBP$_0$ (mmHg)	−0.223	0.121	.069	0.011	0.069	.874	−0.335	0.119	**.006**	0.133	0.076	.085
DBP$_0$ (mmHg)	0.122	0.198	.541	−0.162	0.113	.157	−0.051	0.205	.803	−0.485	0.131	**<.001**
FU-duration (weeks)	−0.251	0.160	.121	−0.099	0.092	.283	−0.031	0.013	**.016**	−0.018	0.008	**.030**
Na$^+$(mmol/L)	−0.273	0.799	.734	−0.704	0.459	.129	0.607	0.760	.427	−0.011	0.486	.982
K$^+$(mmol/L)	−12.162	11.925	.311	−5.051	6.846	.463	−16.925	12.363	.175	−3.339	7.905	.674
Na$^+$/K$^+$	−1.770	1.304	.179	−0.554	0.748	.461	−1.810	1.356	.185	−0.292	0.867	.737

(SBP$_0$: baseline systolic blood pressure; DBP$_0$: baseline diastolic blood pressure; FU: followup; Na$^+$: serum sodium concentration; K$^+$: serum potassium concentration).

spironolactone treatment in resistant hypertension with 24-hour ambulatory BP measurements, thereby eliminating a white-coat effect and at least in part also a placebo effect. In their study, SBP was reduced by 16 mmHg and DBP by 9 mmHg.

The longest followup in all mentioned studies was 15 months. Whether the effect persists over a longer period had not yet been reported. With all the limitations of a retrospective design, our study is the first to show that the BP lowering effect of add-on ARA treatment is profound and persistent even after years of treatment.

Earlier publications have focused on identifying clinical and biochemical predictors for the BP response to ARA treatment. Several studies have shown that neither plasma renin concentration or activity, nor aldosterone or the ARR are good predictors for this response [5, 9, 17, 22, 26], although this may only hold for patients on multidrug regimens [25] related to the interfering effects of many antihypertensives on renin and aldosterone levels [28]. Low serum potassium levels have consistently been shown to be associated with a better response [19, 21, 22, 25]. Other factors potentially related to a better BP response are higher waist circumference, lower aortic pulse wave velocity [22], the absence of DM [23], and a lower baseline HDL cholesterol [21]. In a univariate linear regression analysis, we could not confirm the predictive value of the serum potassium level for BP response. However, the sodium/potassium ratio (as a potential indicator for aldosterone excess) showed a significant correlation with SBP decrease at short followup at univariate analysis. In a multivariate analysis, only higher baseline BP and longer followup duration independently predicted BP response in the long run. Potential explanations for this have been discussed earlier in this section. In our univariate analysis, also haemoglobin, total cholesterol, and LDL for short-term followup and left ventricular hypertrophy and urinary albumin-to-creatinine ratio for long-term followup were identified as potential predictors. Unfortunately, because of too many missing values, these variables were not included in the multivariate analysis to maintain enough statistical power. However, these parameters are important candidates for further studies on determinants of BP lowering by ARAs. Plasma renin and aldosterone levels were not associated with BP response, as has been reported earlier. In our univariate analysis, the ARR was weakly, yet significantly, associated with change in DBP. Considering the median ARR of 9.5 pmol/mU in this patient group, a beta coefficient of 0.027 is probably of little relevance. Also the number of patients with ARR available at baseline was too small to include in the multivariate analysis.

The mechanism that underlies the BP-lowering effect of add-on ARA treatment is most likely induction of natriuresis and diuresis although extrarenal effects of aldosterone blockade may also be of importance, such as a reduction in sympathetic tone and modulation of vascular tone, and in the long run a reduction in vascular stiffness may also play a role (reviewed in [29]). The clinical relevance of these extrarenal mechanisms is unknown. A cross-over trial in patients with low-renin hypertension, an elevated ARR, and a previous favourable BP response to spironolactone

showed that even in this selected population, high-dose thiazide diuretic treatment was as effective as 100 mg of spironolactone, strongly suggesting that natriuresis is the most important mode of action [30]. This also underscores the relevance of dietary salt reduction in resistant hypertension as has been shown elsewhere [31]. In general, ARA treatment was well tolerated and side effects were rare. In 13 patients, side effects were reported (10.6%), most of them presenting with gynaecomastia or hyperkalemia. The occurrence of sex hormone-related side effects with spironolactone is dose dependent [32], and in many cases, these side effects can be prevented by using lower doses. When this is also not tolerated, treatment with eplerenone, being a more specific ARA with virtually no sex hormone-related actions in therapeutic doses, can be considered.

Risk factors for hyperkalemia are advanced age, diabetes mellitus, higher baseline potassium levels [33], and advanced stage 3 nephropathy [34]. The presence of renal function impairment and concomitant use of other diuretics predisposes to the development of renal failure [33]. Frequent monitoring of serum potassium and renal function is warranted in these patients.

Our study has several limitations, the most significant one being its retrospective nature. Because of this, there is an important heterogeneity in patients, treatment, and followup. To properly assess the long-term efficacy of ARA treatment taking into account the large differences in followup, stratification to followup duration was made. This makes the analysis prone to bias with overrepresentation of patients with a good response in the group of prolonged followup. It would have been more ideal to collect patient data at several time points during the followup period, but clinical information in the written files was not always present. Furthermore, biochemical parameters, especially haemoglobin and cholesterol (including HDL and LDL) at baseline, were only available for a limited number of patients, thereby limiting their usefulness for multivariate analysis because of lack of statistical power. Also renin and aldosterone levels were only available for a subset of patients.

This study shows that long-term treatment including an ARA leads to a persistent BP reduction. Whether this is attributable to the ARA itself or to better treatment in general is an important point of consideration. As shown, BP reduction was not accompanied by an increase in total amount of antihypertensive drugs, thereby making a specific effect of the intervention with an ARA more likely. Last, the distinction between patients with EH and PA was solely based on a clinical diagnosis by the patient's physician. A formal confirmation test for PA was only performed in a proportion of the patients labelled with the diagnosis PA. The recent guidelines for the diagnosis and treatment of PA made by the Endocrine Society advise to perform a confirmation test in patients with an ARR of approximately 91 pmol/mU [35]. From the ranges in ARR reported in Table 1, it could be deduced that some of the EH patients actually had PA and that some of the PA patients had been misdiagnosed. However, considering the substantial differences in renin, aldosterone, and potassium levels between our EH and PA patients, we think that the diagnosis was correct in most of the patients.

With all limitations, our results are in favour of a profound and long-term BP lowering effect of ARA treatment in difficult-to-treat hypertension. To assess the magnitude of the response more accurately, a randomized, placebo-controlled trial is needed. With all evidence available, ARAs at moderate dosages are a welcome treatment option in patients with difficult-to-treat or resistant hypertension.

Abbreviations

ACR: Urinary albumin-to-creatinine ratio
ANOVA: Analysis of variance
ARA: Aldosterone-receptor antagonist
ARR: Aldosterone-to-renin ratio
BP: Blood pressure
DBP: Diastolic blood pressure
DDD: Defined daily dose
DM: Diabetes mellitus
ECG: Electrocardiogram
EH: Essential hypertension
HDL: High-density lipoprotein
LDL: Low-density lipoprotein
LVH: Left ventricular hypertrophy
PA: Primary aldosteronism
PAC: Plasma aldosterone concentration
PRC: Plasma renin concentration
RAAS: Renin-angiotensin-aldosterone system
SBP: Systolic blood pressure.

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