**Renal damage in primary aldosteronism: a systematic review and meta-analysis**

# Renal damage in primary aldosteronism: a sistematic review and meta-analysis

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## Abstract

**Objectives.** In experimental animal models, exogenous aldosterone excess has been linked to the progression of renal disease. However, the evidence of an increased risk of renal damage in patients affected by primary aldosteronism (PA) remains controversial. We aimed at evaluating the association between PA and renal damage through a meta-analysis.

**Methods.**We performed a quantitative review of studies evaluating parameters of renal function in patients affected by PA compared with patients affected by non-PA arterial hypertension and in patients affected by PA before and after specific treatment. We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from January 1960 up to August 2017.

**Results.** 44 studies including 4,467 patients with PA and 8,234 patients affected by non-PA arterial hypertension were included. After 8.5 years from hypertension diagnosis, patients with PA had an increased glomerular filtration (GFR) rate compared with non-PA hypertensive patients (by 3.93ml/min IQR [0.60; 7.26]) and a more severe albuminuria (Std. mean difference 0.57 [0.11-1.03]), resulting into a significant association with microalbuminuria (OR 2.15 [1.21; 3.84]). Following specific PA treatment, after a median follow-up of 12 months, a significant reduction in GFR was observed (by -10.91ml/min [-13.61; -8.21]) that was consistent in both patients surgically treated and patients treated with medical therapy. Similarly, a reduction in albumin excretion and an increase in serum creatinine were observed after treatment.

**Conclusions.** Patients affected by PA, compared with patients affected by non-PA arterial hypertension, display a more pronounced target organ damage, which can be mitigated by the specific treatment.

## Introduction

Aldosterone is the principal mineralocorticoid hormone in humans and plays a key role in water and electrolytes homeostasis and blood pressure regulation. According to the classical view of aldosterone actions, the distal nephron is its main target site: through the binding to the mineralocorticoid receptor (MR) aldosterone can promote sodium and water reabsorption and potassium excretion[1].

A large body of evidence supports a pathophysiological link between aldosterone excess, vascular and perivascular inflammation[2], oxidative stress[3] and fibrosis[4] in different animal models. Seminal studies indicate that exogenous administration of mineralocorticoids can induce thrombotic micro- angiopathy of both the medium-sized arteries and the arterioles, associated with ischemic modifications of the glomerular tufts with hyalinization and subsequent development of proteinuria[5,6].

Primary aldosteronism (PA), affecting 6% of the general hypertensive population[7], is the most frequent, but often overlooked[8] cause of secondary hypertension. Patients affected by PA (due to either an aldosterone producing adenoma – APA – or a bilateral adrenal hyperplasia – BAH -) are exposed to chronic aldosterone excess, which stimulates sodium reabsorption and volume expansion, thereby increasing renal perfusion pressure and stimulating glomerular hyperfiltration. Nonetheless, current evidence regarding a link between PA and an increased risk of renal damage is limited and controversial. In fact, while some old reports indicate a low prevalence of renal abnormalities in patients affected by PA[9] more recent studies point towards a partially reversible renal dysfunction[10]. Moreover, individual reports are often inadequate to assess this issue due to small sample size, to the different criteria to evaluate renal function and potential selection bias across studies.

Therefore, we performed a meta-analysis of observational epidemiological studies available in the literature, to ascertain the association between PA and renal damage and to evaluate the effect of a targeted treatment on the same parameters after an adequate follow-up.

## Methods

The present meta-analysis was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment[11] to the Quality of Reporting of Meta-analyses (QUOROM) statement[12], and the Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE)[13].

### Search strategy and selection criteria.

We sought MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials with terms related to PA (e.g., "primary aldosteronism" "hyperaldosteronism", "primary aldosteronism/hyperaldosteronism") and the following terms: "renal damage", "albuminuria", "hyperfiltration" limited to human studies from January 1960 up to August 2017.

Two authors independently evaluated the titles and/or the abstracts (S.M., E.S.) with divergences resolved after consensus and discussion with a third author (P.M.). If potentially pertinent, they were evaluated, by the same authors, as full-text reports according to the following criteria. Studies were included if a) investigating patients with PA compared with non-PA hypertensive patients (as a control group) and/or b) patients with PA before and after targeted treatment, and c) including any data on renal function; while exclusion criteria were (i) duplicate reports (in which case the manuscript reporting the largest sample of patients was selected) (ii) missing control group and (iii) inappropriate report or missing outcome data. We considered for the analysis the following parameters of renal function: i) serum creatinine, ii) estimated glomerular filtration rate (eGFR) or creatinine clearance, iii) quantitative albuminuria, iv) urinary albumin creatinine (uAC) ratio and v) presence of microalbuminuria and proteinuria.

## Study selection

## Data extraction and end-points

Two unblinded independent reviewers (S.M., and E.S.) extracted the following data on pre-specified reports: authors, journal, year of publication, location of the study group, design of the study and baseline features of included patients.

The two co-primary end-points were the eGFR difference between patients affected by PA and non-PA hypertensive patients and the eGFR difference before and after specific treatment for PA; difference in serum creatinine, quantitative evaluation of albuminuria, prevalence of microalbuminuria, proteinuria and uACR ratio were evaluated as secondary end-points.

## Internal validity and quality appraisal

Unblinded independent reviewers (S.M. and E.S.) evaluated the quality of the selected studies on pre-specified data collection forms using modified MOOSE criteria to take into account the specific features of included studies[13]. The independent reviewers separately appraised study design, setting, data source, and statistical methods for multivariable analysis, as well as risk of reporting, selection, and attrition bias (expressed as low, moderate, or high risk of bias).

## Data analysis and synthesis

Continuous variables are reported as mean (standard deviation) or median (IQR). Categorical variables are expressed as n/N (%). Considering the high likelihood of between-study variance, statistical pooling was performed according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals, using RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, and Copenhagen, Denmark). For albuminuria and uAC ratio, standard mean difference (SMD=mean difference between treatment groups divided by the standard deviation) was computed to account for the different Units across

studies. For interpreting the SMD the following indication can be used: small effect, SMD = 0.2; medium effect, SMD = 0.5; and large, SMD = 0.8[14]. A SMD of zero means no differences between the two evaluated treatments or groups. Publication bias was evaluated by graphical inspection of funnel plots. Standard hypothesis testing was set at the two-tailed 0.05 level. Null hypothesis of statistical homogeneity was refuted if $p<0.10$ at Cochran Q test, with I2 values of around 25%, 50%, and 75% representing, respectively, mild, moderate, and extensive statistical inconsistency. A meta-regression analysis with random effect model was performed to appraise the impact of the proportion of the diabetes and the duration of hypertension in each study on the eGFR difference between PA and non-PA hypertensive patients. This analysis was performed with Open meta analyst software.

## Results

The electronic search yielded 9,575 citations that were first evaluated for eligibility at title and/or abstract level (Figure 1).

Of the 105 full text reports assessed, 34 were excluded because of duplicate reports, 22 because not appropriate or with missing outcome data and 5 for lack of appropriate control group and. Finally, 44 studies were included in the analysis (Figure 1 and Supplemental material for complete references' list), to give a total of 4,467 patients with PA and 8,234 non-PA hypertensive patients. Characteristics of the studies included in the final meta-analysis are provided in Table 1. Thirty-five of the included studies investigated patients affected by PA compared with patients affected by non-PA hypertension, 16 investigated patients affected by PA (due to either APA or BAH) before and after targeted treatment and in 7 studies both investigations were available. In 14 out of 44 studies patients with different degree of renal impairment were excluded (Table 1) and two subgroups have been generated (i.e. "Renal disease excluded" and "Renal disease not

excluded”). Additionally, in 16 studies patients with PA and patients affected by non-PA arterial hypertension were matched for potential confounding variables, as detailed in Table S1.

Clinical and biochemical parameters of patients affected by EH and patients affected by PA are detailed in Table S2. The median age of patients with PA and non-PA patients was 50.0 and 51.0 years respectively, while the proportion of females were 45.9% and 44.3% respectively; the proportion of patients affected by diabetes mellitus was 15.7% and 10.5% and the median duration of hypertension were 8.5 and 6.8 years among patients affected by PA and non-PA patients.

**Primary aldosteronism and renal function**

To evaluate renal function in patients affected by PA compared to non-PA hypertensive patients we considered the following parameters: serum creatinine (µmol/L), creatinine clearance or eGFR (the different methods used to calculate/estimate the GFR across studies are detailed in Table S3), albuminuria (mg/day) and uAC ratio (mg/g).

Twenty-four studies comparing 2,702 patients with PA and 6,683 non-PA hypertensive patients showed no difference in mean creatinine values between the two diagnoses (mean difference 0.17 µmol/L [-2.09; 2.44 IQR]), consistently across studies in which patients with renal disease have been excluded or not, as depicted in Figure S1.

In 22 reports, including 2,740 patients with PA and 6,975 non-PA hypertensive patients, GFR data were available. When considering the clinical studies in which patients with renal disease were excluded, the mean GFR was not different between patients affected by PA and non-PA hypertensive patients (mean difference 1.22 mL/min [-3.37; 5.80]). However, when studies including patients with renal disease were considered, patients with PA showed a significantly higher mean GFR compared with non-PA hypertensive patients (by 5.69 ml/min [1.15; 10.22]) (Figure 2), resulting in a significantly higher values in the overall cohort of PA patients (by 3.93 ml/min [0.60; 7.26]).

Notably, urinary albumin excretion, was increased in patients with PA (Std. mean difference 0.57 [0.11;1.03] compared to patients with non-PA arterial hypertension (Figure S2), resulting into an increased risk of albuminuria (OR 2.15 [1.21-3.84]) (Figure S3) but not proteinuria (OR 1.66 [0.63; 4.38]) (Figure S4). Similarly, the uAC ratio did not differ significantly between patients affected by PA and non-PA hypertensive patients (Std. mean difference 0.13 [-0.22; 0.48] (Figure S5), possibly for the relatively low number of studies included in these analyses.

At funnel plot analysis (Figures S6-S9) no small study bias was graphically assessed.

Proportion of patients affected by diabetes across the studies and the duration of hypertension, which might represent important confounding factors while evaluating renal function, did not have a significant impact on the observed effect on GFR as demonstrated by meta-regression analysis (beta -0.011 [-0.163; 0.142] and -0.154 [-1.224; 0.916] respectively) (Figure S10 and S11).

**Renal function before and after PA treatment**

Given the increase in GFR and urinary albumin excretion, we aimed at evaluating the reversibility of the aldosterone-induced renal damage after institution of a targeted treatment for PA.

In an overall population of 1,504 PA patients, after a median follow-up of 12 months [6-24], we could observe a significant increase in serum creatinine (by 9.85 µmol/L [4.26; 15.44]) (Figure S12) and reduction in both the eGFR (by -10.91 ml/min [-13.61; -8.21]) (Figure 3) and the urinary albumin excretion (by -45.10 mg/day [-85.71;-4.50] (Figure S13).

Of note, as indicated by subgroup analysis, the observed effect on GFR was consistent in both surgically and medically treated patients (Figure 3).

## Assessment of publication bias and quality of the studies

None of the included studies was randomized; risk of selection bias is judged to be high in 17% of the studies and moderate in 15%, while the risk of reporting bias was low in 100% of the studies, as reported in Figure S14.

## Discussion

The present meta-analysis, aimed at investigating the renal damage in patients affected by PA, extends our previous findings of a significant association between hyperaldosteronism, cardiac target organ damage, cardio- and cerebrovascular events and metabolic comorbidities[15], further expanding the evidence of a detrimental role of aldosterone excess on the cardio-vascular system.

The main evidence gained from the present analysis is that patients with PA, compared with non-PA hypertensive patients, display a higher GFR (suggestive of glomerular hyperfiltration), which is significantly reduced by the specific treatment, either unilateral adrenalectomy or medical therapy with mineralocorticoid receptor antagonists.

Seminal studies reported that, in patients affected by PA, the renal function curve (pressure-natriuresis relationship) was shifted rightward, with a decrease in the slope[16], changes comparable to those reported in animal models[17]. Patients with PA also showed glomerular hyperfiltration and glomerular capillary hypertension[18], which might depend on a hemodynamic renal adaptation, based on the vasodilation of both afferent and efferent arterioles, as it has been described in renal micro puncture studies on experimental models of DOCA-salt hypertension rats[19].

Consistently with experimental data, patients with PA exhibit a decreased intrarenal vascular resistance and this alteration can be reverted by the introduction of a specific treatment[20]. Sechi et al. suggested that the increased urinary albumin excretion observed in patients affected by PA is ascribable to the glomerular hyperfiltration induced by aldosterone excess; therefore, either

unilateral adrenalectomy in case of an adenoma or treatment with mineralocorticoid receptor antagonists in bilateral PA, might represent the strategy to correct these hemodynamic alterations[20].

The hypothesis that the increased urinary albumin excretion in PA might be a consequence of the relative hyperfiltration, has been debated by some authors. Particularly, Rossi et al. suggested that the increased albuminuria might depend on endothelial dysfunction and the aldosterone-induced renal damage[21], as previously described in experimental and clinical studies[22,23]. In the kidney, aldosterone promotes inflammation[2], fibrosis[4], mesangial cell proliferation[24], podocyte injury[25] and endothelial dysfunction, which might be involved in the development of microalbuminuria[26]. Additionally, these data from experimental studies correlate with the findings from renal biopsies of glomerular damage in kidneys of patients with PA, associated with progressive glomerulosclerosis, tubulointerstitial inflammation and scarring, leading to proteinuria and progressive loss of renal function[27].

In our study, subgroup analysis showed that the increase in GFR and urinary albumin excretion observed in patients with PA is limited to those studies in which patients with a certain degree of renal impairment were not excluded. This finding indicates that relative hyperfiltration in PA might represent a functional adaptive mechanism secondary to the nephron loss, similarly to what occurs in focal segmental glomerulosclerosis[28]. Therefore, a plausible explanation for the increased albuminuria in PA patients can be, in our view, a synergic action of both mechanisms (glomerular hyperfiltration and aldosterone-induced renal damage).

According with the currently available guidelines[29,30], unilateral adrenalectomy and medical therapy with mineralocorticoid receptor antagonists are the recommended treatments for PA. The current study also aimed at evaluating the changes in renal function in patients with PA before and after the introduction of a specific treatment, showing a decrease in glomerular filtration, together with an increase in serum creatinine. On the basis of previous independent studies with similar results[10,31], in the latest years it has been postulated that the treatment of PA could worsen renal

function. However, the most accepted explanation is that PA treatment, abolishing the relative hyperfiltration, might unveil a previously deteriorated renal function[31,33]. Furthermore, our analysis showed a decrease in urinary albumin excretion following specific PA treatment, indicating that patients undergoing an appropriate treatment for PA could witness a slower progression of aldosterone-induced renal damage.

A recent large cohort study showed that PA patients treated with MR antagonists, compared with patients affected by essential hypertension, remain at increased risk for annual decline in eGFR and hence incident chronic kidney disease, while unilateral adrenalectomy effectively mitigate this risk[34]. Similarly, patients with PA on MRA therapy had an augmented risk of cardiovascular events and incident mortality, compared to those with EH, that was circumscribed to the patients whose plasma renin activity remained suppressed on MR antagonists therapy[35]. In our analysis, both unilateral adrenalectomy and medical therapy with MR antagonists showed a similar short-term effect on GFR reduction, however the lack of long-term follow-up data did not allow to compare the effect of adrenalectomy to a long-term therapy with MR antagonists on renal outcomes. We acknowledge that the overall number of studies included for the evaluation of some end-points, such as the risk of proteinuria and albuminuria, was small, making it difficult to draw robust conclusions for these variables.

In conclusion, the results of this meta-analysis show that patients with PA, compared with non-PA hypertensive patients, display a more prominent renal damage, which can be mitigated by the specific treatment (either surgical or medical) through a reduction in glomerular hyperfiltration and urinary albumin excretion. These data provide further strong evidence in favor of the detrimental role of aldosterone excess on the cardio-vascular system, corroborating the results of previous studies and demonstrating that patients affected by PA display less favorable outcomes than patients affected by essential hypertension[15,34,35]. Additionally, long term follow-up studies on large number of patients, aimed at directly compared the impact of medical and surgical approaches

on specific outcomes, including renal function, would be important to further improve the clinical management of patients affected by PA.

## Author contribution

All the authors significantly contributed to the study. S.M. and P.M. devised the study concept; S.M., E.S. and F.D.A. extracted the data; F.B. and F.D.A. performed the statistical analysis, S.M. and E.S. drafted the manuscript; P.M., F.V., L.A.S. and F.S. contributed to the interpretation of the results and critically revised the manuscript. Each author contributed important intellectual content during manuscript drafting or revision and accepts ac-countability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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## Conflict of interest

The authors declare no competing interests.

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1 **Table 1.** Characteristics of the included studies.

| Study ID | Country / years | Design of the study | Number of patients Type of comparison | Exclusion of patients with impaired renal function | Diabetes prevalence (%, PA/non-PA) |
|---|---|---|---|---|---|
| Catena C., 2007 | Italy 1994-2004 | Observational prospective | 56 PA compared with 323 matched non-PA hypertensive patients; 56 PA before and after treatment | Yes; if creatinine clearance <30 mL/min/1.73m$^2$ and/or proteinuria > 1 g | 0/0 (excluded) |
| Chiang W.F., 2013 | Taiwan 2002-2011 | Retrospective | 55 APA before and after treatment | No | 16 |
| Florczak E., 2013 | Poland 2009-2011 | Prospective | 32 PA compared with 155 RHT | Yes; if GFR < 60 mL/min | 18/10 |
| Fourkiotis V., 2013 | Germany 2008-2011 | Prospective multicenter | 29 PA before and after treatment | No | n.a. |
| Freel M., 2012 | Scotland n.a. | n.a. | 27 PA compared with 53 matched non-PA hypertensive patients | No | n.a. |
| Galetta F., 2009 | Italy n.a. | n.a. | 23 PA compared with 24 matched non-PA hypertensive patients | No | 0/0 |
| Halimi J.M., 1995 | France n.a. | Retrospective | 23 PA compared with 46 matched non-PA hypertensive patients | No. Patients were matched for renal function | n.a. |
| Hung C.S., 2013 | Taiwan 2006-2010 | Cross-sectional | 106 PA compared with 31 non-PA hypertensive patients | No | n.a. |
| Iacobellis G., 2010 | Italy 2002-2008 | Prospective | 75 PA compared with 192 non-PA hypertensive patients | Yes; patients with renal disease were excluded | 0/0 (excluded) |
| Iacobellis G., 2016 | Italy 2010-2014 | Prospective | 79 PA compared with 30 non-PA hypertensive patients | Yes; if serum creatinine > 133 µmol/L (1.5 mg/dl) or albuminuria > 300 mg/24 h) | 0/0 (excluded) |
| Iwakura Y., 2014 | Japan 2007-2010 | Prospective | 102 APA and 111 BAH before and after treatment | Yes; if primary renal diseases, diabetes with evident proteinuria, renal artery stenosis, renal cell carcinoma, or other urinary findings such as hematuria and urinary tract infection | 33 |
| Iwakura Y., 2016 | Japan 2009-2012 | Prospective | 94 APA compared with 100 non-PA hypertensive patients 94 APA before and after treatment | See Iwakura Y., 2014 | 14.9/7 |
| Jiang Y., 2016 | China 2009-2012 | Prospective | 242 PA compared with 120 matched non-PA hypertensive patients | No | n.a. |
| Kato J., 2005 | Japan | n.a. | 11 APA before and after treatment | No | n.a. |
| Kimura G., 1987 | Japan n.a. | n.a. | 6 APA before and after adrenalectomy | No | n.a. |
| Kimura G., 1996 | Japan n.a. | n.a. | 6 APA compared with 18 non-PA hypertensive | No | n.a. |

| | | | | | |
|---|---|---|---|---|---|
| | | | patients | | |
| Kobayashi H., 2017 | Japan<br>2006-2016 | Retrospective | 73 PA compared with 24 non-PA hypertensive patients | No | n.a. |
| Kramers B.J., 2017 | Netherlands<br>1972-2013 | Retrospective | 113 PA before and after treatment | No | n.a. |
| Liu G., 2014 | China<br>2008-2013 | n.a. | 50 PA compared with 51 matched non-PA hypertensive patients | Yes; if with moderate severe renal disease | 0/0 (excluded) |
| Luo Q., 2015 | China<br>2009-2011 | Prospective | 216 PA compared with 657 non-PA hypertensive patients | Yes; if GFR < 60 mL/min | n.a. |
| Matsumura K., 2006 | Japan<br>n.a. | n.a. | 25 APA compared with 29 non-PA hypertensive patients | No | n.a. |
| Monticone S., 2017 | Italy<br>2009-2014 | Prospective | 99 PA compared with 1573 non-PA hypertensive patients | No | 5.4/3.9 |
| Morillas P., 2008 | Spain<br>2005-2006 | Prospective | 11 PA compared with 172 non-PA hypertensive patients | No | 27.3/9.4 |
| Muiesan M.L., 2008 | Italy<br>1988-2002 | Retrospective | 125 PA compared with 125 matched non-PA hypertensive patients | No | n.a. |
| Mulatero P., 2013 | Italy<br>1992-2009 | Retrospective | 270 PA compared with 810 matched non-PA hypertensive patients;<br>270 PA before and after treatment | No | 4.1/4.1 matching criterion |
| Murase K., 2013 | Japan<br>2009-2012 | Retrospective | 14 PA compared with 110 non-PA hypertensive patients | No | 100/100 |
| Murata M., 2017 | Japan<br>2004-2015 | Retrospective<br>Multicenter | 292 PA compared with 498 non-PA hypertensive patients | No | 25.7/31.7 |
| Park K.S., 2017 | Korea<br>2000-2015 | Retrospective<br>Multicenter | 48 BAH and<br>221 APA before and after treatment | n.a. | n.a. |
| Pilz S., 2014 | Austria<br>2009-2011 | Prospective | 9 PA compared with 151 non-PA hypertensive patients | No | n.a. |
| Pimenta E., 2011 (1) | Australia<br>n.a. | Prospective<br>(?) | 21 PA compared with 21 matched non-PA hypertensive patients | No | n.a. |
| Pimenta E., 2011 (2) | Australia<br>n.a. | n.a. | 24 APA before and after treatment | No | 0 (excluded) |
| Reincke M., 2009 | Germany | Multicenter<br>Retrospective | 408 PA compared with 408 matched non-PA hypertensive patients | No | 20/15 |
| Ribstein J., 2005 | France<br>n.a. | Prospective | 25 PA compared with 25 matched non-PA hypertensive patients | Yes; if serum creatinine >115 mol/L (1.3 mg/dl) and/or estimated creatinine clearance < 90 mL/min | 0/0 (excluded) |
| Rosa J., 2012 | Czech Republic<br>n.a. | n.a. | 49 PA compared with 49 non-PA hypertensive patients | No | n.a. |
| Rossi G.P., 2006 | n.a.-2004 | Prospective<br>Multicenter | 31 APA and<br>33 BAH compared with | Yes; if serum creatinine >115 µmol/L (1.3 mg/d) | 0/0 (excluded) |

| | | | | | |
|---|---|---|---|---|---|
| | | | 426 non-PA hypertensive patients | and estimated creatinine clearance < 61 mL/min | |
| Savard S., 2013 | France 2001-2006 | Retrospective | 459 PA compared 1290 matched non-PA hypertensive patients | No | 17.1/14.3 |
| Sechi L.A., JAMA 2006 | Italy | | 50 PA compared with 100 non-PA hypertensive patients | Yes; if creatinine clearance <30 mL/min/1.73m$^2$ and/or proteinuria > 1 g/24h | 0/0 (excluded) |
| Sechi L.A., JCEM 2009 | Italy n.a. | Prospective | 54 PA (24 APA, 30 BAH) compared with 100 matched non-PA hypertensive patients | Yes; if creatinine clearance <30 mL/min/1.73m$^2$ and/or proteinuria > 1 g/24h | 0/0 (excluded) |
| Somloova Z., 2010 | Czech Republic 2002-2009 | Retrospective | 100 PA compared with 90 matched non-PA hypertensive patients | Yes; patients with renal failure were excluded | 20/22.2 |
| Takeda R., 1995 | Japan 1984-1987 | Prospective | 224 PA compared with 224 matched non-PA hypertensive patients | No | 0.4/0 |
| Tanase-Nakao K., 2014 | Japan 2006-2013 | n.a. | 45 PA compared with 31 non-PA hypertensive patients | Yes; if pre-operative eGFR < 60 ml/min/1.73 m$^2$ | 11.1/n.a. |
| Turchi F., 2014 | Italy 2003-2011 | Prospective | 66 PA compared with 132 matched non-PA hypertensive patients | No | 15/15 |
| Utsumi T., 2017 | Japan 1995-2014 | Retrospective | 130 APA before and after treatment | Yes; patients with primary renal disease were excluded | 15.4 |
| Wu V.C., 2011 Clin Chim Acta | Taiwan 2003-2007 | Prospective Multicenter | 330 PA compared with 246 non-PA hypertensive patients | No | 12.1/7.3 |

PA = patients with primary aldosteronism; APA = patients with aldosterone producing adenoma; RHT = patients with resistant hypertension; uACR = urinary albumin creatinine ratio; eGFR = estimated glomerular filtration rate; n.app. = not applicable; n.a. = not available; see Supplemental file for complete reference list.

## Figure Legends

**Figure 1.** Flow-chart of literature search and study selection.

**Figure 2.** Forest plot of GFR (ml/min) in patients affected by PA and patients affected by non-PA arterial hypertension. Central squares of each horizontal line represent the mean difference for each study. Horizontal lines indicate the range of the 95% confidence interval and the vertical line at zero indicates no difference between groups.

**Figure 3.** Forest plot of GFR (ml/min) in patients affected by PA before and after treatment, distinguishing between unilateral adrenalectomy and medical treatment. Central squares of each horizontal line represent the mean difference for each study. Horizontal lines indicate the range of the 95% confidence interval and the vertical line at zero indicates no difference between groups.

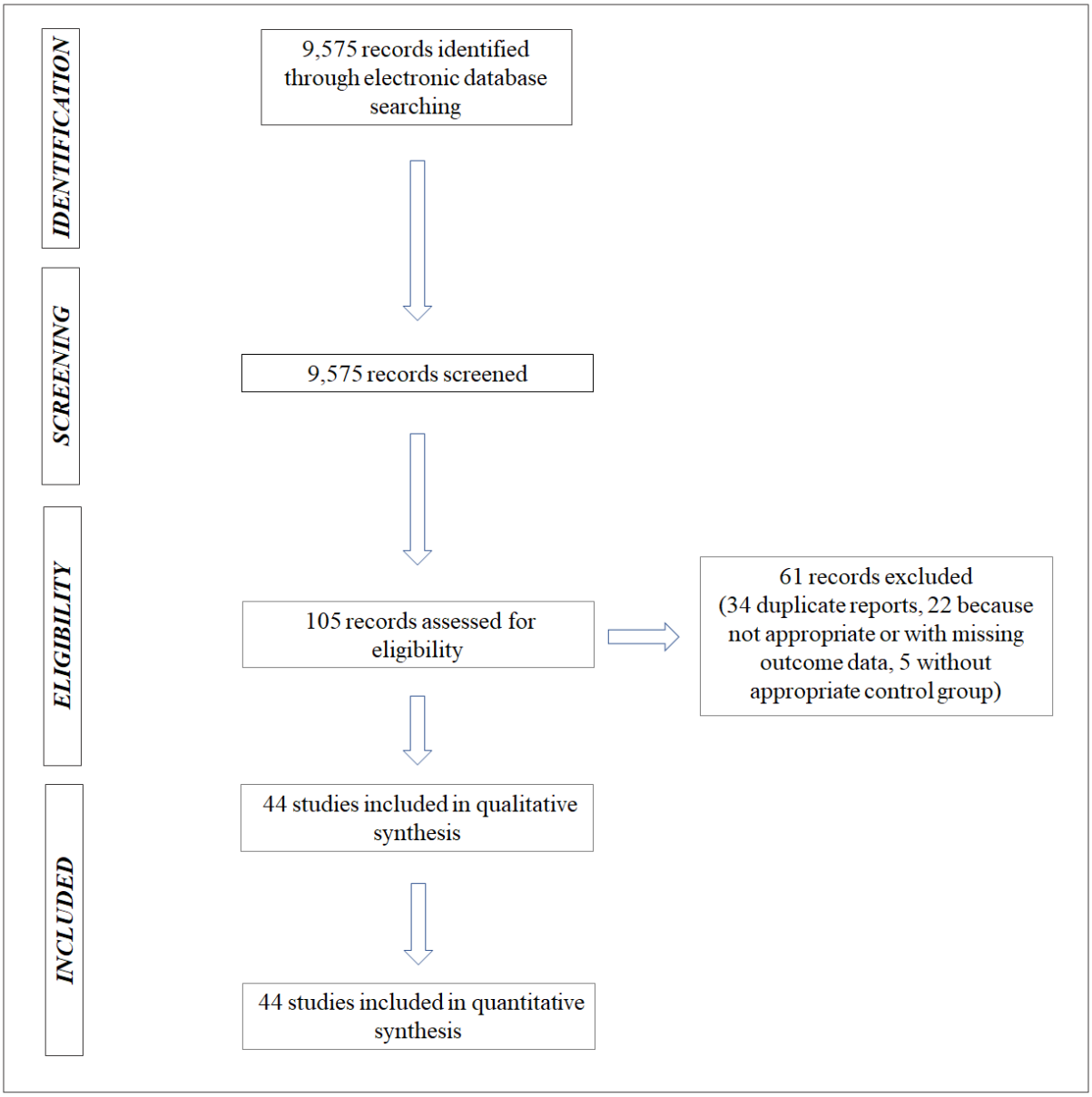
IDENTIFICATION
SCREENING
ELIGIBILITY
INCLUDED
9,575 records identified through electronic database searching
9,575 records screened
105 records assessed for eligibility
61 records excluded (34 duplicate reports, 22 because not appropriate or with missing outcome data, 5 without appropriate control group)
44 studies included in qualitative synthesis
44 studies included in quantitative synthesis

**Figure 1**

| Study or Subgroup | Primary aldosteronism Mean | SD | Total | Non-primary aldosteronism Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **Renal disease excluded** | | | | | | | | |
| Catena C., 2007 | 106 | 31 | 56 | 89 | 34 | 323 | 4.3% | 17.00 [8.07, 25.93] |
| Florczak E., 2013 | 92.1 | 25.4 | 32 | 91 | 19.5 | 155 | 4.2% | 1.10 [-8.22, 10.42] |
| Iwakura Y., 2016 | 78 | 19.39 | 94 | 83 | 20 | 100 | 5.3% | -5.00 [-10.54, 0.54] |
| Liu G., 2014 | 97.3 | 14.8 | 50 | 94.1 | 15.4 | 51 | 5.2% | 3.20 [-2.69, 9.09] |
| Luo Q., 2015 | 109.5 | 29.2 | 216 | 110.8 | 24.3 | 657 | 5.6% | -1.30 [-5.61, 3.01] |
| Ribstein J., 2005 | 102 | 15 | 25 | 95 | 15 | 25 | 4.5% | 7.00 [-1.32, 15.32] |
| Rossi G.P., 2006 | 85.52 | 16.83 | 64 | 92 | 20.64 | 426 | 5.5% | -6.48 [-11.05, -1.91] |
| Tanase-Nakao K., 2014 | 85.1 | 21.3 | 45 | 85.4 | 15.7 | 31 | 4.5% | -0.30 [-8.62, 8.02] |
| **Subtotal (95% CI)** | | | **582** | | | **1768** | **38.9%** | **1.22 [-3.37, 5.80]** |
| Heterogeneity: Tau² = 31.49; Chi² = 28.77, df = 7 (P = 0.0002); I² = 76% | | | | | | | | |
| Test for overall effect: Z = 0.52 (P = 0.60) | | | | | | | | |
| **Renal disease not excluded** | | | | | | | | |
| Freel M., 2012 | 110.1 | 26.8 | 27 | 116.1 | 33.9 | 53 | 3.0% | -6.00 [-19.62, 7.62] |
| Kimura G., 1996 | 128 | 24.5 | 6 | 84 | 12.7 | 18 | 1.9% | 44.00 [23.54, 64.46] |
| Kobayashi H., 2017 | 79.4 | 18 | 73 | 80.5 | 19.3 | 24 | 4.3% | -1.10 [-9.86, 7.66] |
| Monticone S., 2017 | 90.35 | 19.24 | 99 | 90.82 | 18.7 | 1482 | 5.7% | -0.47 [-4.38, 3.44] |
| Muiesan M.L., 2008 | 84 | 25 | 125 | 80 | 19 | 125 | 5.3% | 4.00 [-1.50, 9.50] |
| Mulatero P., 2013 | 105.38 | 32.79 | 246 | 84.46 | 29.49 | 737 | 5.5% | 20.92 [16.30, 25.54] |
| Murase K., 2013 | 65.26 | 17.47 | 14 | 61.6 | 27.69 | 110 | 3.8% | 3.66 [-6.85, 14.17] |
| Murata M., 2017 | 74.84 | 23.38 | 292 | 70.8 | 15.5 | 498 | 5.9% | 4.04 [1.03, 7.05] |
| Pilz S., 2014 | 84 | 15.2 | 9 | 82.1 | 19.1 | 151 | 3.9% | 1.90 [-8.49, 12.29] |
| Pimenta E., 2011 | 136.4 | 44.8 | 21 | 98.8 | 40.1 | 21 | 1.3% | 37.60 [11.88, 63.32] |
| Reincke M., 2009 | 65 | 16 | 408 | 68 | 15 | 408 | 6.0% | -3.00 [-5.13, -0.87] |
| Rosa J., 2012 | 132 | 36 | 49 | 126 | 36 | 49 | 2.9% | 6.00 [-8.26, 20.26] |
| Savard S., 2013 | 85.1 | 24.1 | 459 | 86.7 | 20.7 | 1285 | 6.0% | -1.60 [-4.08, 0.88] |
| Wu V.C., 2011 | 83.5 | 27.3 | 330 | 72.42 | 26.8 | 246 | 5.6% | 11.08 [6.62, 15.54] |
| **Subtotal (95% CI)** | | | **2158** | | | **5207** | **61.1%** | **5.69 [1.15, 10.22]** |
| Heterogeneity: Tau² = 54.56; Chi² = 139.22, df = 13 (P < 0.00001); I² = 91% | | | | | | | | |
| Test for overall effect: Z = 2.46 (P = 0.01) | | | | | | | | |
| **Total (95% CI)** | | | **2740** | | | **6975** | **100.0%** | **3.93 [0.60, 7.26]** |
| Heterogeneity: Tau² = 46.72; Chi² = 171.81, df = 21 (P < 0.00001); I² = 88% | | | | | | | | |
| Test for overall effect: Z = 2.31 (P = 0.02) | | | | | | | | |
| Test for subgroup differences: Chi² = 1.85, df = 1 (P = 0.17), I² = 45.8% | | | | | | | | |

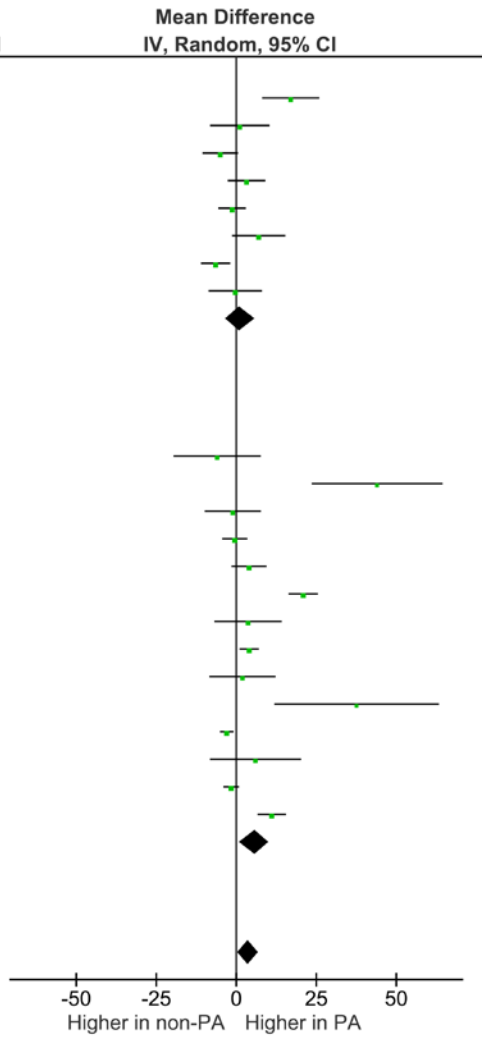


**Figure 2**

| Study or Subgroup | After treatment Mean | SD | Total | Before treatment Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **Adrenalectomy** | | | | | | | | |
| Catena C., 2007 | 87 | 30 | 25 | 105 | 30 | 25 | 2.1% | -18.00 [-34.63, -1.37] |
| Chiang W.F., 2013 | 78.98 | 33.27 | 55 | 93 | 30 | 55 | 3.5% | -14.02 [-25.86, -2.18] |
| Fourkiotis V., 2013 | 78.9 | 19.52 | 18 | 93 | 15.27 | 18 | 3.7% | -14.10 [-25.55, -2.65] |
| Iwakura Y., 2014 | 65 | 20.2 | 102 | 81 | 20.2 | 102 | 7.5% | -16.00 [-21.54, -10.46] |
| Kimura G., 1987 | 80 | 26.94 | 6 | 101 | 24.49 | 6 | 0.8% | -21.00 [-50.13, 8.13] |
| Kramers B.J., 2017 | 72.4 | 18.7 | 67 | 87.8 | 17.4 | 67 | 7.0% | -15.40 [-21.52, -9.28] |
| Mulatero P., 2013 | 86.24 | 26.64 | 20 | 104.57 | 37.46 | 32 | 2.0% | -18.33 [-35.79, -0.87] |
| Park K.S., 2017 | 70.5 | 21.3 | 206 | 81.3 | 22.9 | 206 | 8.5% | -10.80 [-15.07, -6.53] |
| Pimenta E., 2011(2) | 124.4 | 47.6 | 24 | 138.9 | 51.3 | 24 | 0.9% | -14.50 [-42.50, 13.50] |
| Reincke M., 2009 | 64 | 18 | 51 | 73 | 22 | 51 | 5.7% | -9.00 [-16.80, -1.20] |
| Utsumi T., 2017 | 64.7 | 17.3 | 130 | 81.5 | 20.5 | 130 | 8.3% | -16.80 [-21.41, -12.19] |
| Wu V.C., 2011 | 82.6 | 26.7 | 185 | 85.2 | 26.6 | 185 | 7.5% | -2.60 [-8.03, 2.83] |
| **Subtotal (95% CI)** | | | **889** | | | **901** | **57.4%** | **-12.70 [-16.00, -9.40]** |
| Heterogeneity: Tau² = 13.34; Chi² = 21.21, df = 11 (P = 0.03); I² = 48% | | | | | | | | |
| Test for overall effect: Z = 7.54 (P < 0.00001) | | | | | | | | |
| **Medical treatment** | | | | | | | | |
| Catena C., 2007 | 88 | 38.97 | 31 | 108 | 27.84 | 31 | 2.1% | -20.00 [-36.86, -3.14] |
| Fourkiotis V., 2013 | 86.6 | 21.89 | 11 | 95.5 | 12.93 | 11 | 2.5% | -8.90 [-23.92, 6.12] |
| Iwakura Y., 2014 | 69 | 21 | 111 | 79 | 21 | 111 | 7.5% | -10.00 [-15.52, -4.48] |
| Kramers B.J., 2017 | 78.6 | 17.9 | 56 | 89.8 | 17.9 | 56 | 6.6% | -11.20 [-17.83, -4.57] |
| Mulatero P., 2013 | 92.23 | 33.18 | 101 | 105.5 | 32.13 | 214 | 5.7% | -13.27 [-21.04, -5.50] |
| Park K.S., 2017 | 71.6 | 20.9 | 63 | 79.7 | 23.6 | 63 | 5.7% | -8.10 [-15.88, -0.32] |
| Reincke M., 2009 | 66 | 19 | 69 | 64 | 20 | 69 | 6.7% | 2.00 [-4.51, 8.51] |
| Wu V.C., 2011 | 81 | 26.6 | 101 | 87.4 | 27.4 | 101 | 5.9% | -6.40 [-13.85, 1.05] |
| **Subtotal (95% CI)** | | | **543** | | | **656** | **42.6%** | **-8.40 [-12.47, -4.33]** |
| Heterogeneity: Tau² = 16.52; Chi² = 14.37, df = 7 (P = 0.05); I² = 51% | | | | | | | | |
| Test for overall effect: Z = 4.04 (P < 0.0001) | | | | | | | | |
| **Total (95% CI)** | | | **1432** | | | **1557** | **100.0%** | **-10.91 [-13.61, -8.21]** |
| Heterogeneity: Tau² = 17.43; Chi² = 41.94, df = 19 (P = 0.002); I² = 55% | | | | | | | | |
| Test for overall effect: Z = 7.93 (P < 0.00001) | | | | | | | | |
| Test for subgroup differences: Chi² = 2.58, df = 1 (P = 0.11), I² = 61.3% | | | | | | | | |

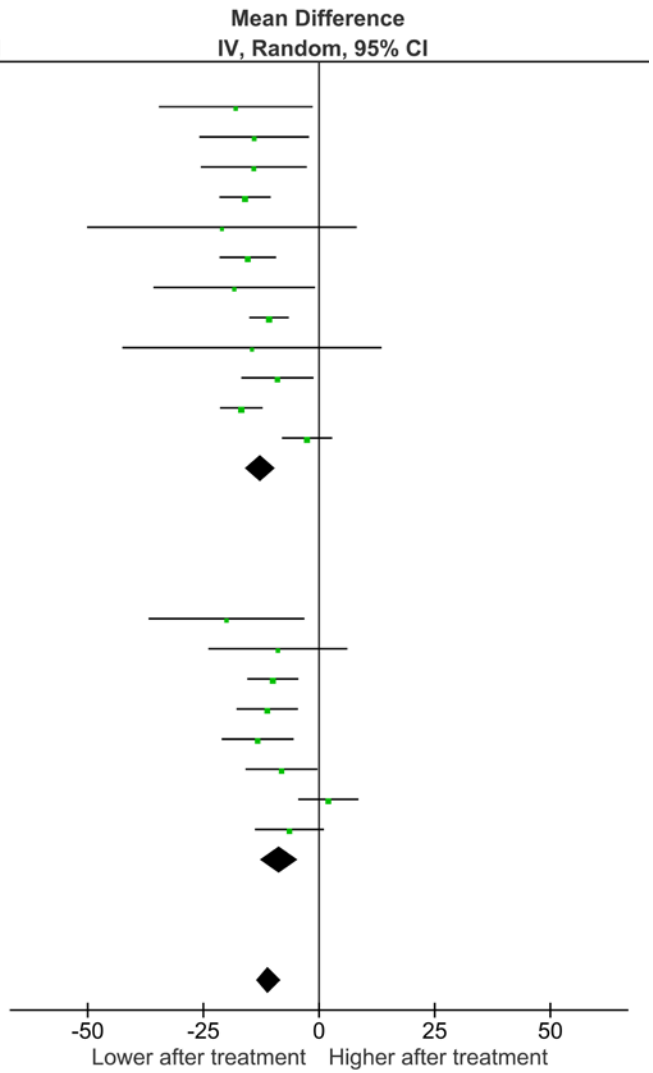


**Figure 3**