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1 **QUALITY OF LIFE IN PRIMARY ALDOSTERONISM: A PROSPECTIVE OBSERVATIONAL STUDY**

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22 **Keywords:** primary aldosteronism, essential hypertension, quality of life, adrenalectomy,  
23 mineralocorticoid receptor antagonist

24 **World count:** 3220 (excluding references and full legend)

For Review Only

## 25 **Abstract**

26 **Background** Previous studies suggested that patients affected by primary aldosteronism (PA)  
27 have impaired quality of life (QOL) compared to the general population, but a direct  
28 comparison with patients affected by essential hypertension (EH) has never been performed.  
29 The aim of the study was to compare the QOL of patients affected by PA to the QOL of patients  
30 affected by EH.

## 31 **Material and methods**

32 We designed a prospective observational study comparing the QOL of patients with PA and  
33 carefully matched patients with EH before and after treatment. We recruited 70 patients with  
34 PA and 70 patients with EH, matched for age, sex, blood pressure levels and intensity of anti-  
35 hypertensive treatment. We assessed QOL at baseline and after specific treatment for PA or  
36 after optimization of medical therapy for patients with EH.

## 37 **Results**

38 Patients with PA displayed impaired QOL compared with the general healthy population, but  
39 similar to patients with EH. Both laparoscopic adrenalectomy and treatment with  
40 mineralocorticoid receptor antagonist allowed an improvement of QOL in patients with PA,  
41 that was more pronounced after surgical treatment. Optimization of blood pressure control by  
42 implementation of antihypertensive treatment (without MR antagonists) allowed a minimal  
43 improvement in only one of eight domains in patients with EH.

## 44 **Conclusions**

45 Patients with PA have impaired QOL, which is likely caused by uncontrolled hypertension  
46 and the effects of intensive anti-hypertensive treatment. Surgical and medical treatment of PA

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47 allows a significant improvement of QOL, by amelioration of blood pressure control and,  
48 after surgical treatment, by reduction of anti-hypertensive treatment.

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## 61 Introduction

62 The World Health Organization considers quality of life (QOL) a key component of “health”  
63 status and recommends to consider the effects of medical treatments by assessing patients’  
64 well-being with health related QOL evaluation.<sup>1</sup> The QOL of patients with primary  
65 aldosteronism (PA) has been neglected until 2010, when a significant reduction of QOL in  
66 patients with aldosterone producing adenoma (APA), compared with the Australian general  
67 population, was reported for the first time.<sup>2</sup> In the following years, these findings were  
68 confirmed in larger cohorts of patients with unilateral PA,<sup>3–6</sup> and similar findings were obtained  
69 in patients with bilateral or idiopathic hyperaldosteronism (IHA).<sup>4,7</sup>

70 Beyond QOL, primary aldosteronism has been associated with anxiety, depressive disorders  
71 and somatization.<sup>8–11</sup> Recent findings suggested that aldosterone levels might correlate with  
72 depressive symptoms in women with PA<sup>12</sup> and, more broadly, previous studies indicated a  
73 correlation between serum aldosterone levels and the prevalence of depressive disorders in  
74 patients without PA.<sup>13,14</sup>

75 Well-being is an essential component of QOL and a previous study reported lower  
76 psychological well-being in patients with PA, compared with normotensive control.<sup>9</sup> A  
77 following study reported contrasting results, with no differences in well-being of patients with  
78 PA compared to Dutch normative data.<sup>11</sup> Several explanations may be offered for the  
79 conflicting results, including the use of different questionnaires, a predominantly male cohort  
80 and the lack of an appropriate control group in one study.

81 PA is the most common cause of endocrine hypertension and affects about 4-6% of patients  
82 with arterial hypertension in the general population.<sup>15,16</sup> Beyond the strict criteria for PA, recent  
83 studies identified an autonomous aldosterone secretion in up to 20% of individuals with  
84 hypertension and up to one fifth of patients with normotension.<sup>17,18</sup> Specific PA treatments,  
85 both unilateral adrenalectomy and medical treatment with mineralocorticoid receptor (MR)

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3 86 antagonists, resulted in significant QOL improvement, that occurred earlier and was more  
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5 87 pronounced in surgically treated patients compared with those medically treated.<sup>4,7</sup>  
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8 88 Some authors proposed that the impaired QOL of patients with PA could be attributed to the  
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10 89 direct effects of aldosterone excess on central nervous system. However, uncontrolled and  
11  
12 90 resistant hypertension could themselves account for a significant impairment of QOL.<sup>19</sup> No  
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14 91 study directly compared the quality of life of patients with PA versus patients with essential  
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16 92 hypertension with similar clinical characteristics. At the same time, in most of the former  
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18 93 studies, QOL was assessed after PA diagnosis,<sup>2,4</sup> making the awareness of the disease a relevant  
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20 94 component in QOL evaluation. Finally, no study compared the effect of specific treatment for  
21  
22 95 PA versus optimization of medical treatment.  
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25  
26 96 In this context, we designed a prospective observational study comparing, for the first time, the  
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28 97 QOL of patients affected by PA (before diagnosis) with patients affected by essential  
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30 98 hypertension (EH), matched for age, sex, blood pressure levels and intensity of drug treatment.  
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32 99 We evaluated the modification of QOL after specific treatment in patients with PA and  
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34 100 compared with QOL modification after optimization of anti-hypertensive therapy in the control  
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36 101 cohort. In order to compare our study with previous findings<sup>2-7</sup>, we adopted RAND SF-36 as  
37  
38 102 tool to investigate QOL in our cohort.  
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## 42 103 **Materials and methods**

### 43 104 *Study Design*

44  
45 105 The protocol was approved by the ethical committee of the hospital A.O.U. Città della Salute  
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47 106 e della Scienza di Torino and written informed consent was obtained from all recruited patients.  
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51 107 Reporting of the study conforms to broad EQUATOR guidelines.<sup>20</sup>  
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54 108 In the QUALity of Life of patients with PA in TORino (QUALITO) study we prospectively  
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56 109 enrolled 140 patients (70 patients with PA and 70 matched controls with EH) from 03/2017 to  
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58 110 09/2019 in Torino, Italy. Patients with PA and EH were matched for sex, age, systolic blood  
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3 111 pressure (SBP) and intensity of antihypertensive drug treatment (quantified by daily defined  
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5 112 dose, calculated with the online tool available at  
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8 113 <https://github.com/ABurrello/PASOPredictor/raw/master/00 - PASO Predictor.xlsm>).<sup>21</sup>  
9

10 114 All the included patients were affected by arterial hypertension, diagnosed according with the  
11  
12 115 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guideline<sup>22,23</sup>;  
13  
14 116 diagnosis of EH was made after the exclusion of all the main secondary forms of arterial  
15  
16 117 hypertension (including hypercortisolism, pheochromocytoma, hyperthyroidism and reno-  
17  
18 118 vascular hypertension), while patients with PA were included following a confirmed diagnosis  
19  
20 119 according to the Endocrine Society guideline and the recent ESH consensus.<sup>24-26</sup> The only  
21  
22 120 exclusion criterion for EH cohort was treatment with MR antagonists at recruitment or at follow  
23  
24 121 up. For PA cohort, exclusion criteria were I) patients under MR antagonist or II) previous  
25  
26 122 adrenalectomy for unilateral PA at recruitment.  
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### 30 123 *Diagnosis of primary aldosteronism*

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33 124 Before screening test, all interfering antihypertensive drugs were stopped (at least 2 weeks for  
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35 125 ACE-I, ARBs and beta blockers and 4 weeks for diuretics). When complete discontinuation of  
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37 126 antihypertensive treatment was not feasible, non-interfering drugs were administered. The  
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39 127 screening test was considered positive in case of serum aldosterone  $\geq 10$  ng/dl and aldosterone  
40  
41 128 to renin ratio (ARR)  $\geq 30$  ng/dl/ng/ml/h or aldosterone to active renin ratio (AARR)  $\geq 2.7$   
42  
43 129 ng/dl/mU/l. Seated saline infusion test (SSIT) or, in case of contraindication, captopril  
44  
45 130 challenge test (CCT), were used as confirmatory tests. PA was considered confirmed in case  
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47 131 of serum aldosterone post-SSIT  $\geq 5$  ng/dl or ARR  $\geq 30$  ng/dl/ng/ml/h after CCT.  
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51 132 Subtype diagnosis was performed by computed tomography of the adrenal glands and  
52  
53 133 unstimulated and/or cosyntropin-stimulated adrenal venous sampling (AVS). A selectivity  
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55 134 index  $\geq 3$  for unstimulated and  $\geq 5$  for stimulated AVS was used to define successful  
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3 135 cannulation of adrenal veins. A lateralization index  $\geq 4$  or  $\geq 3$  with contralateral suppression  
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5 136 (contralateral ratio  $< 1$ ) was used to define unilateral PA.  
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8 137 *Quality of life data collection*

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10 138 36-Item Short Form Health Survey (RAND SF-36) is a self-administered questionnaire used  
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12 139 to assess health-related QOL and validated in the Italian population.<sup>27</sup> RAND SF-36 includes  
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14 140 35 items and 8 different subscales: physical functioning, role limitations due to physical  
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16 141 problems, role limitations due to emotional problems, vitality, general mental health, social  
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18 142 functioning, bodily pain, and general health perceptions.  
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20  
21 143 At baseline, RAND SF-36 was self-administered in patients with PA before confirmatory test  
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23 144 and in patients with EH before optimization of antihypertensive medical treatment.  
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26 145 In the PA cohort, RAND SF-36 was also collected 2 and 6 months after laparoscopic surgical  
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28 146 adrenalectomy or initiation of MR antagonist. RAND SF-36 was collected 6 months after  
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30 147 optimization of medical treatment in patients with EH.  
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33 148 Data of the PA cohort, at baseline and at 6 months, have been compared to the Italian normative  
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35 149 data from “healthy subjects”.<sup>27</sup>  
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38 150 *Statistical methods*

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40 151 IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, New York) was used for statistical  
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42 152 analyses. PRISM software (GraphPad, San Diego, CA) was used for charts and graphs  
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44 153 preparation. Data are expressed as mean  $\pm$  SD for continuous variables with a normal  
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46 154 distribution. Data with non-normal distributions are expressed as median (interquartile range).  
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48 155 Charlson Comorbidity index was used to estimate burden of comorbidity and considered as  
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50 156 categorical variable.<sup>28</sup> Statistical significance between groups was calculated in normally  
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52 157 distributed data by paired t test for groups of matched patients and Student t test for independent  
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54 158 samples in other cases. Mann-Whitney U test was used for non-normally distributed data and  
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56 159 Kruskal-Wallis test for paired samples for non-normally distributed data of matched samples.  
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3 160 Chi-square test was used for qualitative variables. Repeated measure ANOVA was used for  
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5 161 comparison of daily defined dose (DDD) and blood pressure levels during follow up.

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7 162 Linear mixed model is a statistical approach that can be applied in prospective studies for the  
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9 163 analysis of repeated measures. In contrast to repeated measure ANOVA, usually used for  
10 164 repeated measures analysis, mixed models consider both fixed and random effects, allowing a  
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12 165 more accurate analysis of prospective data. Moreover, using random effects for baseline values,  
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14 166 mixed models take into account differences in starting point for each subject.

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17 167 Linear mixed models, with unstructured correlation and maximum likelihood method, were  
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19 168 used for longitudinal comparison of QOL changes and performed with R version 3.6.1. Scores  
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21 169 of the 8 subscales of RAND SF-36 were used as dependent variables. Time, treatment, sex,  
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23 170 diabetes and CCI were considered as fixed factors and potassium, creatinine, age, BMI and  
24  
25 171 duration of hypertension as covariates. 20 different models were evaluated for each subscale  
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27 172 and minimum Akaike information criterion (AIC) was used for model selection (Supplemental  
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29 173 Methods).

## 30 31 174 **Results**

### 32 33 175 *PA and EH cohort*

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38 176 A total of 140 patients were recruited for the QUALITO study in Torino: 70 patients with PA  
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41 177 and 70 patients with EH matched for age, sex, systolic blood pressure and intensity of anti-  
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43 178 hypertensive drug treatment (DDD). Of the 70 patients with PA, 43 were diagnosed as affected  
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45 179 by unilateral PA, 37 of whom underwent laparoscopic adrenalectomy (Figure S1). All the  
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47 180 patients that underwent unilateral adrenalectomy displayed complete biochemical outcome at  
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49 181 6 months follow-up according to PASO criteria.<sup>29</sup> Twenty out of 70 patients with PA were  
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51 182 classified as IHA and 7 patients with undetermined subtype, because unwilling to undergo AVS  
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53 183 or unsuccessful procedure. Thirty patients were treated with MR antagonist (14 with  
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55 184 spironolactone, 16 with potassium canrenoate), including 6 patients with unilateral PA, 19

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3 185 patients with IHA and 5 with undetermined subtype. One of 37 patients after surgical  
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5 186 adrenalectomy and one of 30 patients under MR antagonist were lost at follow up (Figure S1).  
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7 187 Principal clinical and biochemical characteristics of patients with EH and PA are summarized  
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9 188 in Table 1. No significant differences were present between the two cohorts for the evaluated  
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11 189 parameters, except for lower serum potassium in PA cohort.  
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#### 14 190 *Baseline comparison*

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16 191 At baseline, patients with PA had non-significant differences in either of the 8 subscales  
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18 192 compared with matched individuals with EH (Figure 1, Table S1). No differences were present  
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20 193 even after stratification for subtype diagnosis, in patients with unilateral PA and IHA (Table  
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22 194 S2-S3), compared with the respective matched patients with EH.  
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26 195 Compared to Italian normative data of “healthy subjects”,<sup>27</sup> patients with PA displayed lower  
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28 196 score in 5 of 8 domains: physical functioning, role limitations due to physical health problems,  
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30 197 vitality, social functioning and general health perceptions (Figure 1, Table S1), with similar  
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32 198 results in patients with unilateral PA and IHA, with the exception of social functioning, that  
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34 199 did not differ significantly between patients affected by IHA and healthy subjects (Table S2-  
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36 200 S3). **At baseline, independently of PA or EH diagnosis, patients with  $DDD \geq 3$  displayed lower  
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38 201 QOL in two physical subscales than patients with  $DDD < 3$  (Tables S4).**  
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#### 41 202 *Follow up*

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43 203 After surgical adrenalectomy, patient with APA displayed a significant reduction, at 2 and 6  
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45 204 months of follow up, of SBP ( $149 \pm 13$  vs  $124 \pm 11$  vs  $121 \pm 11$  mmHg), diastolic blood pressure  
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47 205 (DBP) ( $92 \pm 9$  vs  $80 \pm 11$  vs  $78 \pm 8$  mmHg) and anti-hypertensive treatment (DDD  $3.05 \pm 1.68$  vs  
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49 206  $1.31 \pm 1.53$  vs  $0.94 \pm 1.26$ ). Patients under MR antagonist showed a reduction of SBP ( $145 \pm 15$   
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51 207 vs  $134 \pm 14$  vs  $131 \pm 13$  mmHg) and DBP ( $88 \pm 9$  vs  $83 \pm 9$  vs  $83 \pm 8$  mmHg) with a non-significant  
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53 208 increase of anti-hypertensive treatment (DDD  $3.07 \pm 1.24$  vs  $3.43 \pm 1.42$  vs  $3.44 \pm 1.44$ ).  
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3 209 Similarly, patients treated with general anti-hypertensive treatment showed SBP and DBP  
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5 210 reduction at 6 months, with increased DDD (Table S5).  
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7 211 We used linear mixed models to compare baseline values with follow up scores at 2 and 6  
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9 212 months after treatment, selecting the best of 20 tested models, for each of the 8 subscales  
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11 213 (Supplemental Methods and Table S6). Effect and statistical significance of fixed factors,  
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13 214 covariates and interactions in each of the 8 subscales are showed in Table S7.  
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15 215 During follow up, patients undergoing unilateral surgical adrenalectomy displayed a significant  
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17 216 improvement in 4 of 8 domains: physical functioning, vitality, general health perceptions and  
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19 217 general mental health, with the latter significant at 2 but not at 6 months. Patients with PA  
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21 218 treated with MR antagonist, had a significant improvement in 2 domains: physical functioning  
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23 219 and general health perceptions. Patients with EH undergoing optimization of anti-hypertensive  
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25 220 treatment without MR antagonist displayed a significant improvement in only one domain  
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27 221 (general mental health) at 6 months of follow up (Figure 2A-B-C, Table S8).  
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### 33 222 *Six months comparison*

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35 223 At 6 months, adrenalectomized patients displayed higher scores in physical activity and general  
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37 224 health perceptions, compared to patients under general anti-hypertensive treatment, and higher  
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39 225 score in social functioning, compared to patients under MR antagonist. Patients with PA under  
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41 226 MR antagonist had higher score of physical functioning compared to patients under general  
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43 227 anti-hypertensive treatment (Figure 2D, Table S9).  
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47 228 Six months after surgery, adrenalectomized patients displayed similar score in 7 of 8 domains,  
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49 229 compared to Italian normative data of healthy subjects,<sup>27</sup> with lower score in only general  
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51 230 health perception. Instead, after 6 months of medical treatment, patients with MR antagonist  
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53 231 had lower scores in 4 of 8 domains compared to healthy subjects (Figure 3, Table S10).  
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### 56 232 **Discussion**

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3 233 QOL is a well-recognized component of health and QOL assessment has an important role in  
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5 234 the evaluation of the impact of diseases on affected patients. Whether the impaired QOL of  
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7 235 patients affected by PA is the result of aldosterone effect on the central nervous system or the  
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9 236 consequence of uncontrolled blood pressure is still an open question.<sup>30</sup>

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11 237 In the QUALITO study we compared, for the first time, the QOL of patients affected by PA to  
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13 238 the QOL of carefully matched patients affected by EH, as control group. The scores of patients  
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15 239 affected by PA were lower than healthy subjects, but not different from those of patients  
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17 240 affected by EH, suggesting that the impairment of QOL in PA could be attributable to  
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19 241 uncontrolled blood pressure and anti-hypertensive treatment, more than a direct effect of  
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21 242 aldosterone excess.

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26 243 Female sex, obesity and metabolic syndrome have been related to reduced QOL in previous  
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28 244 studies.<sup>3,31</sup> Supporting these findings, in our study, sex female had a significant negative impact  
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30 245 on 6 of 8 domains, including both physical and emotional subscales; similarly, high BMI had  
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32 246 a significant negative impact in role limitations due to physical health problems and general  
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34 247 health perception. Considering the known relationship between primary aldosteronism, obesity  
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36 248 and metabolic syndrome, it is possible that the coexistence of these conditions may  
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38 249 synergistically contribute to the reduction of QOL in patients with PA.<sup>32</sup>

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42 250 In agreement with previous studies,<sup>2-4,7</sup> we observed that both surgical and medical treatments  
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44 251 for PA induced a significant improvement in QOL, that was remarkably more pronounced in  
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46 252 the surgery group compared with the MR antagonist group. The optimization of anti-  
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48 253 hypertensive treatment, without MR blockade, in patients affected by EH, resulted into a  
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50 254 minimal increase in only one of 8 domains of QOL. This result suggests that reduction of blood  
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52 255 pressure levels *per se*, is probably not sufficient for a significant improvement of QOL and that  
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54 256 a specific role for MR antagonists, beyond its anti-mineralocorticoid activity, can be  
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56 257 hypothesized.  
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3 258 Multiple factors are likely working synergistically, reducing QOL in patients with hypertension  
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5 259 and PA, including disease awareness, medical treatment and uncontrolled blood pressure.  
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7 260 Knowledge of the disease is a key component of impaired QOL in many conditions. Patients  
8  
9 261 aware of the diagnosis of arterial hypertension have lower QOL than patients unaware of the  
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11 262 disease, independently of blood pressure levels.<sup>33</sup> Therefore, patients' perception of PA-related  
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13 263 cardiovascular risk, the need of invasive procedure for subtype diagnosis (such as adrenal  
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15 264 venous sampling) and lifestyle recommendations (such as dietary modification) can further  
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17 265 impact their QOL. In our study, the questionnaire was administered before PA diagnosis, thus  
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19 266 eliminating the potential bias of disease-awareness.  
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24 267 Another important factor affecting the QOL is represented by anti-hypertensive treatment. **In a**  
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26 268 **previous study**, the QOL in physical and mental components was higher in patients taking < 4  
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28 269 anti-hypertensive medications than in patients taking a higher number of drugs. The association  
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30 270 between number of drugs and mental component was significant even after correction for the  
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32 271 main confounding factors including blood pressure levels.<sup>34</sup> **We confirmed this finding,**  
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34 272 **reporting lower QOL in patients with DDD $\geq$ 3 than patients with DDD<3 at baseline evaluation,**  
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36 273 **independently from the final diagnosis (PA or EH).**  
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40 274 In our study, patients treated with MR antagonist or optimization of anti-hypertensive treatment  
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42 275 achieved blood pressure control by increase of drug treatment. On the counterpart, six months  
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44 276 after surgery, the mean DDD dropped to less than 1 in patients adrenalectomized. This  
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46 277 difference probably contributes to the significant improvement in QOL observed in patients  
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48 278 undergoing surgical treatment for unilateral PA, allowing a normalization of QOL scores in 7  
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50 279 of 8 domains, compared to healthy subjects.  
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54 280 Among patients with hypertension under anti-hypertensive treatment, the highest QOL in  
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56 281 physical component is encountered in those with SBP around 125 mmHg and DBP around 75  
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58 282 mmHg.<sup>34</sup> After surgery, adrenalectomized patients displayed lower blood pressure levels than  
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3 283 patients under MR antagonist or general anti-hypertensive treatment, with values close to the  
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5 284 figures reported above. Therefore, beyond reduction of anti-hypertensive treatment, the  
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7 285 achievement of lowest blood pressure could probably contribute to the better quality of life in  
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9 286 adrenalectomized patients.

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12 287 The importance of psychosocial stress in arterial hypertension has been largely evaluated in  
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14 288 the last decade. A recent study expanded this concept, introducing and highlighting the  
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16 289 importance of allostatic load in arterial hypertension.<sup>35</sup> Allostatic load is the reflection of  
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18 290 cumulative effects of daily life experiences, including ordinary and extra-ordinary events.<sup>36</sup>  
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20 291 Allostatic load is significantly more prevalent in patients with arterial hypertension than  
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22 292 individuals with normotension and patients with hypertension and allostatic load display  
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24 293 significantly decreased quality of life.<sup>35</sup> The role of allostatic load in PA has never been  
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26 294 evaluated. This aspect should probably be investigated in future studies to better elucidate the  
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28 295 development of impaired QOL in PA.

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31 296 Patients with PA treated with MR antagonist displayed a significant increase in the score  
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33 297 related to physical functioning and general health perceptions. In particular, the physical  
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35 298 functioning score was significantly higher after 6 months, compared to patients with EH treated  
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37 299 with medical treatment, without MR blockade. This finding may suggest a direct role of MR  
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39 300 antagonist in the improvement of physical functioning, beyond blood pressure control *per se*.  
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41 301 High aldosterone levels have been associated with significantly lower exercise capacity in  
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43 302 patients with chronic heart failure,<sup>37</sup> and spironolactone significantly improved exercise  
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45 303 tolerance.<sup>38</sup> Spironolactone may act by reduction of myocyte apoptosis and enhancing of  
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47 304 skeletal muscle contractility.<sup>39</sup>

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49 305 The limits of our study are the absence of a control group of patients with PA treated with  
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51 306 optimization of medical treatment without MR blockade, the absence of a control group of  
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53 307 patients with EH treated with MR antagonist, **the absence of a control group of normotensive**  
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3 308 subjects collected in the same setting and the lack of anxiety and depression symptoms  
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5 309 evaluation. The strengths and novelties of this study are the comparison of QOL of patients  
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7 310 with PA with matched patients with EH, the comparison of specific treatments for PA  
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9 311 (adrenalectomy and MR antagonist) *versus* optimization of medical treatment in a similar  
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11 312 group of patients, the diagnosis and subtype diagnosis of PA according to guidelines, and the  
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13 313 administration of the first questionnaire for QOL assessment before PA diagnosis.  
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17 314 In conclusion, patients with PA displayed lower QOL than healthy subjects, but not different  
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19 315 from matched patients with EH. Treating patients affected by APA with surgical adrenalectomy  
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21 316 allows a better control of blood pressure levels, with lower anti-hypertensive treatments,  
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23 317 reaching a significantly higher QOL at medium term follow up than medical therapy alone.  
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25 318 Treatment with MR antagonist allows a significant improvement in physical aspects of QOL  
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27 319 compared to optimization of medical therapy without MR blockade.  
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32

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34

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40 324 and M.T. collected data; F.B., M.A., J.B. analyzed data; S.M., P.M. and F.V. supervised the  
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42 325 entire study; F.B., G.C., S.M., P.M. wrote the original draft; all authors reviewed and edited  
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44 326 the final manuscript.  
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## 441 **Figure Legends**

442 **Figure 1.** Baseline QOL: PA vs. EH-matched controls and healthy subjects. Comparisons were  
443 performed by paired t-test for PA vs. EH and unpaired t-test for PA vs. healthy subjects.

444 QOL=quality of life, PA=primary aldosteronism, EH=essential hypertension, PF=physical  
445 functioning, RLP=role limitations due to physical problems, RLE=role limitations due to

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3 446 emotional problems, V=vitality, GMH=general mental health, SF=social functioning,  
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5 447 BP=bodily pain, GHP=general health perceptions. \* = significant at  $p<0.05$  PA vs. healthy  
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7 448 subjects.  
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12 450 **Figure 2.** Longitudinal comparison of QOL and cross-sectional comparison at 6 months in  
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14 451 patients with different treatments. Comparisons are considered significant at  $p<0.05$ . Figure  
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16 452 **2A-2B-2C:** \* = 6 months vs. Time 0, † = 2 months vs. Time 0. Figure **2D:** \* = adrenalectomy  
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18 453 vs. general anti-HT treatment, † = MR antagonist vs. general anti-HT treatment, ‡ =  
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20 454 adrenalectomy vs. MR antagonist. Estimated mean scores comparison have been performed by  
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22 455 linear mixed models (details in Supplemental Methods).  
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28 457 PF=physical functioning, RLP=role limitations due to physical problems, RLE=role limitations  
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30 458 due to emotional problems, V=vitality, GMH=general mental health, SF=social functioning,  
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32 459 BP=bodily pain, GHP=general health perceptions, MR=mineralocorticoid receptor, anti-  
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34 460 HT=anti-hypertensive.  
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40 462 **Figure 3.** Six months QOL: patients treated with ADX and MRA vs. healthy subjects. \* =  
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42 463 significant at  $p<0.05$  adrenalectomy vs. healthy subjects, † = MR antagonist vs. healthy  
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44 464 subjects. Comparisons were performed by unpaired t-test.  
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47 465 PF=physical functioning, RLP=role limitations due to physical problems, RLE=role limitations  
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49 466 due to emotional problems, V=vitality, GMH=general mental health, SF=social functioning,  
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51 467 BP=bodily pain, GHP=general health perceptions, MR=mineralocorticoid receptor.  
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**Table 1.** Descriptive Statistics

	<b>PA (n = 70)</b>	<b>EH (n=70)</b>	<b>p-value</b>
Age (years)	52±9	54±10	0.199
Sex			1.000
Male	45 (64.3)	45 (64.3)	
Female	25 (35.7)	25 (35.7)	
SBP (mmHg)	146±14	143±13	0.118
DBP (mmHg)	90±10	90±9	0.806
DDD	3.02±1.46	2.83±1.35	0.427
Duration of hypertension (years)	5 (1-10)	7 (1-16)	0.233
Creatinine (mg/dl)	0.87±0.21	0.91±0.19	0.385
Sodium (mmol/l)	141±2	142±2	0.103
Potassium (mmol/l)	3.6±0.5	4.1±0.4	<0.001
BMI (kg/m <sup>2</sup> )	25.9±4.1	26.9±5.4	0.196
Type 2 diabetes mellitus			0.698
No	67 (95.7)	66 (94.3)	
IFG	3 (4.3)	4 (5.7)	
Diabetes	-	-	
Presence of comorbidity by CCI	9 (12.8)	20 (28.6)	0.152

472 PA=primary aldosteronism, EH=essential hypertension, SBP=systolic blood pressure, DBP=diastolic  
473 blood pressure, DDD=daily defined dose, BMI=body mass index, IFG=impaired fasting glucose,  
474 CCI=Charlson Comorbidity Index. Comparisons were performed by unpaired *t*-test for continuous  
475 variables and  $\chi^2$  test for categorical variables.

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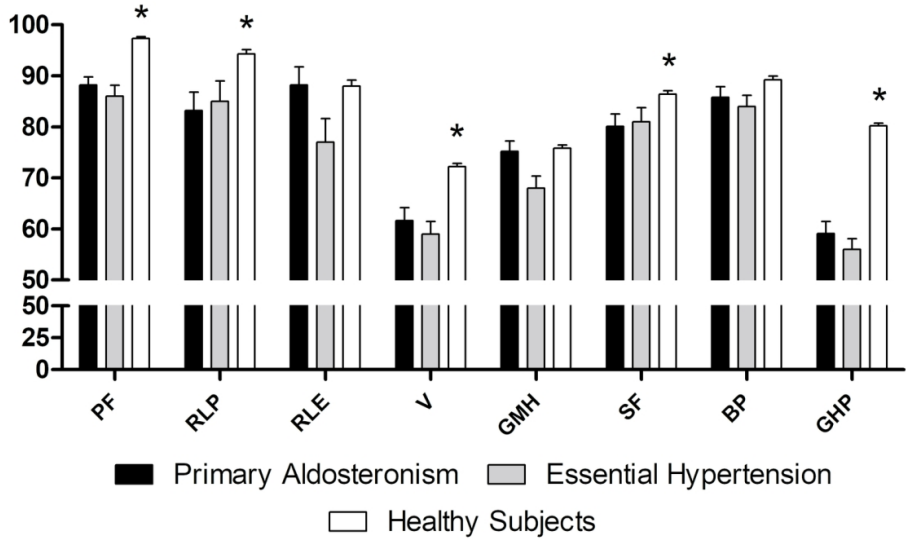


Figure 1. Baseline QOL: PA vs. EH-matched controls and healthy subjects.

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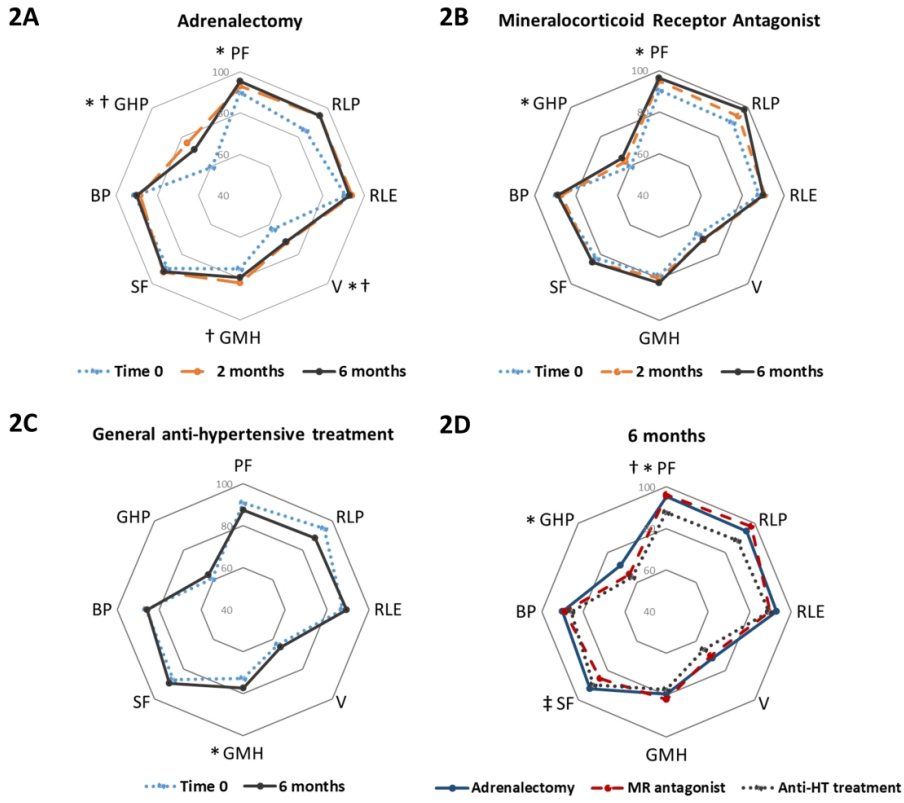


Figure 2. Longitudinal comparison of QOL and cross-sectional comparison at 6 months in patients with different treatments.

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