Quality of Life in Primary Aldosteronism: A Comparative Effectiveness Study of Adrenalectomy and Medical Treatment

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Context: In primary aldosteronism (PA), two subtypes are distinguished: aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia (BAH). In general, these are treated by adrenalectomy (ADX) and mineralocorticoid receptor antagonists (MRA), respectively.

Objective: To compare the effects of surgical treatment and medical treatment on quality of life (QoL).

Design: *Post hoc* comparative effectiveness study within the Subtyping Primary Aldosteronism: A Randomized Trial Comparing Adrenal Vein Sampling and Computed Tomography Scan (SPARTACUS) trial.

Setting: Twelve Dutch hospitals and one Polish hospital.

Participants: Patients with PA (n = 184).

Interventions: ADX or MRAs.

Main Outcome Measures: At baseline and 6-month and 1-year follow-up, we assessed QoL by two validated questionnaires: RAND 36-Item Health Survey 1.0 (RAND SF-36) and European Quality of Life–5 Dimensions (EQ-5D).

Results: At baseline, seven of eight RAND SF-36 subscales and both summary scores, as well as three of five EQ-5D dimensions and the visual analog scale, were lower in patients with PA compared with the general population, especially in women. The beneficial effects of ADX were larger than for MRAs for seven RAND SF-36 subscales, both summary scores, and health change. For the EQ-5D, we detected a difference in favor of ADX in two dimensions and the visual analog scale. Most differences in QoL between both treatments exceeded the minimally clinically important difference. After 1 year, almost all QoL measures had normalized for adrenalectomized

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Abbreviations: ADX, adrenalectomy; APA, aldosterone-producing adenoma; BAH, bilateral adrenal hyperplasia; BMI, body mass index; CI, confidence interval; CT, computed tomography; EQ-5D, European Quality of Life–5 Dimensions; EQ-VAS, European Quality of Life–5 Dimensions visual analog scale; IQR, interquartile range; MCS, mental component summary; MRA, mineralocorticoid receptor antagonist; PA, primary aldosteronism; PCS, physical component summary; QoL, quality of life; RAND SF-36, RAND 36-Item Health Survey 1.0; SD, standard deviation; SPARTUCUS, Subtyping Primary Aldosteronism: A Randomized Trial Comparing Adrenal Vein Sampling and Computed Tomography Scan.

patients. For patients on medical treatment, most QoL measures had improved but not all to the level of the general population.

Conclusion: Both treatments improve QoL in PA, underscoring the importance of identifying these patients. QoL improved more after ADX for suspected APA than after initiation of medical treatment for suspected BAH. (***J Clin Endocrinol Metab*** **103: 16–24, 2018)**

Primary aldosteronism (PA) is a common cause of hypertension, accounting for 5% to 15% of cases (1–3). Two main subtypes are distinguished: aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia (BAH) (1). The generally accepted treatment is adrenalectomy (ADX) for the former and mineralocorticoid receptor antagonists (MRAs) for the latter. Most patients with an APA have a marked clinical benefit from ADX (4–7). However, the comparable effects of MRAs in patients with BAH (4, 8) suggest that this treatment may also be used in patients with an APA.

PA confers a greater risk for cardiovascular events (9) and renal dysfunction (3) than primary hypertension (10). A difference between ADX and MRAs in reducing these risks—for example, in improvement of left ventricular hypertrophy (4, 11) or endothelial function (12)—has never been well established (10). Absence of such a difference would make putting effort in selecting patients for ADX pointless.

A somewhat neglected aspect in patients with PA is the health-related quality of life, or quality of life (QoL) for short. It is commonly defined by the functional effect of an illness or its treatment upon a patient, as perceived by the patient (13). PA is associated with reduced QoL (14) and also psychological symptoms such as anxiety, depression, and stress (15–17).

Given the probable similar effects of ADX and MRAs on blood pressure and the cardiovascular system, QoL could become an important additional determinant of management decisions. Therefore, in this prospective study, we compared the QoL of patients with PA after ADX or initiation of MRAs.

Methods

An expanded methods section is available in the Supplement.

Study design and patients

The data for this comparative effectiveness study are derived from the randomized diagnostic multicenter Subtyping Primary Aldosteronism: A Randomized Trial Comparing Adrenal Vein Sampling and Computed Tomography Scan (SPARTACUS) trial (registered at clinicaltrials.gov as NCT01096654) performed between July 2010 and August 2015 in 12 Dutch teaching and academic hospitals and 1 Polish hospital (18) in which QoL was a predefined secondary end point. This trial compared adrenal computed tomography (CT) scanning and adrenal vein sampling for subtyping of PA. Approval for this study was obtained from institutional review boards of all participating centers, and informed consent was obtained from all participants. Briefly, patients randomized to CT or adrenal vein sampling underwent ADX if, respectively, unilateral adrenal enlargement or unilateral aldosterone hypersecretion with contralateral aldosterone suppression was demonstrated. All other patients received MRA-based treatment. All patients were further treated with conventional antihypertensive drugs according to a treatment algorithm targeting a blood pressure of <135/85 mm Hg using a semiautomatic device or <140/90 mm Hg using office blood pressure (19). Because pretreatment QoL was comparable between the ADX and MRA groups from both study arms, we pooled all patients treated by ADX and MRA from both diagnostic arms. We expressed intensity of antihypertensive treatment as daily defined doses (http://www.whocc.no/ddd/).

Assessment of QoL

QoL was assessed at baseline, 6 months, and 12 months by two validated questionnaires: RAND 36-Item Health Survey 1.0 (RAND SF-36) (20, 21) and the European Quality of Life–5 Dimensions (EQ-5D) instrument (22).

RAND SF-36

The RAND SF-36 comprises 35 items evaluating eight domains: physical functioning, role limitations due to physical problems (role physical), bodily pain, vitality, general health perception, social functioning, role limitations due to emotional problems (role emotional), and mental health. We used norm-based scoring, resulting in age- and sex-adjusted scores in the individual patient (see expanded methods section in the Supplement). The physical component summary (PCS) and the mental component summary (MCS) are summations of the eight weighted subscale (domain) scores. In these summary and subscale scores, 50 represents the age and sex-adjusted mean and 10 the standard deviation (SD) of the general population (higher score indicating higher QoL). Group mean scores below 47 signify decreased QoL (23). The 36th question about health change (range, 0 to 100), referring to general health compared with 1 year ago, is reported separately (20).

EQ-5D

The EQ-5D questionnaire comprises five items relating to current problems in the dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses in each dimension are divided into "no problems," "some or moderate problems," or "extreme problems." The five dimensions are converted to a summary index (EQ-5D index score) obtained by summation of the weighted item scores (24, 25). The EQ-5D also contains a visual analog scale (EQ-VAS),

which allows respondents to place their health status on a range from 0 to 100 (worst to best imaginable health status, respectively) (26).

Statistical analysis

Because we had not prespecified a comparative analysis between surgically and medically treated patients in the SPARTACUS protocol, this is a *post hoc* analysis. We compared baseline characteristics between both treatment groups and QoL between sexes with the use of the χ^2 test for categorical variables and unpaired *t* test for continuous variables in case of normal distribution and the Mann-Whitney *U* test in case of skewed distributions.

For comparison with the general population, we performed one-sample *t* tests for RAND SF-36 subscales, PCS, MCS, and EQ-VAS. We compared the EQ-5D dimensions with the general Dutch (25) and Polish (27) population by calculating a Clopper-Pearson (exact) 95% confidence interval (CI) of the proportion of patients reporting no problems. For comparison of the EQ-5D index score, we used the Wilcoxon signed-rank test.

For the analysis of treatment effect on the RAND SF-36 subscales, summary scores, RAND SF-36 health change, the EQ-5D index, and EQ-VAS scores after 6 and 12 months and the change over time of these scores, we used linear mixed models with these QoL measures as dependent variables. We included time, treatment, sex, and country of residence as fixed factors. In addition, we added matching baseline QoL values, body mass index (BMI), intensity of MRA therapy at baseline, plasma potassium level, plasma aldosterone levels during salt loading test (before and after), and age as covariates, as well as the interaction between time and treatment and between QoL baseline values and treatment, to the model. We discarded factors, covariates, and interactions that did not show a statistically significant ($P \geq 0.1$) result on the outcome of the model, except for treatment, time, and baseline scores. Residual plots from the mixed models were examined to assess the model assumptions.

We analyzed the EQ-5D dimension scores at 6 months and final evaluation by a generalized estimating equation analysis. We only included matching baseline score, time, and treatment as factors because the number of patients reporting problems was small. We enrolled cases in both models on the condition that baseline and at least either the 6-month follow-up or the final evaluation QoL measure was completed.

P values of <0.05 were considered to indicate statistical significance unless stated otherwise. All analyses were performed with the use of SPSS statistics 22.0 for Windows (SPSS, Inc., Chicago, IL).

Results

Follow-up was complete for 184 patients. Response rates of these patients for the RAND SF-36 questionnaires at baseline, 6-month follow-up, and 1-year follow-up were 94%, 93%, and 95%, respectively. For the EQ-5D, these were 94%, 90%, and 96%, respectively.

Baseline characteristics

Both the ADX and the MRA group comprised 92 patients. At baseline, sex, BMI, MRA therapy, and aldosterone levels before and after the salt loading test were different between groups: the ADX group contained more females, used more MRAs, and had lower BMI, whereas plasma aldosterone levels were higher than in the MRA group (Table 1). The baseline QoL scores of all of the RAND SF-36 and all but mobility of the EQ-5D items were not different between ADX and MRA (Table 1).

Baseline QoL of the ADX group

Patients from the ADX group scored worse on six of eight RAND SF-36 subscales and both of its summary scores (Table 2) than the general population. Concerning the EQ-5D dimensions, at baseline, the percentage of patients reporting "no problems" on usual activities, pain/discomfort, and anxiety/depression was lower than in the general population (Table 1). When comparing EQ-5D index scores with the population score, patients with ADX also scored worse at baseline: median 0.86 [interquartile range (IQR), 0.77 to 1.00] vs 0.99 (IQR, 0.84 to 1.00) in the general population ($P < 0.001$). The mean EQ-VAS showed reduced rates as well: 68.9 (SD, 15.2) compared with 80.3 in the general population, $P < 0.001$.

Baseline QoL of the MRA group

Concerning patients on MRAs, scores on five of eight RAND SF-36 subscales and the PCS and MCS were lower compared with the general population (Table 2). The percentage of patients reporting "no problems" on the EQ-5D dimensions of usual activities, pain/discomfort, and anxiety/depression was lower than in the general population (Table 1). The median of the EQ-5D index score in this group was also lower: 0.87 (IQR, 0.78 to 1.00), compared with 0.98 (IQR, 0.84 to 1.00) in the general population ($P < 0.001$). The same applied to the mean EQ-VAS: 72.4 (SD, 16.1) in the MRA group compared with 78.2 in the general population, $P < 0.001$.

Comparisons between QoL after surgical and medical treatment during follow-up

In the mixed model analysis to compare QoL after surgical and medical treatment, we found baseline QoL score to be a statistically significant predictor in all models describing QoL and change in QoL. When baseline score was low, QoL score after 6 and 12 months was lower, but the increase was larger than when baseline score was high.

RAND SF-36

Modeled data (Fig. 1; Supplemental Table 1) showed a larger beneficial effect of ADX than MRAs for seven of eight RAND SF-36 subscales. Both summary scores (and health change) also indicated a benefit of ADX over MRA: at final evaluation, the estimated PCS was 53.0 for ADX and 50.0 for MRA, with a mean difference of 3.0 (95% CI, 0.9 to 5.1); for MCS, this was 50.4 for ADX

Table 1. Baseline Characteristics According to Treatment Group

Characteristics	ADX (n = 92)	MRA (n = 92)	*P* Value
Male, n (%)	66 (71.7)	78 (84.8)	0.03
Age, y	51.8 (10.1)	54.4 (8.8)	0.07
Polish, n (%)	12 (13.0)	22 (23.9)	0.06
BMI, kg/m^2, median (IQR)	27.5 (25.2–30.5)	29.4 (26.7–32.6)	0.02
AVS/CT, n (%)	46 (50)	46 (50)	1.00
Systolic ambulatory blood pressure 24 h, mm Hg	147 (17)	145 (19)	0.22
Diastolic ambulatory blood pressure 24 h, mm Hg	91 (11)	89 (11)	0.06
DDD antihypertensive medication, median (IQR)	3 (2–4)	3 (2–4)	0.88
DDD MRAs, median (IQR)	0 (0–0.6)	0 (0–0)	0.04
Serum potassium, mEq/L	3.5 (0.5)	3.6 (0.4)	0.05
Plasma aldosterone, ng/dL, median (IQR)	20.8 (13.9–34.3)	17.0 (13.0–25.3)	0.03
Post-SLT plasma aldosterone, ng/dL, median (IQR) (n = 80/n = 80)	19.1 (12.2–32.5)	12.6 (10.1–17.3)	<0.001
RAND SF-36 subscales (n = 88/n = 85)			
Subscales			
Physical functioning	48.2 (10.5)	47.9 (12.3)	0.88
Role physical	43.9 (12.1)[a]	46.8 (12.3)[a]	0.13
Bodily pain	51.5 (9.7)	49.9 (9.8)	0.29
General health	44.0 (10.0)[a]	44.1 (10.7)[a]	0.96
Vitality	41.4 (10.9)[a]	42.9 (10.8)[a]	0.35
Social functioning	43.9 (11.8)[a]	46.0 (11.4)[a]	0.26
Role emotional	46.0 (12.7)[a]	48.3 (11.5)	0.21
Mental health	46.2 (11.1)[a]	47.0 (9.2)[a]	0.61
PCS	45.7 (10.8)[a]	46.0 (11.7)[a]	0.84
MCS	43.0 (11.9)[a]	45.4 (10.3)[a]	0.15
Health change, median (IQR)	50 (25–50)	50 (25–50)	0.61
EQ-5D (n = 88/n = 84)			
Dimensions (% reporting no problems)			
Mobility	89.8	76.5	0.02
Self-care	97.7	96.5	0.62
Usual activities	71.6[a]	76.2[a]	0.49
Pain/discomfort	51.1[a]	48.2[a]	0.70
Anxiety/depression	69.3[a]	69.4[a]	0.99
EQ-5D index, median (IQR)	0.856 (0.774–1.00)[a]	0.868 (0.775–1.00)[a]	0.90
EQ-VAS	68.9 (15.2)[a]	72.4 (16.1)[a]	0.08

Data presented as mean (SD) unless stated otherwise. For the RAND SF-36 subscales and both summary scores, raw scores were converted into *z* scores using mean and SD in a healthy Dutch population and then transformed to *t* scores (resulting in a mean of 50 and an SD of 10 in the healthy Dutch population). Aldosterone ng/dL to pmol/L conversion factor 27.74. Population scores for EQ-5D dimensions are presented in Table 3. For the EQ-5D index score, maximum = 1. For the EQ-VAS, range is 0 to 100. AVS, adrenal vein sampling; DDD, defined daily dose; SLT, salt loading test.

[a]Lower percentage compared with general population ($P < 0.05$).

and 46.4 for MRA, with a mean difference of 4.1 (95% CI, 1.5 to 6.7). For social functioning, mental health, and MCS, this difference was only present at final evaluation. For physical functioning and role limitations due to physical problems, the significance of the difference depended on baseline scores—that is, the lower the baseline score, the more distinct the difference between treatments (Supplemental Table 1).

EQ-5D

Odds ratios for reporting problems on two dimensions of the EQ-5D, usual activities and pain/discomfort, were in favor of ADX during follow-up (Fig. 2; Table 3). The difference in EQ-5D index score between treatment groups did not reach statistical significance. Modeled data showed higher EQ-VAS scores in patients treated by ADX (Supplemental Table 1).

Clinical parameters in relation to QoL

At final evaluation, no differences were found in blood pressure and potassium between treatment groups (Supplemental Table 2). Intensity of (non-MRA) antihypertensive medication was stronger in the MRA group than in the ADX group (Supplemental Table 2). Intensity of antihypertensive medication (including MRAs) at final evaluation was an important determinant of the difference in QoL between treatment groups (Supplemental Table 3). Intensity of MRA-based treatment was not added to these models as this resulted in a statistically significant contribution for only one domain.

Antiandrogenic adverse events of MRAs (gynecomastia, mastopathy, menstrual disturbances, erectile dysfunction, and decreased libido) were present in 1 patient in the ADX group (1.1%) and 52 patients in the MRA group (56.5%). Of these 52 patients, 31 were

Table 2. Mean Differences of RAND SF-36 Normalized *t* Scores Between Patients and General Dutch Population at Baseline and Final Evaluation

	Mean Difference With Reference Population[a] (95% CI)	
Characteristic	**ADX**	**MRA**
Baseline		
Subscales		
Physical functioning	−1.8 (−4.0 to 0.4)	−2.1 (−4.7 to 0.6)
Role physical	−6.1 (−8.6 to −3.5)	−3.2 (−5.9 to −0.5)
Bodily pain	1.5 (−0.6 to 3.6)	−0.1 (−2.2 to 2.0)
General health	−6.0 (−8.1 to −3.9)	−5.9 (−8.2 to −3.6)
Vitality	−8.6 (−11.0 to −6.3)	−7.1 (−9.4 to −4.8)
Social functioning	−6.1 (−8.5 to −3.6)	−4.0 (−6.5 to −1.6)
Role emotional	−4.0 (−6.7 to −1.3)	−1.7 (−4.2 to 0.8)
Mental health	−3.8 (−6.2 to −1.5)	−3.0 (−5.0 to −1.1)
PCS	−4.3 (−6.6 to −2.0)	−4.0 (−6.5 to −1.4)
MCS	−7.0 (−9.5 to −4.5)	−4.6 (−6.8 to −2.3)
Follow-up evaluation (1 y)	n = 84	n = 91
Subscales		
Physical functioning	2.5 (0.7 to 4.3)	−0.4 (−2.8 to 2.0)
Role physical	1.1 (−1.0 to 3.2)	−0.2 (−2.6 to 2.2)
Bodily pain	4.0 (2.1 to 5.9)	1.3 (−0.9 to 3.4)
General health	0.8 (−1.4 to 3.0)	−4.4 (−6.6 to −2.2)
Vitality	−0.8 (−3.0 to 1.3)	−6.1 (−8.1 to −4.1)
Social functioning	0.2 (−2.0 to 2.4)	−3.0 (−5.6 to −0.5)
Role emotional	0.7 (−1.6 to 2.9)	−0.7 (−3.0 to 1.7)
Mental health	0.8 (−1.4 to 3.1)	−3.7 (−5.8 to −1.5)
PCS	2.4 (0.3 to 4.5)	−1.5 (−4.0 to 0.9)
MCS	−0.2 (−2.4 to 2.1)	−4.0 (−6.3 to −1.8)

[a]Compared with general Dutch population in which 50 represents the mean and 10 the SD.

switched to eplerenone (33.7%). An additional 12 patients were switched to eplerenone for other reasons (13.0%).

Change in QoL

ADX group

Supplemental Table 1 shows that all measures of the RAND SF-36 and EQ-5D increased from baseline to final evaluation at 12 months. From 6- to 12-month follow-up, we observed a further increment only for the RAND SF-36 subscale of social functioning.

MRA group

In this group, five of eight RAND SF-36 subscales, both summary scores, and the EQ-5D index score increased between baseline and 1-year follow-up, albeit to a lesser extent than after ADX. From 6 months until the final evaluation at 12 months, we found no further increase in any of the QoL measures (Supplemental Table 1).

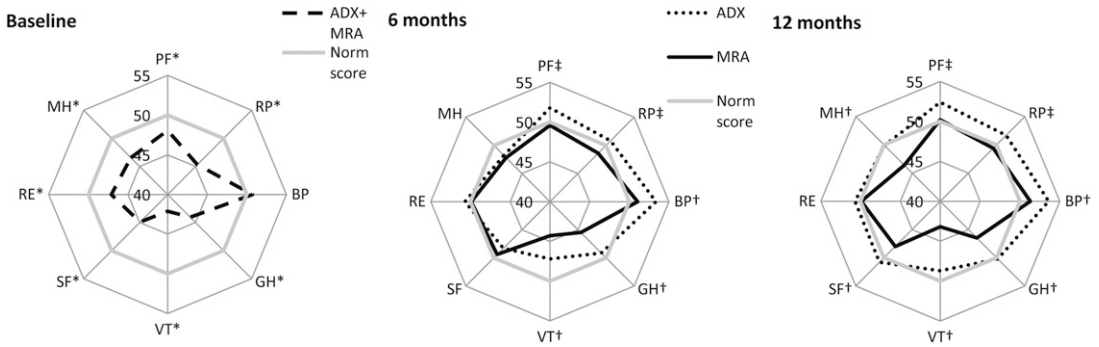

Figure 1. Mean baseline scores and estimated means after 6 and 12 months of RAND SF-36 subscale scores for both treatment groups according to mixed models. *$P < 0.05$ for difference between patients with PA (ADX and MRA combined) and norm score. †$P < 0.05$ for difference between ADX and MRA. ‡Difference depending on baseline score. Estimates at 6 and 12 months are based on mixed models in which equal baseline values (mean scores of all patients) were assumed. No differences between baseline RAND SF-36 scores of ADX and MRA were present. Norm score for subscales was based on Dutch reference population. BP, bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role limitations due to emotional problems; RP, role limitations due to physical problems; SF, social functioning; VT, vitality.

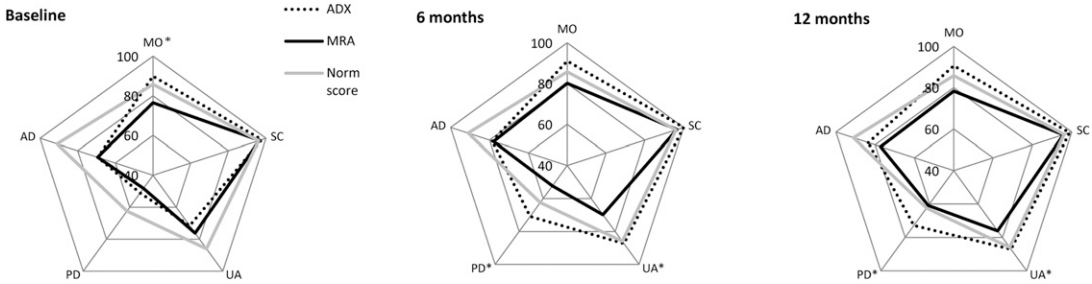

Figure 2. Percentages of patients reporting no problems on EQ-5D dimensions at baseline, 6 months, and 12 months. *$P < 0.05$ for difference between ADX and MRA. Significance is based on generalized estimating equation analyses (Table 3). Norm scores based on Dutch and Polish reference population. AD, anxiety/depression; MO, mobility; PD, pain/discomfort; SC, self-care; UA, usual activities.

QoL at final evaluation compared with the general population

ADX group

For the patients treated by ADX, we found no differences in six RAND SF-36 subscales and MCS at final evaluation compared with the general population. For two subscales and PCS, the scores were even higher (Table 2). Four dimensions of the EQ-5D, the EQ-5D index [median, 1.00 (IQR, 0.84 to 1.00) vs 0.99, P = 0.12], and EQ-VAS scores (mean 78.5, SD 11.8, vs 80.3, P = 0.17) were equal to those of the general population. Patients still scored lower only on the EQ-5D dimension of anxiety/depression (Table 4).

MRA group

For the MRA group, RAND SF-36 scores were still lower after 1 year for social functioning, mental health, vitality, and general health and for MCS compared with those of the general population. Scores on the other subscales and the PCS were not different (Table 2). The EQ-5D dimensions of anxiety/depression and usual activities showed a lower percentage of patients reporting "no problems" (Table 3).

Table 3. Odds Ratios for Reporting Problems on EQ-5D Dimensions During Follow-up According to Generalized Estimating Equation Analyses

Dimension	ADX/MRA, Adjusted Odds Ratio (95% CI)
Mobility	0.52 (0.23–1.20)
Self-care	0.14 (0.01–2.50)
Usual activities	0.35 (0.17–0.75)
Pain/discomfort	0.52 (0.30–0.91)
Anxiety/depression	0.79 (0.39–1.60)

Odds ratios are based on a general estimating equation model in which treatment, time, and baseline scores were included as factors. For example, an odds ratio of 0.52 for mobility means that the odds for reporting problems for mobility after ADX is 0.52 times the odds in case of MRA (in this case statistically nonsignificant). This was adjusted for the baseline score. Time was not a statistically significant factor in any dimension (i.e., odds ratios apply to the 6- and 12-month evaluation).

Also, scores of the EQ-5D index [median, 0.92 (IQR, 0.81 to 1.00) vs 0.98 (IQR, 0.84 to 1), $P < 0.001$] and the EQ-VAS (mean 72.1, SD 17.8 vs 78.2, P = 0.002) were lower than those of the general population.

Sex differences

At baseline, female patients had a lower QoL (RAND SF-36: PCS, physical functioning, social functioning, general health, and role physical; EQ-5D: two dimensions, VAS and index score; Supplemental Table 4). During follow-up, sex was not a predictor of (change in) QoL in our mixed models, except for the PCS, for which the female patients scored higher (ADX: men 51.3, women 54.3; MRA: men 48.3; women 51.1; all at a baseline score of 46.0, independent of time point, P = 0.035).

RAND SF-36 analysis of Dutch patients only

The aforementioned results pertain to the entire cohort, comprising 150 Dutch and 34 Polish patients, using Dutch RAND SF-36 normative scores. Because Polish normative scores are not available, we also analyzed the Dutch patients separately to circumvent bias. This analysis yielded baseline and follow-up results similar to those of the entire cohort for the comparison of the RAND SF-36 measures with the general population (Supplemental Table 5).

Discussion

The main findings of our prospective study are that treatment of PA results in substantial improvement of the QoL of patients with PA and that this improvement 1 year after ADX for APA not only exceeds that of the patients treated by MRAs for BAH but also restores the QoL to the level of the general population.

To our knowledge, this is the first prospective evaluation of QoL comparing the treatment modalities ADX and MRA with a follow-up of 1 year. The previously described lower QoL in patients with PA compared with the general population (14, 28, 29) is confirmed by our study.

Table 4. Percentage of Patients Reporting No Problems on EQ-5D Dimensions at Final Evaluation for Both Treatment Groups and the General Population

	Reporting No Problems at Follow-up Evaluation (1 Year), % (95% CI)		General Population,[a] %	
EQ-5D Dimension	ADX	MRA	ADX	MRA
Mobility	90.6 (82.3–95.8)	78.3 (68.4–86.2)	87.4	84.2
Self -care	98.8 (93.6–1.0)	95.7 (89.2–98.8)	96.8	95.3
Usual activities	87.1 (78.0–93.4)	76.1[b] (66.1–84.4)	87.0	84.9
Pain/discomfort	72.9 (62.2–82.0)	60.9 (50.1–70.9)	64.0	60.9
Anxiety/depression	83.5[b] (73.9–90.7)	77.2[b] (67.2–85.3)	93.1	88.9

[a]Calculated from data of Dutch and Polish reference population based on composition (age, sex, and country of residence) of both groups.

[b]Lower percentage compared with general population ($P < 0.05$).

An explanation for the impaired QoL is the direct effect of aldosterone on neurons in the central nervous system receiving and integrating information on fluid, electrolyte, and cardiovascular status, leading to alterations in central sympathetic nervous system output and thereby disturbed psychological function (30). Administration of aldosterone in rats caused anxiety-like behavior (31), whereas administration of an MRA was observed to result in anxiolytic effects (32). Administration of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers has been reported to have anxiolytic effects and improve mood in humans (33, 34). To which extent aforementioned effects are related to the mineralocorticoid receptors in the brain is unknown.

We showed that before treatment, female patients with PA had a lower QoL compared with men. Although Apostolopoulou *et al.* (17) observed more anxiety in female patients with PA than in male patients, the same group could not detect any differences in QoL between both sexes before treatment (29). Females harbor KCNJ5 somatic mutations more often than males, and it may be surmised that phenotype depends on such a mutation. However, the presence of a KCNJ5 mutation has not been associated with a more severe phenotype of PA (35). Our results also show that women benefit more than men from both treatments regarding this PCS. This is in line with findings on hypertension, another aspect of health, that show that female sex is a predictor for cure of hypertension after ADX (36, 37). In a cross-sectional study, female patients with PA treated by ADX scored better on the physical component of QoL compared with medically treated female patients (29). In a prospective trial in patients treated with MRAs, an improvement was seen in QoL 6 months after initiating medical treatment with spironolactone and/or amiloride (28). In contrast to our findings, in only one domain of QoL, the medically treated patients scored worse compared with patients who had undergone ADX (14), and no differences were found with the general population at follow-up.

Incomplete blockade of the mineralocorticoid receptors might explain the observed differences in QoL between the ADX group and the MRA group. This difference can be further explained by the side effects of the used antihypertensive medication, as illustrated by the reduced difference in QoL between both treatments after adjusting for intensity of antihypertensive therapy (Supplemental Table 3). Especially MRAs are associated with many side effects (38). Blood pressure itself, being identical in both groups, is unlikely to have influenced QoL at final evaluation.

The minimally clinically important difference is 0.09 to 0.28 SD for the RAND SF-36 subscales and summary scores (39), 0.0747 for the EQ-5D index (40), and 7 for the EQ-VAS (41), but it has to be noted that these cutoff values have not been established in patients with PA. With the exception of physical functioning, role limitations, bodily pain, and the EQ-VAS, most QoL differences we observed between ADX and MRA are larger and thus seem to be of clinical relevance (Supplemental Table 1).

A possible explanation for not finding a statistically significant difference between the ADX and the MRA group in the EQ-5D index score, as well as three of five EQ-5D dimensions, is the ceiling effect of the EQ-5D. This effect is considered present if >15% of respondents report the highest possible score. In our population, this was 41% at baseline. Such patients cannot show improvement (42).

A limitation of our study is that all patients with APA were treated with ADX. However, it is impossible to obtain ethical approval for a randomized trial because ADX is generally accepted to be the preferred treatment of APA (43). The biology of APA and BAH may differ, and these differences may lead to a difference in QoL. However, we observed no solid differences in QoL at baseline between patients with APA and BAH. Furthermore, we adjusted for baseline scores and for confounders. Because surgery is no option for patients with

BAH, our findings are especially relevant to patients with APA. It is likely that our findings in BAH would also apply to medically treated patients with APA. For the RAND SF-36, we used Dutch reference scores for the Polish subjects because Polish normative data are lacking. We overcame this by adjustment for country of residence. Moreover, a separate analysis of the Dutch patients yielded similar results.

The differences between QoL in both treatment groups may be underestimated if patients with BAH are present in the ADX group, which is suggested by the 50% discordance between CT and adrenal vein sampling results in the SPARTACUS study.

In conclusion, QoL in PA is better 1 year after ADX than 1 year after initiation of MRAs. However, both treatment modalities improve QoL, which is relevantly impaired before treatment compared with the general population. Our findings underscore the need to identify patients with PA and support the practice to select patients who are amenable for ADX.

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