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A disease-specific Quality of Life questionnaire for primary aldosteronism

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Abstract

Objective: To develop a primary aldosteronism (PA) disease-specific Health-Related Quality of Life (HRQoL) questionnaire.

Methods: We included newly diagnosed patients with PA (n = 26), and patients with PA after adrenalectomy (n = 25) or treated with mineralocorticoid receptor antagonists (n = 25). According to the guidelines for developing HRQoL questionnaires from the European Organization for Research and Treatment of Cancer (EORTC): Phase I: systematic literature review followed by focus group meetings with patients (n = 13) resulting in a list of 94 HRQoL issues. Relevance of issues was rated by 18 other patients and by health care professionals (n = 15), resulting in 30 remaining issues. Phase II: selected issues were converted into questions. Phase III: the provisional questionnaire was pre-tested by a third group of patients (n = 45) who also completed the EORTC core Quality of Life questionnaire (QLQ-C30). Psychometric testing resulted in a final selection of questions with their scale structure.

Results: After the collection and selection of HRQoL issues a provisional questionnaire consisting of 30 items was formed. Of these items, 26 could be assigned to one of the four scales ‘physical and mental fatigue’, ‘anxiety and stress’, ‘fluid balance’ and ‘other complaints’ cumulatively accounting for 68% of variation in all items. All scales had good reliability and validity. There was a significant correlation of all four scales with the QLQ-C30 in most cases.

Conclusions: We developed the first PA-specific HRQoL questionnaire (PA-QoL) using standard, methodologically proven guidelines. After completion of the final validation (phase IV, international field testing), the questionnaire can be implemented into clinical practice.

Key Words

- hyperaldosteronism
- quality of life
- patient health questionnaire
- development

Introduction

Primary aldosteronism (PA) is a common cause of hypertension, accounting for 5–15% of hypertensive patients (1, 2, 3). PA is categorized in an aldosterone-producing adenoma (APA) or bilateral adrenal hyperplasia (BAH). When unilateral aldosterone hypersecretion is suspected (APA), patients generally undergo adrenalectomy (ADX).

Patients with BAH receive a mineralocorticoid receptor antagonist (MRA).

Over the last decade, there has been increasing interest in the patient perspective with the assessment of HRQoL, commonly defined by the functional effect of an illness and/or its treatment upon a patient, as perceived by the patient (4).
HRQoL studies in patients with PA demonstrated a reduced HRQoL compared to reference values (5, 6) and improvement in HRQoL after ADX (5) and during MRA-based treatment (6). Furthermore, psychological symptoms impairing HRQoL in patients with PA have been reported: occurrence of anxiety disorders and stress is higher than in the general population (7) and in patients with essential hypertension (8). Also, depression, somatization, psychological distress and a lower level of well-being among patients with PA compared to healthy controls have been demonstrated (8). This can be explained by overstimulation of the abundantly present mineralocorticoid receptors in brain structures that are involved in fear and anxiety (9), as well as the multiple drugs needed to control blood pressure and hypokalemia (and thereby adverse reactions) to which patients affected by PA are frequently exposed. Additionally, uncontrolled hypertension, especially when it cannot be explained by their physician and diagnostic delay can increase anxiety and stress.

For the assessment of HRQoL, it is usually recommended that a generic HRQoL questionnaire (assessing multiple domains of HRQoL) is combined with a disease-specific questionnaire (assessing HRQoL aspects relevant for a specific disease) (10). In previously conducted studies among patients with PA, HRQoL was assessed with a generic HRQoL questionnaire (for example the Short Form 36 General Health Survey (SF-36)). No disease-specific HRQoL questionnaire for patients with PA is currently available. Therefore, the aim of this study was to develop a PA-specific HRQoL questionnaire in order to be able to assess HRQoL and the effect of treatment in PA more accurately.

Methods

Patients and study design

The European Organization for Research and Treatment of Cancer (EORTC) is an independent, non-profit cancer research organization which coordinates and conducts international translational and clinical research to improve the standard of cancer treatment for patients. The EORTC Quality of Life Group is dedicated to the development of HRQoL questionnaires. We decided to develop our questionnaire according to their guidelines for developing HRQoL questionnaires as this is the most widely used and comprehensive guideline in the field (11, 12, 13). The questionnaire will not be part of the EORTC portfolio, since the latter is primarily designed for use in cancer clinical trials, but the guideline can be used in other research settings and clinical practice as well (11).

Below we describe the different phases of development of a PA-specific HRQoL questionnaire. All patients included in this study were treated at the Radboud University Medical Center, had been diagnosed with PA (aldosterone after intravenous salt loading test >280 pmol/L or 140–280 pmol/L and positive consensus of PA by an expert panel) (14) and had sufficient Dutch language skills (15). All patients have undergone subtyping by adrenal vein sampling (cut-off value for selectivity index ≥3 and for lateralization index ≥4). The Ethics Committee of the Radboud University Medical Center judged that no detailed review was warranted given the non-intrusive and non-experimental character of this study. We obtained written informed consent of all patients.

Phase I

This phase was aimed at compiling an exhaustive list of HRQoL issues relevant to patients with PA. For this purpose, three sources were used. First, we performed an extensive systematic literature search identifying all studies investigating HRQoL related constructs as well as physical and mental symptoms in patients with PA, published previously (16). The review resulted in a list of issues. Second, we organized two patient focus group meetings. We invited 43 patients, of whom 13 were willing to participate: one meeting for untreated patients (no previous ADX and no use of MRA; n=5) and one for patients treated by ADX (n=4) or with MRA (n=4). Treated patients were included in order to explore treatment-related HRQoL issues. Furthermore, these patients could also contribute to the issues they experienced before treatment, by remembering the changes caused by the treatment and comparing pre- and post-treatment period. In these qualitative interviews, we collected all possible relevant issues for HRQoL in a semi-structured way. Additionally we asked the patients to describe their experience and to provide information freely. Finally, they were asked to add missing issues on a form, in view of privacy matters. We recorded these meetings and wrote out these recordings verbatim. From these, two authors (MV and AN) made a list of issues and combined this with the items from the list from the literature review.

We presented this combined list to health care professionals (HCP n=15) with expertise in the field of PA from different countries and with different professional background and to another group of 18 patients (untreated n=6; ADX n=6; MRA n=6, invited n=39). These were all

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asked to indicate the relevance on a four-point Likert scale (1=not at all; 2=a little bit; 3=moderately; 4=extremely) and to select a maximum of 15 most important issues. An issue was selected for inclusion in Phase II on the condition that the mean score for both patients and HCPs was >2 and/or that >30% of the patients stated an issue as important. We also asked them to indicate missing issues, serving as our third source for HRQoL issues.

**Phase II**

We converted the final list of HRQoL issues into Dutch questions (items) fitting the following response options ‘not at all’, ‘a little’, ‘quite a bit’ and ‘very much’. When available, we used phrases that had been used previously in EORTC HRQoL modules (17).

The Dutch questions were then translated into English by applying an iterative forward-backward procedure (18).

**Phase III**

We asked 45 patients not included in phase I (untreated \(n=15\); ADX \(n=15\); MRA \(n=15\), invited \(n=54\)) to fill out the provisional questionnaire together with the EORTC core cancer quality of life questionnaire (QLQ-C30) online in Castor EDC (Ciwit B.V. 2017) or, when preferred, on paper. The QLQ-C30 served as a generic HRQoL questionnaire for validation purposes and is a standard item in this phase according to the EORTC guideline (11). When specific HRQoL items are included in the provisional questionnaire, there should be an adequate correlation with the QLQ-C30. Most questions (1–26) referred to the patient’s experience during the last week, some (27–30) to the patient’s experience during the last 4 weeks. Additionally they underwent a debriefing in which they had to indicate whether they felt any questions to be confusing, intrusive, annoying or upsetting. Furthermore, we asked patients to indicate any missing questions. For every item we checked the following criteria for inclusion in the final questionnaire (response categories: 1=not at all; 2=a little; 3=quite a bit; 4=very much): 1. Mean score >1.5; 2. Prevalence ratio >30% (number of patients reporting score 2, 3 or 4); 3. Range >2 points; 4. Responses of scores in categories 1/2 and 3/4 >10%; 5. No significant concerns expressed by patients; 6. Response >95%. When >2 criteria were not met in the total group (\(n=45\)) nor in the untreated group (\(n=15\)), we did not include the item in the final questionnaire. Items with low correlation with the total of other items were excluded for the final factor analysis (initial communalities <0.1, see data analysis). For the issues added in the last step of phase I (missing issues), patients had to indicate the relevance and importance according to phase I and issues were included in the final questionnaire on corresponding condition (mean score >2 and/or >30% of the patients stated an issue as important).

For a disease-specific HRQoL questionnaire, it is not possible to include healthy or essential hypertension controls for any comparison in this phase, because not all questions are applicable for them.

**Data analysis**

We performed all analyses in SPSS version 22.0 for Windows (SPSS Inc.). We used descriptive statistics for phase I and phase III.

We tested the suitability of the data for exploratory factor analysis with the Kaiser–Meyer–Olkin (KMO) method, of which the value must be >0.5 (19). Initial communalities, estimates of the variance in each variable accounted for by all factors, were determined (\(R^2\) between one variable and all others in multiple regression analysis). We used exploratory factor analysis to explore the underlying constructs, explaining significant portions of variance. We based the number of constructs on the Kaiser–Guttman rule (the amount of the total variance explained by that factor must be >1) and the Cattell’s scree plot. We analyzed the factor loadings to explain the meaning of each construct. This was done by oblique rotation, which assumes that the factors could be related, simplifying their interpretation. Only items with factor loadings of >0.325 were retained for further analysis.

We performed multi-trait scaling analysis to confirm the scale structure found in exploratory factor analysis. We examined for item-scale convergent validity, corrected for overlap. We tested item-scale discriminant validity by comparing the correlation of each item with its own scale versus the other scales. Convergent and discriminant validity are subtypes of construct validity. Demonstration of both convergent and discriminant validity implicates construct validity, that is the questions are actually measuring what they are supposed to measure.

We tested reliability by measuring Cronbach’s alpha coefficient, of which the preferred level is >0.7 (20). Additionally convergent and discriminant validity were examined by calculating Spearman’s correlations between the scales and the items and between the scales/items and those of the EORTC QLQ-C30 (21). For the inclusive criterion, we considered an item-scale correlation of >0.40 (corrected for overlap) as adequate.
The exclusive criterion was met on the condition that the correlation with the other scales was lower than the correlation with the corresponding scale. When both criteria were met, we concluded that there was scaling fulfillment (20).

For the summed (scale) scores, all answers of the items contributing to the scale were summed, with a higher score corresponding with a lower HRQoL. Finally, we compared all summed scale scores and the total score (also added up) of the three patient groups with the Kruskal–Wallis H test.

Results

Phase I

The patient characteristics are listed in Supplementary Table 1 (see section on supplementary data given at the end of this article). We included 15 studies in our systematic review (16), from which we extracted 66 HRQoL issues. Both focus group meetings resulted in an additional 28 issues. These 94 issues were rated by 18 patients (mean age 53 years) and 15 HCP (ten Dutch and five other European professionals; six internist-vascular specialists, six endocrinologists, two nurses and one surgeon). This resulted in the removal of 65 issues. As more than one patient indicated ‘edema’ as missing issue, we added this to the list.

Phase II

The resulting 30 issues were converted into questions, resulting in the provisional PA-QoL. Whenever possible, we selected questions from the EORTC item bank (http://www.eortc.be/itemlibrary/), a collection of all available EORTC (HRQoL) questionnaires. The issues for which no corresponding question was available in the EORTC item bank (n = 11) were converted into questions after consensus by MV, JD and OH, in line with the EORTC style.

Phase III

All questionnaires were filled out completely. This was done online by 37 patients and on paper by eight patients. Patient characteristics are shown in Table 1. Response information is provided in Table 2. The time for completion of the provisional PA-QoL was ≤ 10 min for 24 patients, 11 to 15 min for 15 patients, 16 to 20 min for three patients and 21 to 25 min for three patients. Two patients indicated gynecomastia as a missing item. Therefore, this item was added as a single item only for men on spironolactone.

We excluded item 24 about impaired concentration based on our pre-defined criteria (mean score was <1.5 for the total group as well as for the untreated patients, prevalence ratio <30% and responses of scores ‘quite a bit’/‘very much’ <10%). We treated the item regarding erectile dysfunction as a single item. The KMO value for the remaining 28 items was 0.78. All initial communalities were >0.1. Four factors were identified, cumulatively accounting for 68% of variation in all items (respectively 48, 9, 6 and 5%). The oblique rotation of the exploratory factor analysis resulted in factor loadings and correlations which are shown in Table 3. We adopted a cut-off value of 0.325 for factor loadings. In other words, only those

Table 1 Characteristics of the patient groups involved in phase III.

| Characteristics                        | Untreated (n = 15) | MRA-based treatment* (n = 15) | Adrenalectomy (n = 15) |
|----------------------------------------|-------------------|-------------------------------|------------------------|
| Gender M/F                             | 9/6               | 13/2                          | 12/3                   |
| Age (years)b                           | 50.7 ± 10.4       | 59.6 ± 10.3                   | 55.7 ± 8.3             |
| Subtype APA/BAH                        | 9/5               | 0/15                          | 15/0                   |
| Years since diagnosis of PA (SLT)b     | <1                | 4.6 ± 1.4                     | 3.8 ± 0.8              |
| Years since diagnosis of hypertensionb | 11.3 ± 8.7        | 17.2 ± 12.3                   | 15.6 ± 12.1            |
| Years since (start of) treatmentb      | NA                | 3.9 ± 1.8                     | 2.7 ± 0.4              |
| Hypokalemia yes/nod                    | 11/4              | 2/13                          | 0/15                   |
| Systolic BP at first visitb            | 159 ± 23          | 162 ± 22                      | 155 ± 18               |
| Diastolic BP at first visitb           | 94 ± 12           | 92 ± 9.8                      | 92 ± 14                |
| Number of antihypertensive drugs at first visitb | 2 (1–3) | 2 (1–4) | 2 (1–3) |
| Renin concentration (SLT at T = 0) (mU/L)ac,i | 4.9 (2.0–8.5) | 3.4 (3.0–4.6) | 5.1 (3.0–9.2) |
| Aldosterone concentration (SLT at T = 4 h) (nmol/L)ac,ii | 0.48 (0.33–0.77) | 0.38 (0.31–0.47) | 0.49 (0.32–1.09) |

*Spironolacton (n = 6), epleronon (n = 8), methyldopa (n = 1, due to pregnancy wish); a mean ± SD; b unknown in one patient; c at time of filling out questionnaire; d median (25th–75th percentile); e pre-treatment; f n = 11/13/10 (missings due to renin activity measurements in other patients), if renin was <3 (n = 11) it was considered as renin = 3, reference values 6.2–65 mU/L; g n = 8, reference value <0.28 nmol/L confirms PA; h n = 14.

APA, aldosterone-producing adenoma; BAH, bilateral adrenal hyperplasia; NA, not applicable; PA, primary aldosteronism; SLT, salt loading test.
Table 2: Item descriptive statistics of 45 patients with (treated) primary aldosteronism (phase III).

| Item | Question | Mean | Distribution of responses (n = 45)* |
|------|----------|------|------------------------------------|
|      |          | Total (n = 45) | Untreated (n = 15) | MRA (n = 15) | ADX (n = 15) | 1 | 2 | 3 | 4 |
| 1    | Have you had headaches? | 1.38 | 1.53 | 1.40 | 1.20 | 30 | 13 | 2 | 0 |
| 2    | Have you had muscle weakness? | 1.38 | 1.40 | 1.60 | 1.23 | 33 | 8 | 3 | 1 |
| 3    | Have you been physically limited? | 1.73 | 2.00 | 1.87 | 1.33 | 24 | 13 | 4 | 4 |
| 4    | Have you lacked energy? | 1.89 | 2.20 | 1.93 | 1.53 | 17 | 19 | 6 | 3 |
| 5    | Have you felt restless or agitated? | 1.47 | 1.80 | 1.40 | 1.20 | 30 | 10 | 4 | 1 |
| 6    | Have you felt physically exhausted? | 1.56 | 1.93 | 1.53 | 1.20 | 27 | 14 | 1 | 3 |
| 7    | Have you felt mentally exhausted? | 1.47 | 1.67 | 1.40 | 1.33 | 31 | 10 | 1 | 3 |
| 8    | Have you had to urinate frequently during the day? | 1.69 | 1.87 | 1.60 | 1.60 | 22 | 15 | 8 | 0 |
| 9    | Have you had to urinate frequently at night? | 2.04 | 2.07 | 2.27 | 1.80 | 11 | 23 | 9 | 2 |
| 10   | Have you felt overly thirsty? | 1.58 | 1.93 | 1.47 | 1.33 | 28 | 8 | 9 | 0 |
| 11   | Have you taken large quantities of fluid? | 1.56 | 1.87 | 1.33 | 1.47 | 28 | 9 | 8 | 0 |
| 12   | Have you woken up for long periods during the night? | 1.71 | 1.53 | 1.93 | 1.67 | 23 | 14 | 6 | 2 |
| 13   | Have you, as far as you know, snored? | 2.09 | 2.33 | 1.87 | 2.07 | 15 | 16 | 9 | 5 |
| 14   | Did you feel sleepy during the day? | 1.84 | 2.20 | 1.67 | 1.67 | 16 | 22 | 6 | 2 |
| 15   | Have you felt tired (not rested) when you woke up? | 1.84 | 2.20 | 1.80 | 1.53 | 20 | 14 | 9 | 2 |
| 16   | Have you worried about the consequences of your high blood pressure? | 1.64 | 2.07 | 1.57 | 1.40 | 24 | 15 | 4 | 2 |
| 17   | Have you been worried about the consequences of the elevated levels of aldosterone? | 1.76 | 2.27 | 1.67 | 1.33 | 21 | 16 | 6 | 2 |
| 18   | Have you worried about your treatment causing future health problems? | 1.71 | 1.87 | 1.93 | 1.33 | 22 | 15 | 7 | 1 |
| 19   | Have you been worried about the side effects of your treatment? | 1.71 | 2.00 | 1.80 | 1.33 | 23 | 14 | 6 | 2 |
| 20   | Have you felt frustrated about the number of pills that you are taking? | 1.93 | 2.20 | 1.87 | 1.73 | 22 | 10 | 7 | 6 |
| 21   | Have you felt impatient? | 1.49 | 1.67 | 1.60 | 1.20 | 29 | 11 | 4 | 1 |
| 22   | Did you feel irritable? | 1.69 | 2.00 | 1.67 | 1.40 | 22 | 16 | 6 | 1 |
| 23   | Did you get angry easily? | 1.58 | 1.73 | 1.60 | 1.40 | 25 | 15 | 4 | 1 |
| 24b  | Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1.36 | 1.40 | 1.33 | 1.33 | 32 | 11 | 1 | 1 |
| 25   | Have you had difficulty remembering things? | 1.58 | 1.60 | 1.60 | 1.53 | 23 | 19 | 2 | 1 |
| 26   | Have you had swelling in your legs or ankles? | 1.47 | 1.80 | 1.40 | 1.20 | 31 | 9 | 3 | 2 |
| 27   | Have you felt frustrated about a possible delay in the diagnosis of primary aldosteronism? | 1.49 | 2.00 | 1.33 | 1.13 | 31 | 6 | 8 | 0 |
| 28   | Have you felt worried about the diagnosis? | 1.53 | 2.07 | 1.33 | 1.20 | 28 | 11 | 5 | 1 |
| 29   | Have you had decreased libido? | 1.82 | 1.93 | 1.80 | 1.73 | 25 | 8 | 7 | 5 |
| 30   | For men: Did you have difficulty obtaining or maintaining an erection? | 1.68 | 1.78 | 2.08 | 1.17 | 22 | 4 | 5 | 3 |

Patients were untreated, after adrenalectomy (ADX) or on mineralocorticoid receptor antagonists (MRA).

*1 = not at all; 2 = a little; 3 = quite a bit; 4 = very much; aitem deleted based on pre-defined criteria (see text).

The multi-trait analysis showed that scaling assumptions were not met for one item in three of the four scales (Table 4). The reliability of all scales was adequate. There was a significant correlation of all four scales with the EORTC QLQ-C30 in most cases (Table 5). We named the scales physical and mental fatigue, anxiety and stress, fluid balance and other complaints.

The summed scale scores were the highest for the untreated patients and the lowest for the patients after ADX (Table 6). This was statistically significant for scale 2 and for the total of all 28 items (item concerning erectile dysfunction not included).

Discussion

We have developed the first disease-specific HRQoL questionnaire for patients with PA, the PA-QoL, consisting of the 30 most relevant items, according to an established guideline (11). This preliminary analysis resulted in four scales, all with a fair reliability and validity. There is an adequate correlation with the validated EORTC...
Table 3  Rotated component matrix of all items with a factor loading >0.325.

| Scale                        | Item | Description                   | Factor loadings | Correlations |
|------------------------------|------|-------------------------------|-----------------|--------------|
| Physical and mental fatigue  | 2    | Muscle weakness               | −0.391          | −0.645       |
|                              | 3    | Physically limited            | −0.663          | −0.806       |
|                              | 4    | Lack energy                   | −0.531          | −0.783       |
|                              | 6    | Physically exhausted          | −0.331          | −0.706       |
|                              | 7    | Mentally exhausted            | −0.777          | −0.882       |
|                              | 12   | Woken up long period night    | −0.633          | −0.668       |
|                              | 14   | Sleepy daytime                | −0.582          | −0.766       |
|                              | 15   | Tired wake up                 | −0.326          | −0.641       |
|                              | 25   | Problems remember             | −0.682          | −0.663       |
|                              | 29   | Decreased libido              | −0.454          | −0.602       |
| Anxiety and stress           | 5    | Restless agitated             | −0.463          | 0.623        |
|                              | 16   | Worries high blood pressure   | −0.663          | −0.714       |
|                              | 17   | Worries aldosterone           | −0.988          | −0.947       |
|                              | 18   | Worries future health         | −0.704          | −0.820       |
|                              | 19   | Worries side effects          | −0.864          | −0.893       |
|                              | 20   | Frustrated number pills       | −0.432          | −0.551       |
|                              | 27   | Frustrated delay diagnosis    | −0.645          | −0.733       |
|                              | 28   | Worries diagnosis             | −0.842          | −0.818       |
| Fluid balance                | 9    | Urinate night                 | 0.426           | 0.566        |
|                              | 10   | Thirsty                       | 0.737           | 0.802        |
|                              | 11   | Fluids                        | 0.779           | 0.789        |
| Other complaints             | 1    | Headaches                     | 0.654           | 0.724        |
|                              | 8    | Urinate frequently day        | 0.663           | 0.674        |
|                              | 22   | Irritable                     | 0.757           | 0.893        |
|                              | 23   | Angry                         | 0.668           | 0.779        |
|                              | 26   | Swelling legs ankles          | 0.448           | 0.510        |

QLQ-C30 questionnaire. Also, the PA-QoL demonstrates the differences in HRQoL between the different treatment groups, with the lowest QoL in untreated patients and the highest in patients treated by ADX, as established before (22).

This is the first study which assessed all specific and relevant QoL issues in patients with PA, with contributions of 76 patients with PA. The items included in the provisional questionnaire cover a range of difficulties that patients with PA are facing. Some of them can be directly assigned to the pathophysiological effects of high aldosterone, such as edema, disturbances of the fluid balance and muscle weakness (mediated by hypokalemia). The questionnaire also consists of a number of mental issues, which is in line with earlier findings (16). Sleeping disorders and snoring might be due to the association of PA with obstructive sleep apnea (23). Finally, a decreased libido and erectile dysfunction might be the result of spironolactone, as this mineralocorticoid receptor antagonist has anti-androgen activity (24). All these issues are specific for PA and are not covered by a general HRQoL questionnaire. Remarkably the specific issues concerning depression and generalized anxiety were not included in phase III because relevance and importance was judged low by patients and HCPs, although these problems are known from the literature as associated with PA (16).

Table 4  Results of multi-trait analysis.

| Scale | N  | Mean (s.d.) | Cronbach’s α | Item-scale convergent validity (inclusive criterion) | Item-scale divergent validity (exclusive criterion) | Scaling fulfillment |
|-------|----|-------------|---------------|----------------------------------------------------|---------------------------------------------------|--------------------|
|       |    |             |               | Range (mean) of item-scale correlations | Number of item-scale correlations | Range (mean) of correlations with other scales | Number of items with higher correlations with other scale | Number of items that meet criterion 1 and 2 |
| 1     | 10 | 16.8 (6.7)  | 0.93          | 0.39–0.79 (0.64) | 9/10 | 0.23–0.76 (0.44) | 0/10 | 9/10 |
| 2     | 8  | 13.2 (5.5)  | 0.92          | 0.51–0.87 (0.69) | 8/8 | 0.29–0.74 (0.42) | 1/8 | 7/8  |
| 3     | 3  | 5.2 (2.0)   | 0.77          | 0.55–0.67 (0.61) | 3/3 | 0.31–0.52 (0.42) | 0/3 | 3/3  |
| 4     | 5  | 7.8 (2.9)   | 0.84          | 0.37–0.81 (0.62) | 4/5 | 0.25–0.77 (0.48) | 0/5 | 4/5  |

aCorrelation between items and hypothesized scale; bnumber of item-scale correlation that meet minimum standard for convergent validity (≥0.40); ccorrelation between items and other scales; dnumber of items that have higher correlation with at least one of the other scales compared to that with the hypothesized scale.
This study confirms the impaired HRQoL of patients with PA, and its improvement by treatment. An impaired HRQoL has been reported by various studies before (5, 6, 16, 22, 25), as well as the improvement after therapy (5, 6, 16, 22, 26). In our study, patients after ADX have a better disease-specific HRQoL than patients on MRA-based treatment. This is in line with our earlier findings with a generic HRQoL questionnaire (22). However, in other studies, this relation between therapy for PA and QoL has been questioned (6, 25). This inconsistency might have been the result of a too small number of patients and/or the use of a general/less extensive HRQoL questionnaire. As the PA-QoL is disease-specific, it has presumably more potential to discriminate.

A few limitations should be taken into account. Firstly, the PA-QoL has not yet been tested in a large group of patients from different countries. Therefore, the created scales have a preliminary status. Furthermore, because the scaling is mainly a result of statistical procedures, the grouped items are not always consistent with how we would create scales intuitively. Therefore, the scale structure needs to be confirmed in a large international sample of patients with PA.

Also, one item regarding gynecomastia (‘Have you had sore or enlarged nipples or breasts?’) was added to the questionnaire specifically for men using spironolactone as a single item. The relevance will be checked in the final phase. Moreover, when interpreting the outcome of the PA-QoL, we have to take into account the possibility of a selection bias, which might have influenced the scores (in all groups) in phase III, assuming that patients with more complaints are more willing to participate for example. However, we do not think this has influenced the final questionnaire because a lot of issues were eliminated in the following phases due to the elaborated process of constructing this questionnaire. Finally, the gender distribution in phase III might have influenced our results. It has been suggested in previous studies that (untreated) female patients are more affected regarding mental QoL (25), anxiety and depression (7, 8, 27). In our study, more male patients were included, especially in the post-treatment groups. This is a result of a structural higher percentage of men compared to women with PA that are treated in our hospital.

### Table 5 Correlations between EORTC QI-Q30 and scales/items PA-QoL.

| EORTC QLQ-C30 | Scales | Single items |
|---------------|--------|--------------|
|               | 1      | 2            | 3              | 4              | **  
| Physical functioning<sup>a</sup> | −0.77** | −0.37* | −0.47** | −0.67** | −0.18 | −0.51** |
| Role functioning<sup>a</sup> | −0.77** | −0.52* | −0.45** | −0.61** | −0.16 | −0.43** |
| Emotional functioning<sup>a</sup> | −0.78** | −0.53** | −0.48** | −0.73** | −0.29 | −0.65** |
| Cognitive functioning<sup>a</sup> | −0.73** | −0.54** | −0.50** | −0.74** | −0.46** | −0.68** |
| Social functioning<sup>a</sup> | −0.72** | −0.63** | −0.38** | −0.52** | −0.33* | −0.66** |
| Global QoL/health status | −0.63** | −0.58** | −0.41** | −0.63** | −0.33* | −0.51** |
| Fatigue | 0.87** | 0.45** | 0.45** | 0.75** | 0.21 | 0.50** |
| Nausea/vomiting | 0.54** | 0.30* | 0.30* | 0.39** | 0.20 | 0.26 |
| Pain | 0.60** | 0.29 | 0.13 | 0.36* | 0.06 | 0.30* |
| Dyspnea | 0.63** | 0.26 | 0.27 | 0.52** | 0.06 | 0.30* |
| Sleep/insomnia | 0.60** | 0.52** | 0.33* | 0.49** | 0.32* | 0.42** |
| Appetite loss | 0.51** | 0.34* | 0.43** | 0.52** | 0.33* | 0.58** |
| Constipation | 0.07 | −0.05 | 0.04 | 0.15 | 0.26 | −0.06 |
| Diarrhea | 0.27 | 0.18 | 0.20 | 0.26 | 0.06 | 0.24 |
| Financial difficulties | 0.28 | 0.32* | 0.30* | 0.27 | 0.27 | 0.19 |

<0.40 weak correlation, 0.40–0.60 moderate and >0.60 high.

<sup>a</sup>A high score for these functional scales represents a high/healthy level of functioning; *P < 0.05; **P < 0.01.

### Table 6 Comparison of treatment groups for outcomes provisional PA HRQoL questionnaire.

| Scale | Items (n) | Untreated (n = 15) | MRA-based treatment (n = 15) | Adrenalectomy (n = 15) | P value |
|-------|-----------|-------------------|-------------------------------|------------------------|--------|
| 1 Physical and mental fatigue | 10 | 18 (14–22) | 14 (12–21) | 13 (11–17) | 0.134 |
| 2 Anxiety and stress | 8 | 9 (8–12) | 13 (9–14) | 9 (8–12) | 0.006 |
| 3 Fluid balance | 3 | 6 (4–7) | 4 (4–6) | 4 (3–5) | 0.112 |
| 4 Other complaints | 5 | 8 (6–12) | 7 (5–10) | 6 (5–9) | 0.192 |
| Total | 28 | 38 (23–43) | 42 (36–49) | 49 (40–64) | 0.027 |

Data expressed as medians (25th–75th percentile).
MRA, mineralocorticoid receptor antagonists.

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The PA-QoL could be used in clinical as well as research setting to measure an important outcome, especially from the patients’ perspective. This will allow a more optimal and precise mapping of the impaired HRQoL in patients with PA and make physicians more aware of the potential HRQoL issues that patients with PA are dealing with. Furthermore, it will help them to inform patients adequately and to identify those who most suffer from PA-related health problems, other than hypertension or hypokalemia.

The final phase of the development of the PA-QoL will assess responsiveness to change and cross-cultural validity. The larger number of patients will help to fully validate the scales. We expect that this will also result in a significant difference between treatment groups in all subscales. In our study for two out of three subscales, there was a non-significant trend, probably due to the limited number of patients in each group (n = 15).

In conclusion, we developed the first PA-specific HRQoL questionnaire using standard, methodologically proven guidelines. This questionnaire can be of value in the care for patients with PA. After final validation in phase IV is completed, it can be implemented into practice.

Supplementary data
This is linked to the online version of the paper at https://doi.org/10.1530/EC-19-0026.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References
1 Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, Young WF Jr, Montori VM & Endocrine Society. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. Journal of Clinical Endocrinology and Metabolism 2008 93 3266–3281. (https://doi.org/10.1210/jc.2008-0104)
2 Mulatero P, Stowasser M, Loh KC, Fardella CE, Gordon RD, Mosso L, Gomez-Sanchez CE, Veglio F & Young WF Jr. Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. Journal of Clinical Endocrinology and Metabolism 2004 89 1045–1050. (https://doi.org/10.1210/jc.2003-031337)
3 Rossi GP, Bernini G, Desideri G, Fabris B, Ferri C, Giacchetti G, Letizia C, Maccario M, Mannelli M, Matterello MJ, et al. Renal damage in primary aldosteronism: results of the PAPY study. Hypertension 2006 48 232–238. (https://doi.org/10.1161/01.HYP.0000230444.01215.6a)
4 Schipper H, Clinch JJ & Olweny CLM. Quality of Life Studies: Definitions and Conceptual Issues. New York, NY, USA: Raven Press Ltd, 1990.
5 Sukor N, Kogovscek V, Gordon RD, Robson D & Stowasser M. Improved quality of life, blood pressure, and biochemical status following laparoscopic adrenalectomy for unilateral primary aldosteronism. Journal of Clinical Endocrinology and Metabolism 2010 95 1360–1364. (https://doi.org/10.1210/jc.2009-1763)
6 Ahmed AH, Gordon RD, Sukor N, Pimenta E & Stowasser M. Quality of life in patients with bilateral primary aldosteronism before and during treatment with spironolactone and/or amiloride, including a comparison with our previously published results in those with unilateral disease treated surgically. Journal of Clinical Endocrinology and Metabolism 2011 96 2904–2911. (https://doi.org/10.1210/jc.2011-0138)
7 Sonino N, Fallo F & Fava GA. Psychological aspects of primary aldosteronism. Psychotherapy and Psychosomatics 2006 75 327–330. (https://doi.org/10.1055/s-0026-6799351)
8 Sonino N, Tomba E, Genesia ML, Bertello C, Mulatero P, Veglio F, Fava GA & Fallo F. Psychological assessment of primary aldosteronism: a controlled study. Journal of Clinical Endocrinology and Metabolism 2011 96 8878–8883. (https://doi.org/10.1210/jc.2010-2723)
9 Korte SM. Corticosteroids in relation to fear, anxiety and psychopathology. Neuroscience and Biobehavioral Reviews 2001 25 117–142. (https://doi.org/10.1016/S0149-7634(01)00002-1)
10 Ware JE Jr, Gandek B, Gayer R & Deng N. Standardizing disease-specific quality of life measures across multiple chronic conditions: development and initial evaluation of the QOLI Disease Impact Scale (QDIS(R)). Health and Quality of Life Outcomes 2016 14 84. (https://doi.org/10.1186/s12955-016-0483-x)
11 Blazevy J, Sprangers MA, Cull A, Groenvold M & Bottomley A. EORTC: Quality of Life Group: Guidelines for Developing Questionnaire Modules. Brussels, Belgium: European Organization for Research and Treatment of Cancer, 2002.
12 Sprangers MA, Cull A, Bjordal K, Groenvold M, Aaronson NK & EORTC Study Group on Quality of Life. The European Organization for Research and Treatment of Cancer approach to quality of life assessment: guidelines for developing questionnaire modules. Quality of Life Research 1993 2 287–295. (https://doi.org/10.1007/BF00434800)
13 Sprangers MA, Cull A, Groenvold M, Bjordal K, Blazevy J & Aaronson NK. The European Organization for Research and Treatment of Cancer approach to developing questionnaire modules: an update and overview. Quality of Life Research 1998 7 291–300. (https://doi.org/10.1023/A:1008890401133)
14 Velema M, Linssen E, Hermus A, Groenewoud H, van der Wilt GJ, van Herwaarden AE, Lenders J, Timmers HJLM & Deinum J. A prediction model for primary aldosteronism when the salt loading test is inconclusive. Endocrine Connections 2018 7 1308–1314. (https://doi.org/10.1530/EC-18-0358)
15 Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shihata H, Stowasser M & Young WF Jr. The management of
primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society clinical practice guideline. Journal of Clinical Endocrinology and Metabolism 2016 101 1889–1916. (https://doi.org/10.1210/jc.2015-4061)

16 Velema MS, de Nooijer AH, Burgers VWG, Hermus ARMM, Timmers HJLM, Lenders JWM, Husson O & Deinum J. Health-related quality of life and mental health in primary aldosteronism: a systematic review. Hormone and Metabolic Research 2017 49 943–950. (https://doi.org/10.1055/s-0043-121706)

17 Bottomley A, Vachalec S, Bjordal K, Blazeby J, Flechtner H & Ruyskart P. The development and utilisation of the European Organisation for Research and Treatment of Cancer quality of life group item bank. European Journal of Cancer 2002 38 1611–1614. (https://doi.org/10.1016/S0959-8049(02)00125-9)

18 Dewolf L, Koller M, Velikova G, Johnson CD, Scott N & Bottomley A. European Organization for Research and Treatment of Cancer Quality of Life Group Translation Procedure. Brussels, Belgium: European Organization for Research and Treatment of Cancer, 2009.

19 Kaiser HF. An index of factorial simplicity. Psychometrika 1974 39 31–36. (https://doi.org/10.1007/BF02291575)

20 Nunally JC & Bernstein IH. Psychometric Theory, 3rd ed. New York, NY, USA: McGraw-Hill, 1994.

21 Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A & on behalf of the EORTC. The EORTC QLQ-C30 Scoring Manual, 3rd edn. Brussels, Belgium: European Organisation for Research and Treatment of Cancer, 2001.

22 Velema M, Dekkers T, Hermus A, Timmers H, Lenders J, Groenewoud H, Schultz Kool L, Langenhuijsen J, Prejbisz A, van der Wilt GJ, et al. Quality of life in primary aldosteronism: a comparative effectiveness study of adrenalectomy and medical treatment. Journal of Clinical Endocrinology and Metabolism 2018 103 16–24. (https://doi.org/10.1210/jc.2017-01442)

23 Prejbisz A, Kolodziejczyk-Kruk S, Lenders JWM & Januszewicz A. Primary aldosteronism and obstructive sleep apnea: is this a bidirectional relationship? Hormone and Metabolic Research 2017 49 969–976. (https://doi.org/10.1055/s-0043-122887)

24 Corvol P, Michaud A, Merard J, Freifeld M & Mahoudeau J. Antiandrogenic effect of spiroloctones: mechanism of action. Endocrinology 1975 97 52–58. (https://doi.org/10.1210/endo-97-1-52)

25 Kunzel HE, Apostolopoulou K, Pallaf A, Gerum S, Merke K, Schulz S, Fischer E, Brand V, Bidlingmaier M, Endres S, et al. Quality of life in patients with primary aldosteronism: gender differences in untreated and long-term treated patients and associations with treatment and aldosterone. Journal of Psychiatric Research 2012 46 1650–1654. (https://doi.org/10.1016/j.jpsychires.2012.08.025)

26 Kawasaki Y, Kaigo Y, Izumi H, Kawamorita N, Yamashita S, Adachi H, Mitsuoka K, Ito A, Ishidoya S & Arai Y. MP37-19 short-term impact on health-related quality of life of laparoscopic adrenalectomy for primary aldosteronism in Japanese patients. Journal of Urology 2017 197 (4 Supplement 1) e483. (https://doi.org/10.1016/j.juro.2017.02.1151)

27 Apostolopoulou K, Kunzel HE, Gerum S, Merke K, Schulz S, Fischer E, Pallaf A, Brand V, Bidlingmaier M, Endres S, et al. Gender differences in anxiety and depressive symptoms in patients with primary hyperaldosteronism: a cross-sectional study. World Journal of Biological Psychiatry 2014 15 26–35. (https://doi.org/10.3109/156229 75.2012.665480)

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