Study Heterogeneity and Estimation of Prevalence of Primary Aldosteronism: a Systematic Review and Meta-regression Analysis

Sabine C. Käyser*[1], Tanja Dekkers*[2], Hans J. Groenewoud[3], Gert Jan van der Wilt[3], J. Carel Bakx†[1], Mark C. van der Wel[1], Ad R. Hermus[2], Jacques W. Lenders[2,4], Jaap Deinum[2]

[1]Department of Primary and Community Care, [2]Department of Internal Medicine, [3]Department for Health Evidence, [1–3]Radboud University Medical Center, Nijmegen, The Netherlands, [4]Department of Internal Medicine III, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany.

Context: For health care planning and allocation of resources realistic estimation of the prevalence of primary aldosteronism is necessary. Reported prevalences of primary aldosteronism are highly variable, possibly due to study heterogeneity.

Objective: To identify and explain heterogeneity in studies that aimed to establish the prevalence of primary aldosteronism in hypertensive patients.

Data Sources: PubMed, EMBASE, Web of Science, Cochrane Library, and reference lists from 1–1–1990 to 31–1–2015.

Study Selection: Description of an adult hypertensive patient population with confirmed diagnosis of primary aldosteronism.

Data Extraction: Dual extraction and quality assessment.

Data Synthesis: 39 studies provided data on 42510 patients (9 studies, 5896 patients, from primary care). Prevalence estimates varied from 3.2 to 12.7% in primary care and from 1 to 29.8% in referral centers. Heterogeneity was too high to establish point estimates (I^2 = 57.6% in primary care and 97.1% in referral centers). Meta-regression analysis showed higher prevalences in studies 1. published after 2000; 2. from Australia; 3. aimed at assessing prevalence of secondary hypertension; 4. that were retrospective; 5. that selected consecutive patients; 6. not using a screening test. All studies had minor or major flaws.

Conclusions: This study demonstrates that it is pointless to claim low or high prevalence of primary aldosteronism based on published reports. Because of the significant impact of a diagnosis of primary aldosteronism on health care resources and the necessary facilities, our findings urge for a prevalence study whose design takes into account the factors identified in the meta-regression analysis.

Primary aldosteronism (PA) is assumed to be the most frequent form of secondary hypertension. However, the actual prevalence of PA is however a matter of continuing debate. Clarity regarding the prevalence of PA is highly relevant, as it has strong implications for future policy decisions concerning screening strategies for PA.

Identifying PA as the underlying cause of (therapy resistant) hypertension is considered important for two reasons. First, PA is associated with an increased rate of car-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received February 23, 2016. Accepted May 3, 2016.

Abbreviations:

diovascular complications (1–3). Second, specific treatment by mineralocorticoid receptor antagonists or adrenalectomy is effective in reducing these cardiovascular complications (4–6) and health costs (7). Therefore, an early diagnosis and treatment of PA are key for increasing the chance of improvement and even cure of hypertension, and for preventing cardiovascular complications (8–10).

In primary care centers, reported prevalences vary from 6 to 13%; in secondary care centers, prevalences of 23 to almost 30% have been reported (11–13).

In this article, we provide a systematic review and meta-analysis on the prevalence of PA in both primary care and referral centers, conducted according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology (MOOSE)) guidelines (14). In our attempt to obtain a reliable estimate of the prevalence of PA, we encountered substantial methodological heterogeneity. Therefore, we also set out to identify those factors that contribute to the wide variability in estimates of PA prevalence, using meta-regression analysis.

Materials and Methods

Data Sources and Searches

The objectives and methods of this meta-analysis, including databases which were to be searched, search terms, inclusion criteria and method of analysis were defined before the start of the review and not modified thereafter. Reporting of this systematic review is in accordance with the MOOSE statement, a structured checklist for reporting meta-analyses (14).

We conducted a systematic search on four electronic databases: PubMed, EMBASE, Web of Science and the Cochrane Library were searched for English, German, French, Spanish and Dutch articles on the prevalence of PA published between 1 January 1990 and 31 January 2015. We used the following search terms :

(*("Hyperaldosteronism"[Mesh]) OR (hyperaldosteronism[Title/Abstract]) OR (aldosteronism[Title/Abstract]) OR (Conn syndrome[Title/Abstract]) OR (Conns syndrome[Title/Abstract]) OR (Conn's syndrome[Title/Abstract]) OR (hyperaldosteronism[Other Term]) OR (aldosteronism[Other Term]) OR (Conn syndrome[Other Term]) OR (Conn's syndrome[Other Term])*)

AND

(*("Prevalence"[Mesh]) OR (prevalence[Title/Abstract]) OR (prevalences[Title/Abstract]) OR (occurrence[Title /Abstract]) OR (occurrences[Title/Abstract]) OR ("Incidence"[Mesh]) OR (incidence[Title/Abstract]) OR (incidences[Title/Abstract]) OR ("Epidemiology"[Mesh]) OR ("epidemiology"[Subheading]) OR (epidemiology [Title/Abstract]) OR (epidemiologic[Title/Abstract]) OR (epidemiological[Title/Abstract]) OR (prevalence [Other Term]) OR (prevalences[Other Term]) OR (incidence[Other Term]) OR (incidences[Other Term]) OR (occurrence[Other Term]) OR (occurrences[Other Term]) OR (epidemiology[Other Term]) OR (epidemiologic[Other Term]) OR (epidemiological[Other Term])*) (see Search in the Supplemental Data).

We checked reference lists of all provisionally included studies (ie, studies that were eligible for further assessment) and reviews for additional, relevant studies published in or after 1990. When articles could not be retrieved from electronic databases or national university archives, we contacted the corresponding authors.

We merged search results from the four databases and checked automatically and manually for duplicates (SK and TD). We used no restrictions other than language and year of publication. Studies published before 1990 were excluded to reduce excessive diversity in used assays, cut-off values and confirmation tests. The final literature search was performed on 17th February 2015.

Study Selection

Two researchers (SK and TD) independently assessed eligibility of retrieved articles on title and abstract. Full-text articles were retrieved if necessary.

Studies were considered eligible for inclusion if they met the following criteria:

1. Data presented as an original study, short report or letter on the prevalence of PA;
2. Prospective, retrospective or cross-sectional study design;
3. Study population of adult patients (≥18 years of age) with hypertension;
4. Use of a confirmation test (intravenous (IV) salt loading test (iv SLT), oral SLT, captopril suppression test, or fludrocortisone suppression test) to verify the diagnosis of PA (performed in at least 50% of the patients with positive screening test) (13).

Studies were excluded if:

1. The prevalence of PA was investigated in patient groups with a specific morbidity (eg, diabetes mellitus);
1. The article was a case-report;
2. The reported prevalences were solely based on aldosterone-renin ratio (ARR) or on another screening test, CT-scan results, adrenal venous sampling, blood pressure (BP) response to spironolactone or on postoperative histopathology reports.

Disagreements on eligibility were resolved by consensus among the two reviewers or, when necessary, by a third researcher (JD).

Data Extraction and Quality Assessment

Two researchers (SK and TD) independently scored all included studies on a data extraction form for author(s), year of publication, country, study design, health care setting (primary care or referral center), number of included patients, patient characteristics (gender, age, severity of hypertension), number of patients with hypokalemia, antihypertensive medication, screening method(s) with cut-off value(s), position during screening method (supine vs not supine), number of patients in whom screening was positive, confirmation method(s) with cut-off value(s), number of patients with a positive screening who underwent confirmation, the prevalence of PA, and if the study was included or excluded for analysis. Differences in extraction were resolved by consensus or, if necessary, by a third researcher (JD).

We contacted corresponding authors (by email or telephone) in case of missing or ambiguous information. If there was an indication that the same group of patients was used in multiple papers on PA prevalence, we contacted corresponding authors to

check. In case of multiple reports, we included the study in which the methods were reported in most detail.

After the final inclusion, SK and TD rated the methodological quality and risk of bias in individual studies using the "Methodological evaluation of Observational REsearch (MORE) – Observational Studies of Incidence or Prevalence of Chronic Diseases" protocol (15). This protocol comprises the following items:

1) Funding, ethical approval, conflict of interest;

2) Aim of the study and study design;

3) External validity: population, patient selection, inclusion criteria, sampling bias;

4) Internal validity: source of measurements, validation and reliability of estimates, type of outcome.

The MORE protocol provides a descriptive quality assessment of individual studies without an overall quality score.

Data Synthesis and Analysis

To estimate the prevalence of PA, we computed random effect pooled proportions for primary care and referral centers separately (16). Logit transformation was used to get quantities from prevalence.

To explore sources of heterogeneity, we performed random effects logistic regression analysis with prevalence of PA as dependent variable (17, 18). We based the choice of variables on controversies discussed in the Endocrine Society Guideline (13) and on our expectations of explanatory factors for bias in prevalence studies. We distinguished three categories of potential predictors of prevalence estimates:

1) Time: studies published in different periods (two categories: 1990 till 2000, and after 2000);

2) Geographic region where studies were performed: Asia, Australia, Europe, Latin America and United States of America (USA);

3) Factors concerning study design:

a. Data collection (prospective or retrospective);

b. Study objective (to assess the prevalence of PA, to assess the prevalence of secondary hypertension, other);

c. Method of patient selection (consecutive, convenience, self selection). We defined convenience as arbitrarily selected individuals from the target population other than general such that each individual had uncontrolled probability of selection (19);

d. Limited to therapy resistant hypertension or not;

e. Plasma potassium level at inclusion (normokalemia or hypokalemia (serum potassium $\leq$ 3.5 mmol/L));

f. Medication regimen (medication adjusted according to the Endocrine Society guideline, medication adjusted otherwise, only mineralocorticoid receptor antagonists (MRAs) discontinued or medication unchanged) (13);

g. Potassium level at confirmation testing (corrected hypokalemia or normokalemia);

h. Type of screening test (ARR-based test, no screening test, other screening test);

i. Number of screening tests (one test or multiple tests);

j. Patient position during screening tests (supine or not supine);

k. Cut-off levels used for screening tests (unrestrictive or restrictive). We included only studies using ARR-based tests. Unrestrictive was arbitrarily defined as an ARR cut-off value of 20–60 (aldosterone in ng/dL and renin in ng/mL/h); restrictive was defined as an ARR cut-off level of $>$ 60 or an ARR cut-off level of 20–60 with a plasma aldosterone level of $>$ 15 ng/dL and/or a suppressed renin level.

l. Percentage of patients with positive screening who underwent a confirmation test (100% or $\geq$ 80% or 50%–80%);

m. Type of confirmation test (iv SLT, oral SLT, captopril suppression test, fludrocortisone suppression test) (13);

n. Cut-off levels used for the iv SLT confirmation test (unrestrictive or restrictive). Unrestrictive was defined if the used cut-off level of plasma aldosterone after saline was $\geq$ 8 ng/dL, and restrictive if that cut-off level was $<$ 8 ng/dL. The number of studies concerning other confirmation tests were too low for analysis of the effects of different cut-off levels.

We explored the association of each of these factors with the estimate of the prevalence of PA individually in a univariate analysis. To correct for correlations between factors among studies, we built a model with the set of explanatory factors that remained significant in a multivariable model. We set the entry-level of potentially valid predictors for the model at $P = .10$. Because of the relatively low number of studies in primary care, we could only develop a model for referral centers.

Because sex is not considered a factor in the diagnosis of PA and studies were unselective with respect to gender, we did not take sex into account in the statistical analysis.

Association between predictive factors and the prevalence estimates of PA was reported as odds ratios (OR) and their 95% confidence intervals (CI). Prevalence of PA as predicted by the model was compared with the observed prevalence in the articles.

Statistical analysis

We used the statistical package Meta 4.1–0 in the program R version 3.1.3 (manufacturer: the R Foundation for Statistical Computing), to build forest plots and to compute the random effect pooled proportions. Package Meta 4.1–0 is specialized to perform meta-analyses. We also used the program SAS version 9.2 (manufacturer: SAS Institute Incorporated) to perform a random effect logistic regression analysis using Procedure Glimmix (Proc Glimmix). In this model the prevalence of PA is predicted by six explanatory variables. We used study as subject in the analysis, which means that the linear predictor contains an intercept term that randomly varies the level of the study.

Results

Search Results and Study Selection

The literature search in PubMed, EMBASE, Web of Science and the Cochrane Library provided 2614 articles, of which 1679 remained after removal of duplicate entries. After review of title and abstract, we excluded 1586 papers (Figure 1), with 93 potentially relevant articles remaining. By reference checking, four more articles were found of which one was also included. After full-text reading of all provisionally included articles, we excluded 60 articles (Supplemental Table 1). The main reason for exclusion was the lack of a confirmation test to verify the diagnosis of PA (31 studies). Two articles reported on more than one study, resulting in 39 studies (=patient cohorts) derived

from 36 articles. Overall concordance on (de)selection of studies between the two raters was high: inter-rater agreement was 95%, Cohen's kappa was 0.89 (0.79 – 0.99).

Prevalence of Primary Aldosteronism in Primary Care

Of the 39 studies included, nine were performed within a primary care setting (Table 1 and Supplemental Table 2). The number of patients included ranged from 52 to 3000 (median 347), with a total of 5896. PA prevalences ranged from 3.2% to 12.7%.

Prevalence of Primary Aldosteronism in Referral Centers

Thirty studies were conducted in hypertension referral centers, providing data for 36 614 patients (Table 1 and Supplemental Table 2). The number of included patients varied from 50 to 7343 (median 322.5). PA prevalence ranged from 1.0% to 29.8%.

Differences across Studies in the Reported Prevalence of Primary Aldosteronism

Forest plots show the weighted mean and the confidence intervals for the prevalence of PA (Figure 2 and Figure 3; Supplemental Figure 1). Heterogeneity (I^2) was large: in primary care, $I^2 = 57.6\%$ (0 – 78%); in referral centers, $I^2 = 97.1\%$ (96.7 – 97.5%). Therefore, we used meta-regression analysis to explore possible sources of heterogeneity (see below).

Prevalence of Hypokalemia in Patients with Primary Aldosteronism

Twenty-eight of the 39 studies reported the number of PA patients with hypokalemia. In primary care studies

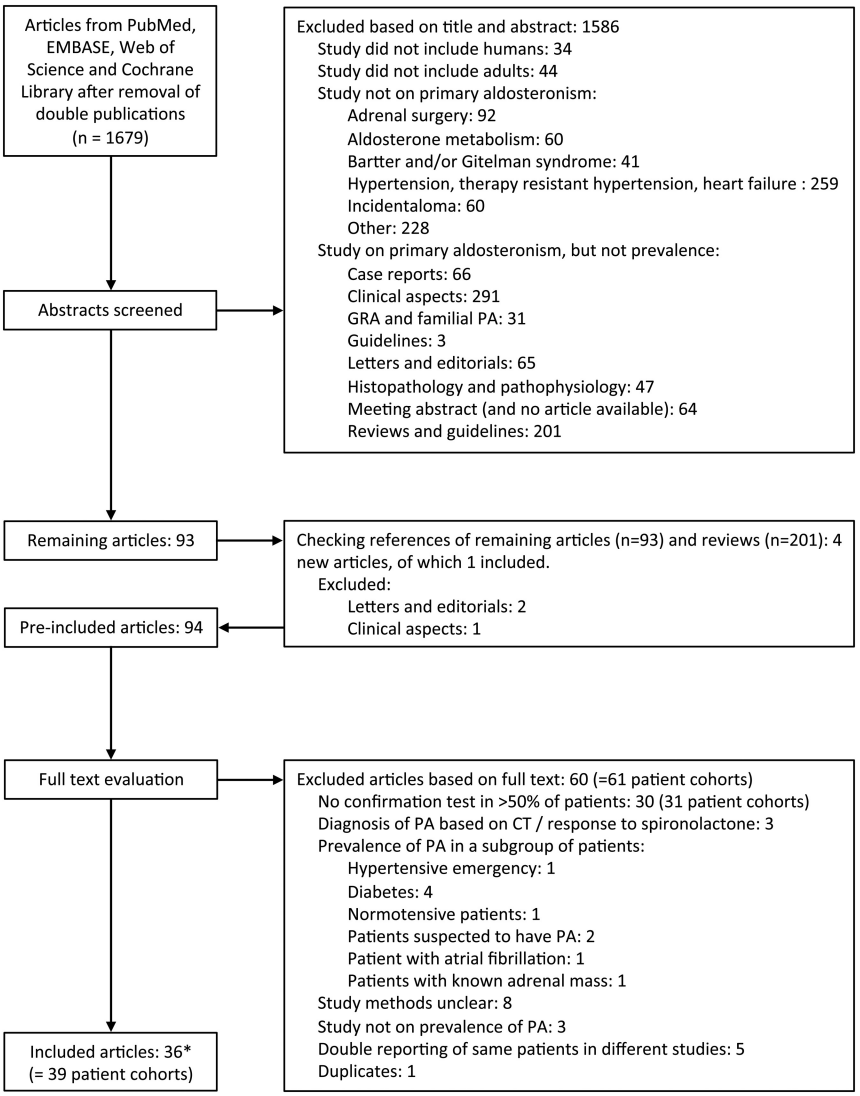

Figure 1. Flow Diagram of Studies Considered for Systematic Review *The 36 articles contain 39 studies (patient cohorts). Mulatero, 2004 (20) and Rossi, 1998 (21) report 5 respectively 3 cohorts of which 4 respectively 1 were included. The reason for exclusion for exclusion of the cohorts are explained in Supplemental Table 1. As a result 36 (included articles) + 60 (excluded articles) = 94.

Table 1. Summary of Studies on Prevalence of Primary Aldosteronism in Primary Care and Referral Centers

Author, year (ref)	Country	Setting	Design	Period	n	Population	Screening test	Confirmation test	Prevalence
Gordon, 1993 (22)[a]	Australia	PC	Prosp	NR	52	HT	ARR	FST	11.5%
Loh, 2000 (23)[a]	Singapore	PC	Prosp	1998	350	HT	ARR and PAC	IV SLT	4.6%
Mosso, 2003 (24)[a]	Chile	PC	Retro, prosp[b]	1998–2002	609	HT	ARR	FST	6.1%
Omura, 2004 (25)[a]	Japan	PC	Prosp	1995–1999	1020	New HT	PAC and PRA	Captopril test	6.0%
Schwartz, 2005 (26)[a]	USA	PC	Prosp	2000–2002	118	HT	No screening	Oral SLT	12.7%
Westerdahl, 2006 (27)	Sweden	PC	Cross	NR	200	HT	ARR	FST	8.5%
Williams, 2006 (28)[a]	USA	PC	Cross	1996–2005	347	HT	ARR and PAC	Oral SLT	3.2%
Fogari, 2007 (29)	Italy	PC	Prosp	1999–2002	3000	HT	ARR	IV SLT	5.9%
Westerdahl, 2011 (30)	Sweden	PC	Cross	NR	200	New HT	ARR	FST	5.5%
Anderson, 1994 (31)	USA	RC	Prosp	1976–1991	4429	HT	IV SLT	Oral SLT	1.4%
Gordon, 1994 (32)[a]	Australia	RC	Retro	1992–1993	199	HT	ARR	FST	8.5%
Abdelhamid, 1996 (33)	Germany	RC	Prosp	NR	3900	HT	Urinary aldo	IV SLT	6.6%
Brown,1996 (34)	Australia	RC	Prosp	1988–1992	74	HT	ARR	IV SLT and FST	2.7%
Rossi, 1998 (21)	Italy	RC	Prosp	NR	320	HT	ARR	IV SLT	5.9%
Lim, 2000 (35)[c]	UK	RC	Prosp	1995–1997	465	HT	ARR	FST	8,8%
Rossi, 2002 (36)	Italy	RC	Prosp	1997–1999	1046	HT	ARR post-captopril	IV SLT	6.3%
Trenkel, 2002 (37)	Germany	RC	Prosp	1997–1999	146	HT	ARR	IV SLT	1.4%
Martell, 2003 (38)[a]	Spain	RC	Prosp	2000–2002	50	RHT	No screening	IV SLT	15.9%
Stowasser, 2003 (39)[a]	Australia	RC	Prosp	2000–2002	300	HT	ARR	FST	18%
Strauch, 2003 (40)[a]	Czech Republic	RC	Retro	1997–2001	402	HT	ARR	IV SLT	19.2%
Calhoun, 2004 (41)	USA	RC	Prosp	2000–2002	114	RHT	Urinary aldo and PRA	Oral SLT	29.8%
Mulatero, 2004 (20)[d]	Italy	RC	Retro	1994–2002	7343	HT	ARR and PAC	IV SLT	8.0%
	USA	RC	Retro	1999	1112	HT	ARR and PAC	Oral SLT	10.8%
	Singapore	RC	Retro	1995–2001	3850	HT	ARR and PAC	IV SLT	4.6%
	Chile	RC	Retro	2000–2002	914	HT	ARR	FST	7.2%
Milliez, 2005 (1)[a]	France	RC	Prosp	1997–1999	5438	HT	ARR and PAC	Captopril test	2.3%
Nishizaka, 2005 (42)	USA	RC	Prosp	2000–2004	265	RHT	Urinary aldo	Oral SLT	21.9%
Rossi, 2006 (43)	Italy	RC	Prosp	2001–2004	1125	New HT	ARR[e]	Captopril test[f]	11.2%
Douma, 2008 (44)[a]	Greece	RC	Retro	1988–2008	1616	RHT	ARR and SAC	IV SLT and FST	11.3%
Morillas, 2008 (45)	Spain	RC	Prosp	2005–2006	183	HT	ARR and PAC	IV SLT	6.0%
Ribeiro, 2009 (46)	Brazil	RC	Prosp	2007	105	HT	ARR	IV SLT	1.0%
Di Murro, 2010 (47)[a]	Italy	RC	Retro	2007–2008	325	New HT	ARR and PAC	IV SLT	13.2%
Matrozova, 2010 (48)[a,g]	Bulgaria	RC	Prosp	2005–2008	376	HT	ARR and PAC	Captopril test	6,9%
Pedrosa, 2011 (49)	Brazil	RC	Cross	2008–2010	125	RHT	ARR	IV SLT	5.6%
Rios, 2011 (50)	Argentina	RC	Prosp	2006–2009	123	HT	ARR	IV SLT	6.5%
Sigurjonsdottir, 2012 (51)[a,h]	Sweden	RC	Prosp	2000–2003	122	HT	ARR and SA	Oral SLT	13,9%
Yin, 2012 (52)[a]	China	RC	Prosp	2007–2010	313	HT	ARR	Captopril and IV SLT	12.5%
Sang & Jiang, 2013 (53)[a]	China	RC	Cross	2010–2011	1656	RHT	ARR	IV SLT	7.1%
Jansen, 2014 (54)[a]	Netherlands	RC	Prosp	2006–2011	178	RHT	No screening	IV SLT	15.2%

Abbreviations: aldo, aldosterone; ARR, Aldosterone to Renin Ratio; Cross, Cross-sectional; FST, Fludrocortisone Suppression Test; HT, Hypertension; IV SLT, Intravenous Sodium Loading Test; n, number of patients; NR, Not Reported; Oral SLT, Oral Sodium Loading Test; PAC, Plasma Aldosterone Concentration; PC, Primary Care; PRA, Plasma Renin Activity; Prosp, Prospective; RC, Referral Center; ref, reference; Retro, Retrospective; RHT, Resistant Hypertension; SAC, Serum Aldosterone Concentration.

[a] Additional data received from author. [b] Study design: partly retrospective. [c] In this review, only patients who were assessed by our pre-defined inclusion criteria were included in the analysis (prevalence is 41/464 = 8.8%). However, usually when cited, a prevalence of 9.2% is reported (56). [d] Due to missing number of included patients, the study from Australia (Brisbane) is excluded. [e] ARR ≥40 and/or post-captopril ARR ≥30 and/or LDH-score ≥0.50. [f] ARR ≥40 plus post-captopril ARR ≥30 and/or LDH-score ≥ 0.50. [g] Patients who were analyzed because of an incidentaloma were excluded. [h] Patients studied in primary care were excluded due to <50% confirmation test.

hypokalemia was present in 0% to 37.5% of the patients with confirmed PA (n = 6). In referral centers hypokalemia ranged from 0% to 67% among patients with confirmed PA (n = 22). Five studies (two primary care studies (26, 28) and three studies from referral centers (32, 34, 38)) restricted inclusion to normokalemic patients (Supplemental Table 3).

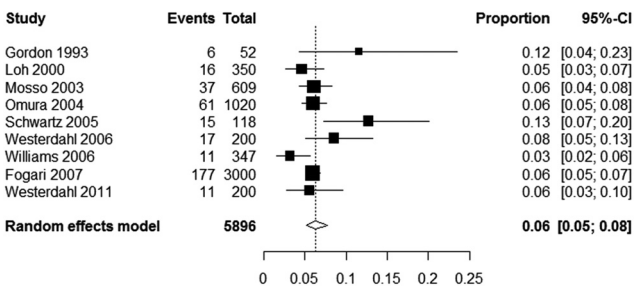

Figure 2.

Prevalence of Primary Aldosteronism in Patients with Varying Severity of Hypertension

Seven studies provided data on patients with resistant hypertension and 5 studies reported on the relation between prevalence of PA and severity of hypertension. The weighted man PA prevalence was 5.5%, 4.2%, 10.2% and 16.4% for high-normal BP, stage 1-, stage 2-, and stage 3-hypertension, respectively (20, 24, 43, 48, 50).

Differences in Diagnostic Methods

The methods and cut-offs used for screening and confirmation tests varied widely between the included studies.

The ARR with or without the use of an absolute level of plasma aldosterone, with varying cut-off values and restrictions, was used for screening in 29 of 39 studies. In 4 studies, no screening test was performed and in 6, other screening tests were used. For confirmation of PA were used: iv SLT (n = 20), oral SLT (n = 7), captopril suppression test (n = 5), fludrocortisone suppression test (n = 4), or a combination of two confirmation tests (n = 3).

Medication regimens during the diagnostic process were reported in most studies and varied from unaltered regimen to complete cessation of all hypertensive medication. In fifteen studies, medication regimen was based on the Endocrine Society Clinical Practice Guideline (13).

Quality Assessment

The results of the quality assessment using the MORE protocol showed that all studies had minor flaws including assessment of sampling bias and type of outcome. More importantly, five studies were classified as having a major flaw because of a patient exclusion rate of > 10%. For individual quality assessments, see Supplemental Table 4 and Supplemental Figure 2. Some descriptive items or items concerning internal and external validity were neither reported nor addressed in many studies such as role of funding, precision and reliability of estimates, and consideration of sampling bias.

Meta-regression Analysis

In primary care, univariate analysis showed a significant association between PA-prevalence and five factors: year of publication ($P < .001$), region ($P < .001$), study objective ($P < .001$), medication regimen ($P = .04$), and type of screening test (P=<0.001) (Supplemental Table 5). The highest prevalence estimates were found when the publication year was before 2000, when the study was performed in Australia, when the primary study objective was other than to assess the prevalence of PA, when medication regimen was unchanged, and when no screening test was performed.

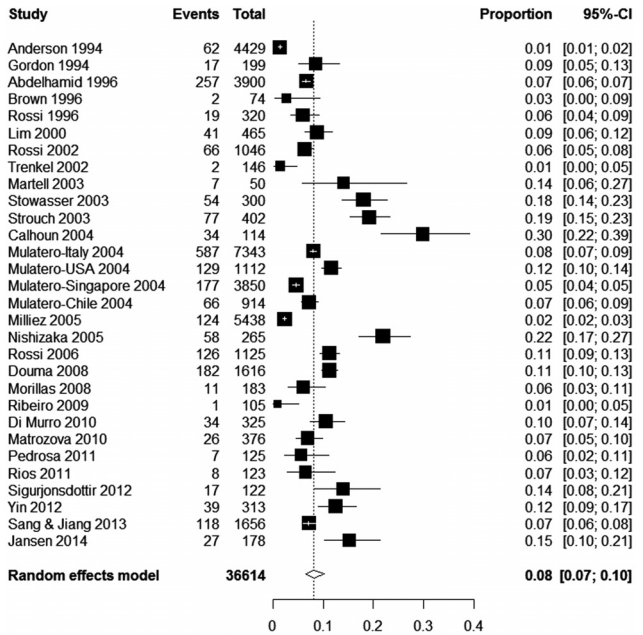

Figure 3. Abbreviations: GRA, Glucocorticold Remediable Aldosteronism; PA, Primary Aldosteronism.

Univariate Analysis

Univariate analysis in referral centers showed a significant association between PA-prevalence and five variables: year of publication ($P = .04$), study objective ($P = .02$), method of patient selection ($P < .0001$), type of hypertension ($P = .01$), and type of screening test ($P < .001$). The highest prevalence estimates were found when the year of publication was after 2000, when the primary study objective was other than to assess the prevalence of PA, when patient inclusion was consecutive, when the study population comprised patients with therapy resistant hypertension, and when no screening test was performed.

Multivariate Analysis

By combining the possible explanatory variables in a single model (only possible for referral centers), we found a set of six variables to independently affect the prevalence of PA: year of publication (P=<0.001), region ($P = .002$), study design ($P = .004$), study objective ($P = .044$), method of patient selection ($P < .001$), and type of screening test ($P = .02$) (Table 2). This model for referral centers showed the highest prevalence in studies that were performed after 2000, when the study was performed in Australia, when the study was retrospective, when the study objective was to assess the prevalence of secondary hypertension, when patient inclusion was consecutive, and in studies in which no screening test was performed.

In order to clarify the prediction of the random effect logistic regression model, we provide a table with examples how variation of the six explanatory variables affects the predicted prevalence (Supplemental Table 6).

Discussion

In this systematically performed review and meta-regression analysis we confirm the previously reported wide variations in prevalences, both in studies performed in the primary care setting (3.2–12.7%) and in those performed in referral centers (1.0–29.8%). While previous reviews and meta-analysis studies (57–59) reported mean prevalences, our study shows that it is pointless to provide point estimates in the absence of reporting contextual key factors. We established several factors that, at least partially,

Table 2. Solutions for the Fixed Effects of the Random Effect Logistic Regression Model in Referral Centers

Variable	Description OR	OR (95% CI)	Overall P-value
Publication Year	2000-current *vs.* 1990–2000	9.29 (3.17–27.16)	<0.001
Region	USA *vs.* Europe	4.88 (2.07–11.57)	0.002
	Latin America *vs.* Europe	0.53 (0.28–1.01)	
	Asia *vs.* Europe	1.50 (0.71–3.17)	
	Australia *vs.* Europe	5.57 (1.94–15.99)	
Study Design	Retrospective *vs.* Prospective	2.31 (1.39–3.84)	0.004
Study Objective	Prevalence PA *vs.* Other	1.71 (0.81–3.62)	0.044
	Prevalence Secondary HT *vs.* Other	2.83 (1.12–7.17)	
	Prevalence PA *vs.* Prevalence Secondary HT	0.60 (0.40–0.91)	
Patient Selection Method	Consecutive *vs.* Convenience	4.95 (1.82–13.48)	<0.001
	Self Selection *vs.* Convenience	3.40 (0.90–12.89)	
	Consecutive *vs.* Self Selection	1.46 (0.88–2.42)	
Screening Test	No Screening *vs.* Other	3.25 (1.51–7.01)	0.02
	ARR *vs.* Other	0.75 (0.39–1.43)	
	No Screening *vs.* ARR	4.36 (1.52–12.54)	

The model estimates the prevalence of PA as a function of the six above mentioned variables. The resulting ORs (according to the model) represent the ratios of the odds for PA of two groups.

Abbreviations: ARR, Aldosterone to Renin Ratio; HT, Hypertension; OR, Odds Ratio; PA, Primary Aldosteronism.

are responsible for the gross heterogeneity among studies on prevalence of primary aldosteronism.

In our analysis studies in referral centers published after 2000 showed a nearly 9-fold higher odds for the prevalence than studies before 2000, and this was independent from other factors. This might be explained by increasing awareness of the presence of primary aldosteronism over time.

The very first studies that investigated the prevalence of PA were performed in centers in Australia in self-selected patients or on the basis of retrospective data (22, 32). This might partially explain why studies from Australia have a more than 5.5-fold higher odds than those that were carried out in Europe. An alternative explanation is that the prevalence of PA is indeed higher in Australia. Studies performed in the USA also showed a nearly 5-fold higher odds. Whether this is due to the same reasons as may apply to Australian studies cannot be ascertained.

It is plausible that prospective studies are more appropriate to estimate prevalences. Our finding that retrospective studies report higher prevalences than prospective ones suggest that the current 'epidemic' of PA is partly explained by reliance on retrospective studies (60).

It is difficult to explain why studies that had the objective to assess the prevalence of secondary hypertension showed a nearly 3-fold higher prevalence of PA than studies that had other objectives, including studies that had the objective to assess specifically the prevalence of PA. However, the latter category was small and this may be a fortuitous finding.

The higher yield in the diagnosis of PA when testing consecutive patients than using other methods of patient selection is to be expected since less patients will be missed.

As a screening test, most studies (n = 20) used the ARR. The reliability of the ARR is disputed because of its susceptibility to disturbances by external factors, variable cut-off levels and its mediocre sensitivity and specificity (26, 54, 61, 62). This might explain why studies that did not use any screening test showed the highest prevalences. One can speculate that when using the ARR, some patients may be missed and this would argue for performing directly a confirmation test when attempting to detect PA.

Variation in Diagnostic Strategies

The test conditions, medication regimens and cut-offs used for screening and confirmation tests varied largely among the included studies. It is generally accepted that patients with an elevated ARR should undergo further confirmatory testing to establish the diagnosis of PA (13). For this reason, we chose to include only those studies that used some kind of confirmatory testing.

As use of medication can affect the laboratory results of plasma aldosterone, renin and ARR, the Endocrine Society guideline advocates adjustment of medication so that plasma aldosterone and renin are minimally affected. In contrast, several studies have suggested that screening and confirmation testing is still reliable when patients continue their antihypertensive medication during testing (63, 64). Our meta-regression model confirms that adjustment of medication regimen has no effect on the prevalence of PA. This challenges the Endocrine Society Guideline's recommendation (13).

Hypokalemia is often viewed as a clue to screen for PA although only about one third of the patients with PA presented with hypokalemia. The wide range of hypokalemia in the studies underlines that hypokalemia is not a prerequisite for further testing for PA. Moreover, (mild) hypokalemia may also reflect diuretic treatment of essential hypertension.

Importance of Proper Prevalence Estimates for Case Identification

As recently noted by Funder, considerably less than 1% of the hypertensive patients are screened for PA each year, not to mention diagnosed and properly treated (65). While the prevalence of PA remains under debate, undiagnosed and untreated PA has important medical implications, such as the detrimental effect on the cardiovascular and renal systems due to aldosterone (1–4, 66–74). Proper treatment of PA, both surgically or with medication, appears to reduce the risk of both cardiovascular and renal complications (71, 75). It is therefore self-evident that identifying PA in hypertensive patients has important benefits. In order to design a strategy for identification of PA or to allocate health care resources to PA, it is important to know the prevalence of PA among hypertensive patients. Although our study shows that this knowledge is currently insufficient, it also provides us with clues as to what factors cause underor overestimation of the prevalence of PA. Based on that, we would urge to perform a multicontinental prospective study in which consecutive hypertensive patients are screened for PA by a standardized confirmation test.

Limitations

We performed separate analyses for primary care and referral centers because the variables that determine the prevalence evidently differ between primary care and referral centers. Unfortunately, the model built with the set of explanatory factors derived from the univariate analysis, could only be used for the studies performed in the referral centers because of the relatively low number of studies in the primary care setting. A final limitation is that we did not exclude any articles by quality assessment because the validated protocol (MORE) we used for our quality assessment is not developed to 'weight' or to exclude studies. However, studies with a 'major flaw' according to the MORE-protocol, did not show higher or lower prevalences than studies without 'major flaws' (not shown).

Conclusions

This study of 5896 patients in primary care and 36 614 patients in referral centers demonstrates that the wide range in reported prevalences of primary aldosteronism is associated with year of publication, study region, study objective, modes of data collection, patient selection, and use of screening test. The heterogeneity of studies precludes a reliable estimate of the prevalence of PA. Because of the significant impact of a diagnosis of primary aldosteronism on health care resources and the necessary facilities, our findings urge for better designed prospective prevalence studies. Prerequisites for such a study are international or even intercontinental agreement on a uniform screening and a confirmation test. Next a survey by screening and, if screening is positive, a confirmation test for PA of all hypertensive patients should be performed, in both primary care and referral centers, with all untested patients being accounted for.

Acknowledgments

Address all correspondence and requests for reprints to: Jaap Deinum, MD, PhD, Radboud University Medical Center, Department of Internal Medicine, Postbus 9101, 6500 HB Nijmegen, The Netherlands, Phone: +31 24 361 88 19, Fax: +31 24 363 51 26, E-mail: jaap.deinum@radboudumc.nl.

* Both authors contributed equally to the work.

† Dr. C. Bakx died during the study.

Disclosure Summary: SK, TD, HG, GW, MW, and AH have nothing to declare. JD received a grant from the Dutch Organization for Health Research and Development (ZonMw, grant number 171 002 102) and participates in EU Horizon 2020 grant No. 633 983, ENSAT-HT. JL received a grant from the Dutch Organization for Health Research and Development (ZonMw, grant number 171 002 102) and from the Deutsche Forschungsgemeinschaft (LE 3660/1–1 KFO 252).

This work was supported by .

References

1. **Milliez P, Girerd X, Plouin PF, Blacher J, Safar ME, Mourad JJ.** Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. *J Am Coll Cardiol*. 2005;45:1243–1248.
2. **Abad-Cardiel M, Alvarez-Alvarez B, Luque-Fernandez L, Fernandez C, Fernandez-Cruz A, Martell-Claros N.** Hypertension caused by primary hyperaldosteronism: increased heart damage and cardiovascular risk. *Rev Esp Cardiol (Engl Ed)*. 2013;66:47–52.
3. **Mulatero P, Monticone S, Bertello C, Viola A, Tizzani D, Iannaccone A, Crudo V, Burrello J, Milan A, Rabbia F, Veglio F.** Long-term cardio- and cerebrovascular events in patients with primary aldosteronism. *J Clin Endocrinol Metab*. 2013;98:4826–4833.
4. **Catena C, Colussi G, Nadalini E, Chiuch A, Baroselli S, Lapenna R, Sechi LA.** Cardiovascular outcomes in patients with primary aldosteronism after treatment. *Arch Intern Med*. 2008;168:80–85.
5. **Rossi GP, Cesari M, Cuspidi C, Maiolino G, Cicala MV, Bisogni V, Mantero F, Pessina AC.** Long-term control of arterial hypertension and regression of left ventricular hypertrophy with treatment of primary aldosteronism. *Hypertension*. 2013;62:62–69.
6. **Turchi F, Ronconi V, di Tizio V, Ceccoli L, Boscaro M, Giacchetti G.** Primary aldosteronism and essential hypertension: Assessment of

cardiovascular risk at diagnosis and after treatment. *Nutr Metab Cardiovasc Dis*. 2013.
7. **Sywak M, Pasieka JL.** Long-term follow-up and cost benefit of adrenalectomy in patients with primary hyperaldosteronism. *Br J Surg*. 2002;89:1587–1593.
8. **Streeten DH, Anderson GH, Jr., Wagner S.** Effect of age on response of secondary hypertension to specific treatment. *Am J Hypertens*. 1990;3:360–365.
9. **Celen O, O'Brien MJ, Melby JC, Beazley RM.** Factors influencing outcome of surgery for primary aldosteronism. *Arch Surg*. 1996; 131:646–650.
10. **Sawka AM, Young WF, Thompson GB, Grant CS, Farley DR, Leibson C, van Heerden JA.** Primary aldosteronism: Factors associated with normalization of blood pressure after surgery. *Ann Intern Med*. 2001;135:258–261.
11. **Eide IK, Torjesen PA, Drolsum A, Babovic A, Lilledahl NP.** Low-renin status in therapy-resistant hypertension: a clue to efficient treatment. *J Hypertens*. 2004;22:2217–2226.
12. **Calhoun DA, Nishizaka MK, Zaman MA, Harding SM.** Aldosterone excretion among subjects with resistant hypertension and symptoms of sleep apnea. *Chest*. 2004;125:112–117.
13. **Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, Stowasser M, Young WF Jr.** The management of primary aldosteronism: case detection, diagnosis, and treatment of patients: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2016 [Epub ahead of print]
14. **Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB.** Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008–2012.
15. **Shmaliyan T, Ansari M. T., Raman G., Berkman N., Grant M., Janes G., Maglione M., Moher D., Nasser M., Robinson K., Segal J., Tsouros S.** Development and implementation of the standards for evaluating and reporting epidemiologic studies on chronic disease incidence or prevalence. *American journal of public health research*. 2013;1:183–190.
16. **DerSimonian R, Laird N.** Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
17. **Sutton AJ, Higgins JP.** Recent developments in meta-analysis. *Stat Med*. 2008;27:625–650.
18. **Thompson SG, Higgins JP.** How should meta-regression analyses be undertaken and interpreted? *Stat Med*. 2002;21:1559–1573.
19. **Shamliyan TA, Kane RL, Ansari MT, Raman G, Berkman ND, Grant M, Janes G, Maglione M, Moher D, Nasser M, Robinson KA, Segal JB, Tsouros S.** Development quality criteria to evaluate nontherapeutic studies of incidence, prevalence, or risk factors of chronic diseases: pilot study of new checklists. *J Clin Epidemiol*. 2011;64:637–657.
20. **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. *J Clin Endocrinol Metab*. 2004;89: 1045–1050.
21. **Rossi GP, Rossi E, Pavan E, Rosati N, Zecchel R, Semplicini A, Perazzoli F, Pessina AC.** Screening for primary aldosteronism with a logistic multivariate discriminant analysis. *Clin Endocrinol (Oxf)*. 1998;49:713–723.
22. **Gordon RD, Ziesak MD, Tunny TJ, Stowasser M, Klemm SA.** Evidence that primary aldosteronism may not be uncommon: 12% incidence among antihypertensive drug trial volunteers. *Clin Exp Pharmacol Physiol*. 1993;20:296–298.
23. **Loh KC, Koay ES, Khaw MC, Emmanuel SC, Young WF, Jr.** Prevalence of primary aldosteronism among Asian hypertensive patients in Singapore. *J Clin Endocrinol Metab*. 2000;85:2854–2859.
24. **Mosso L, Carvajal C, Gonzalez A, Barraza A, Avila F, Montero J, Huete A, Gederlini A, Fardella CE.** Primary aldosteronism and hypertensive disease. *Hypertension*. 2003;42:161–165.
25. **Omura M, Saito J, Yamaguchi K, Kakuta Y, Nishikawa T.** Prospective study on the prevalence of secondary hypertension among hypertensive patients visiting a general outpatient clinic in Japan. *Hypertens Res*. 2004;27:193–202.
26. **Schwartz GL, Turner ST.** Screening for primary aldosteronism in essential hypertension: diagnostic accuracy of the ratio of plasma aldosterone concentration to plasma renin activity. *Clin Chem*. 2005;51:386–394.
27. **Westerdahl C, Bergenfelz A, Isaksson A, Wihl A, Nerbrand C, Valdemarsson S.** High frequency of primary hyperaldosteronism among hypertensive patients from a primary care area in Sweden. *Scand J Prim Health Care*. 2006;24:154–159.
28. **Williams JS, Williams GH, Raji A, Jeunemaitre X, Brown NJ, Hopkins PN, Conlin PR.** Prevalence of primary hyperaldosteronism in mild to moderate hypertension without hypokalaemia. *J Hum Hypertens*. 2006;20:129–136.
29. **Fogari R, Preti P, Zoppi A, Rinaldi A, Fogari E, Mugellini A.** Prevalence of primary aldosteronism among unselected hypertensive patients: a prospective study based on the use of an aldosterone/renin ratio above 25 as a screening test. *Hypertens Res*. 2007;30:111–117.
30. **Westerdahl C, Bergenfelz A, Isaksson A, Nerbrand C, Valdemarsson S.** Primary aldosteronism among newly diagnosed and untreated hypertensive patients in a Swedish primary care area. *Scand J Prim Health Care*. 2011;29:57–62.
31. **Anderson GH, Jr., Blakeman N, Streeten DH.** The effect of age on prevalence of secondary forms of hypertension in 4429 consecutively referred patients. *J Hypertens*. 1994;12:609–615.
32. **Gordon RD, Stowasser M, Tunny TJ, Klemm SA, Rutherford JC.** High incidence of primary aldosteronism in 199 patients referred with hypertension. *Clin Exp Pharmacol Physiol*. 1994;21:315–318.
33. **Abdelhamid S, Muller-Lobeck H, Pahl S, Remberger K, Bonhof JA, Walb D, Rockel A.** Prevalence of adrenal and extra-adrenal Conn syndrome in hypertensive patients. *Arch Intern Med*. 1996;156: 1190–1195.
34. **Brown MA, Cramp HA, Zammit VC, Whitworth JA.** Primary hyperaldosteronism: a missed diagnosis in 'essential hypertensives'? *Aust N Z J Med*. 1996;26:533–538.
35. **Lim PO, Dow E, Brennan G, Jung RT, MacDonald TM.** High prevalence of primary aldosteronism in the Tayside hypertension clinic population. *J Hum Hypertens*. 2000;14:311–315.
36. **Rossi E, Regolisti G, Negro A, Sani C, Davoli S, Perazzoli F.** High prevalence of primary aldosteronism using postcaptopril plasma aldosterone to renin ratio as a screening test among Italian hypertensives. *Am J Hypertens*. 2002;15:896–902.
37. **Trenkel S, Seifarth C, Schobel H, Hahn EG, Hensen J.** Ratio of serum aldosterone to plasma renin concentration in essential hypertension and primary aldosteronism. *Experimental and Clinical Endocrinology, Diabetes*. 2002;110:80–85.
38. **Martell N, Rodriguez-Cerrillo M, Grobbee DE, Lopez-Eady MD, Fernandez-Pinilla C, Avila M, Fernandez-Cruz A, Luque M.** High prevalence of secondary hypertension and insulin resistance in patients with refractory hypertension. *Blood Press*. 2003;12:149–154.
39. **Stowasser M, Gordon RD, Gunasekera TG, Cowley DC, Ward G, Archibald C, Smithers BM.** High rate of detection of primary aldosteronism, including surgically treatable forms, after 'non-selective' screening of hypertensive patients. *J Hypertens*. 2003;21:2149–2157.
40. **Strauch B, Zelinka T, Hampf M, Bernhardt R, Widimsky J, Jr.** Prevalence of primary hyperaldosteronism in moderate to severe hypertension in the Central Europe region. *J Hum Hypertens*. 2003; 17:349–352.
41. **Calhoun D, Nishizaka M, Zaman A.** Low prevalence of white-coat hypertension in subjects with resistant hypertension and hyperaldosteronism. *J Hypertens*. 2004;22:S206–S206.
42. **Nishizaka MK, Pratt-Ubunama M, Zaman MA, Cofield S, Calhoun DA.** Validity of plasma aldosterone-to-renin activity ratio in African American and white subjects with resistant hypertension. *Am J Hypertens*. 2005;18:805–812.

43. **Rossi GP, Bernini G, Caliumi C, Desideri G, Fabris B, Ferri C, Ganzaroli C, Giacchetti G, Letizia C, Maccario M, Mallamaci F, Mannelli M, Mattarello MJ, Moretti A, Palumbo G, Parenti G, Porteri E, Semplicini A, Rizzoni D, Rossi E, Boscaro M, Pessina AC, Mantero F.** A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. *J Am Coll Cardiol*. 2006;48:2293–2300.
44. **Douma S, Petidis K, Doumas M, Papaefthimiou P, Triantafyllou A, Kartali N, Papadopoulos N, Vogiatzis K, Zamboulis C.** Prevalence of primary hyperaldosteronism in resistant hypertension: a retrospective observational study. *Lancet*. 2008;371:1921–1926.
45. **Morillas P, Castillo J, Quiles J, Nunez D, Guillen S, Bertomeu-Gonzalez V, Pomares F, Bertomeu V.** [Prevalence of primary aldosteronism in hypertensive patients and its effect on the heart]. *Rev Esp Cardiol*. 2008;61:418–421.
46. **Ribeiro MJ, Figueiredo Neto JA, Memoria EV, Lopes Mde C, Faria Mdos S, Salgado Filho N, Oliveira TC.** Prevalence of primary hyperaldosteronism in a systemic arterial hypertension league. *Arq Bras Cardiol*. 2009;92:39–45.
47. **Di Murro A, Petramala L, Cotesta D, Zinnamosca L, Crescenzi E, Marinelli C, Saponara M, Letizia C.** Renin-angiotensin-aldosterone system in patients with sleep apnoea: prevalence of primary aldosteronism. *J Renin Angiotensin Aldosterone Syst*. 2010;11:165–172.
48. **Matrozova JA, Zacharieva SZ, Kirilov GG, Boyanov MA.** Prevalence of primary aldosteronism among bulgarian hypertensive patients. *Central European Journal of Medicine*. 2010;5:399–405.
49. **Pedrosa RP, Drager LF, Gonzaga CC, Sousa MG, de Paula LK, Amaro AC, Amodeo C, Bortolotto LA, Krieger EM, Bradley TD, Lorenzi-Filho G.** Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. *Hypertension*. 2011;58:811–817.
50. **Rios MC, Izquierdo A, Sotelo M, Honnorat E, Rodriguez Cuimbra S, Catay E, Popescu BM.** [Aldosterone/renin ratio in the diagnosis of primary aldosteronism]. *Medicina (B Aires)*. 2011;71:525–530.
51. **Sigurjonsdottir HA, Gronowitz M, Andersson O, Eggertsen R, Herlitz H, Sakinis A, Wangberg B, Johannsson G.** Unilateral adrenal hyperplasia is a usual cause of primary hyperaldosteronism. Results from a Swedish screening study. *BMC Endocr Disord*. 2012;12:17.
52. **Yin G, Zhang S, Yan L, Wu M, Xu M, Li F, Cheng H.** Effect of age on aldosterone/renin ratio (ARR) and comparison of screening accuracy of ARR plus elevated serum aldosterone concentration for primary aldosteronism screening in different age groups. *Endocrine*. 2012;42:182–189.
53. **Sang X, Jiang Y, Wang W, Yan L, Zhao J, Peng Y, Gu W, Chen G, Liu W, Ning G.** Prevalence of and risk factors for primary aldosteronism among patients with resistant hypertension in China. *J Hypertens*. 2013;31:1465–1471; discussion 1471–1462.
54. **Jansen PM, van den Born BJ, Frenkel WJ, de Bruijne EL, Deinum J, Kerstens MN, Smulders YM, Woittiez AJ, Wijbenga JA, Zietse R, Danser AH, van den Meiracker AH.** Test characteristics of the aldosterone-to-renin ratio as a screening test for primary aldosteronism. *J Hypertens*. 2014;32:115–126.
55. **Fardella CE, Mosso L, Gomez-Sanchez C, Cortes P, Soto J, Gomez L, Pinto M, Huete A, Oestreicher E, Foradori A, Montero J.** Primary hyperaldosteronism in essential hypertensives: prevalence, biochemical profile, and molecular biology. *J Clin Endocrinol Metab*. 2000;85:1863–1867.
56. **Fardella CE, Mosso L.** Authors' response: Prevalence of primary aldosteronism in unselected hypertensive populations - Screening and definitive diagnosis. *J Clin Endocrinol Metab*. 2001;86:4003–4004.
57. **Jansen PM, Boomsma F, van den Meiracker AH, Dutch AI.** Aldosterone-to-renin ratio as a screening test for primary aldosteronism–the Dutch ARRAT Study. *Neth J Med*. 2008;66:220–228.
58. **Hannemann A, Wallaschofski H.** Prevalence of primary aldosteronism in patient's cohorts and in population-based studies–a review of the current literature. *Horm Metab Res*. 2012;44:157–162.
59. **Plouin PF, Amar L, Chatellier G.** Trends in the prevalence of primary aldosteronism, aldosterone-producing adenomas, and surgically correctable aldosterone-dependent hypertension. *Nephrol Dial Transplant*. 2004;19:774–777.
60. **Kaplan NM.** Is there an unrecognized epidemic of primary aldosteronism? *Con. Hypertension*. 2007;50:454–458; discussion 454–458.
61. **Gordon RD.** The challenge of more robust and reproducible methodology in screening for primary aldosteronism. *J Hypertens*. 2004;22:251–255.
62. **Tomaschitz A, Pilz S.** Aldosterone to renin ratio–a reliable screening tool for primary aldosteronism? *Horm Metab Res*. 2010;42:382–391.
63. **Seifarth C, Trenkel S, Schobel H, Hahn EG, Hensen J.** Influence of antihypertensive medication on aldosterone and renin concentration in the differential diagnosis of essential hypertension and primary aldosteronism. *Clin Endocrinol (Oxf)*. 2002;57:457–465.
64. **Mulatero P, Rabbia F, Milan A, Paglieri C, Morello F, Chiandussi L, Veglio F.** Drug effects on aldosterone/plasma renin activity ratio in primary aldosteronism. *Hypertension*. 2002;40:897–902.
65. **Funder JW.** Primary aldosteronism: clinical lateralization and costs. *J Clin Endocrinol Metab*. 2012;97:3450–3452.
66. **Reincke M, Rump LC, Quinkler M, Hahner S, Diederich S, Lorenz R, Seufert J, Schirpenbach C, Beuschlein F, Bidlingmaier M, Meisinger C, Holle R, Endres S, Participants of German Conn's R.** Risk factors associated with a low glomerular filtration rate in primary aldosteronism. *J Clin Endocrinol Metab*. 2009;94:869–875.
67. **Born-Frontsberg E, Reincke M, Rump LC, Hahner S, Diederich S, Lorenz R, Allolio B, Seufert J, Schirpenbach C, Beuschlein F, Bidlingmaier M, Endres S, Quinkler M, Participants of the German Conn's R.** Cardiovascular and cerebrovascular comorbidities of hypokalemic and normokalemic primary aldosteronism: results of the German Conn's Registry. *J Clin Endocrinol Metab*. 2009;94:1125–1130.
68. **Nishimura M, Uzu T, Fujii T, Kuroda S, Nakamura S, Inenaga T, Kimura G.** Cardiovascular complications in patients with primary aldosteronism. *Am J Kidney Dis*. 1999;33:261–266.
69. **Rossi GP, Cesari M, Cuspidi C, Cicala MV, Seccia MT, Mantero F, Pessina AC.** Changes of left ventricular filling indexes during long-term follow-up after adrenalectomy or medical treatment for primary aldosteronism. *Hypertension*. 2010;56(5):e78–e79.
70. **Tsioufis C, Tsiachris D, Dimitriadis K, Stougiannos P, Missovoutos P, Kakkavas A, Stefanadis C, Kallikazaros I.** Myocardial and aortic stiffening in the early course of primary aldosteronism. *Clin Cardiol*. 2008;31:431–436.
71. **Catena C, Colussi G, Lapenna R, Nadalini E, Chiuch A, Gianfagna P, Sechi LA.** Long-term cardiac effects of adrenalectomy or mineralocorticoid antagonists in patients with primary aldosteronism. *Hypertension*. 2007;50:911–918.
72. **Muiesan ML, Salvetti M, Paini A, Agabiti-Rosei C, Monteduro C, Galbassini G, Belotti E, Aggiusti C, Rizzoni D, Castellano M, Agabiti-Rosei E.** Inappropriate left ventricular mass in patients with primary aldosteronism. *Hypertension*. 2008;52:529–534.
73. **Rizzoni D, Muiesan ML, Porteri E, Salvetti M, Castellano M, Bettoni G, Tiberio G, Giulini SM, Monteduro C, Garavelli G, Agabiti-Rosei E.** Relations between cardiac and vascular structure in patients with primary and secondary hypertension. *J Am Coll Cardiol*. 1998;32:985–992.
74. **Holaj R, Zelinka T, Wichterle D, Petrak O, Strauch B, Widimsky J.** Increased intima-media thickness of the common carotid artery in primary aldosteronism in comparison with essential hypertension. *J Hypertens*. 2007;25:1451–1457.
75. **Catena C, Colussi G, Sechi LA.** Treatment of Primary Aldosteronism and Organ Protection. *Int J Endocrinol*. 2015;2015:597247.