Study Heterogeneity and Estimation of Prevalence of Primary Aldosteronism: A Systematic Review and Meta-Regression Analysis

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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: Our objective was 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 January 1, 1990, to January 31, 2015, were used as data sources.

Study Selection: Description of an adult hypertensive patient population with confirmed diagnosis of primary aldosteronism was included in this study.

Data Extraction: Dual extraction and quality assessment were the forms of data extraction.

Data Synthesis: Thirty-nine studies provided data on 42 510 patients (nine 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; 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, and 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. (***J Clin Endocrinol Metab*** **101: 2826–2835, 2016)**

Primary aldosteronism (PA) is assumed to be the most frequent form of secondary hypertension; however, the actual prevalence of PA is a matter of continuing debate. Clarity regarding the prevalence of PA is highly relevant because 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

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Abbreviations: ARR, aldosterone-renin ratio; MORE, Methodological Evaluation of Observational Research; PA, primary aldosteronism; SLT, salt-loading test.

reasons. First, PA is associated with an increased rate of cardiovascular 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 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 that 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 Meta-analysis of Observational Studies in Epidemiology 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; these were searched for English, German, French, Spanish, and Dutch articles on the prevalence of PA published between January 1, 1990, and January 31, 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])) (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 (S.C.K. and T.D.). We used no restrictions other than language and year of publication. Studies published before 1990 were excluded to reduce excessive diversity in used assays, cutoff values, and confirmation tests. The final literature search was performed on February 17, 2015.

Study selection

Two researchers (S.C.K. and T.D.) 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 (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);
2. The article was a case report;
3. The reported prevalences were solely based on aldosterone-renin ratio (ARR) or on another screening test, computed tomography scan results, adrenal venous sampling, blood pressure 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 (J.D.).

Data extraction and quality assessment

Two researchers (S.C.K. and T.D.) 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 cutoff value(s), position during screening method (supine vs not supine), number of patients in whom screening was positive, confirmation method(s) with cutoff 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 (J.D.).

We contacted corresponding authors (by e-mail 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, S.C.K. and T.D. 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;
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 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. Cutoff levels used for screening tests (unrestrictive or restrictive). We included only studies using ARR-based tests. Unrestrictive was arbitrarily defined as an ARR cutoff value of 20–60 (aldosterone in ng/dl and renin in ng/ml/h); restrictive was defined as an ARR cutoff level of more than 60 or an ARR cutoff level of 20–60 with a plasma aldosterone level of more than 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. Cutoff levels used for the IV SLT confirmation test (unrestrictive or restrictive). Unrestrictive was defined if the used cutoff level of plasma aldosterone after saline was at least 8 ng/dl, and restrictive if that cutoff level was lower than 8 ng/dl. The number of studies concerning other confirmation tests was too low for analysis of the effects of different cutoff 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 and their 95% confidence intervals. 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 (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 (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: interrater agreement was 95%, Cohen's kappa was 0.89 (0.79–0.99).

Prevalence of PA 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 PA 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 PA

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

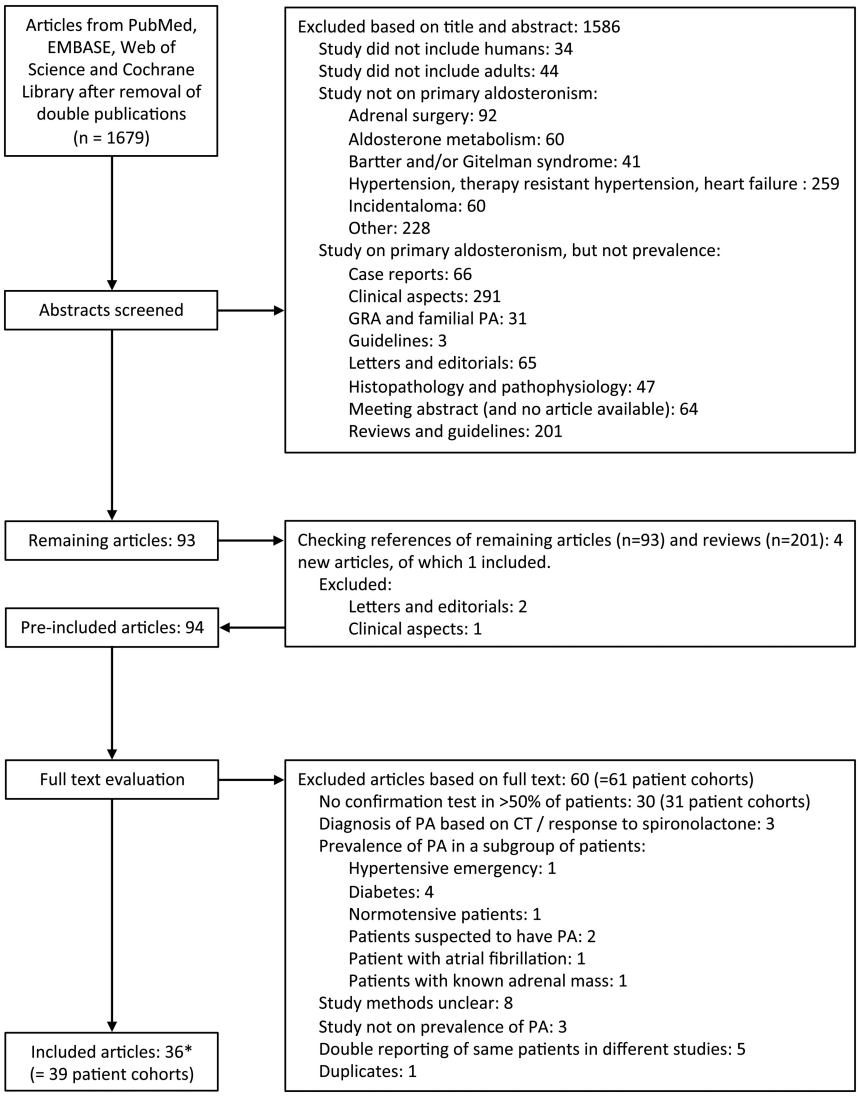

Figure 1. Flow diagram of studies considered for systematic review. Mulatero (20) and Rossi (21) report five and three cohorts, respectively, of which four and one, respectively, were included. The reason for exclusion of the cohorts are explained in Supplemental Table 1. As a result 36 (included articles) + 60 (excluded articles) = 94. *The 36 articles contain 39 studies (patient cohorts).

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]	United States	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]	United States	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)	United States	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)	United States	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
	United States	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)	United States	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, IV 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 predefined 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] Because of missing number of included patients, the study from Australia (Brisbane) is excluded.

[e] ARR ≥40 and/or post-captopril ARR ≥30 and/or LDF (logistic discriminant function) score ≥0.50.

[f] ARR ≥40 plus post-captopril ARR ≥30 and/or LDF score ≥ 0.50.

[g] Patients who were analyzed because of an incidentaloma were excluded.

[h] Patients studied in primary care were excluded because of a <50% confirmation test.

referral centers, I^2 = 97.1% (96.7–97.5%). Therefore, we used meta-regression analysis to explore possible sources of heterogeneity (see the following section).

Prevalence of hypokalemia in patients with PA

Twenty-eight of the 39 studies reported the number of PA patients with hypokalemia. In primary care studies, hypokalemia was present in 0–37.5% 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).

Prevalence of PA in patients with varying severity of hypertension

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

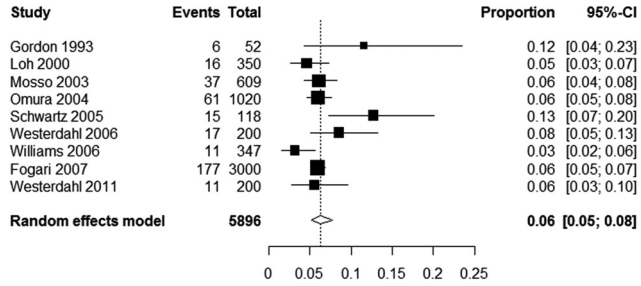

Figure 2. Forest plot for the prevalence of primary aldosteronism in primary care.

Differences in diagnostic methods

The methods and cutoffs 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 cutoff values and restrictions, was used for screening in 29 of 39 studies. In four studies, no screening test was performed and in six, 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 15 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 more than 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.

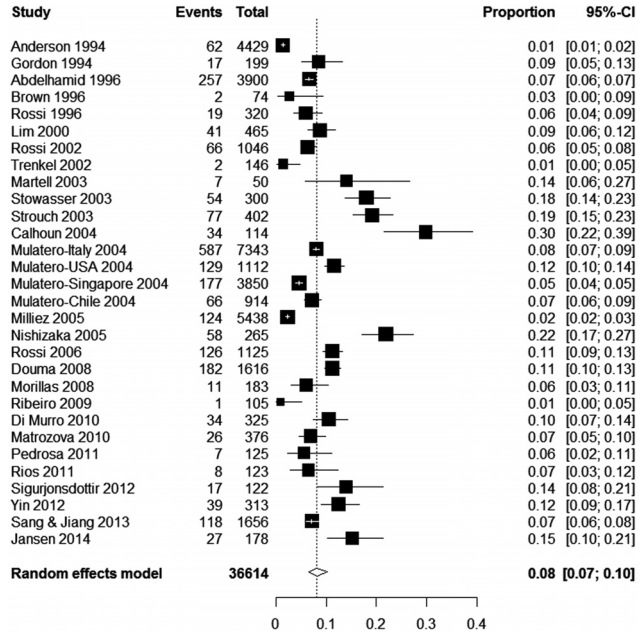

Figure 3. Forest plot for the prevalence of primary aldosteronism in referral centers. GRA, glucocorticoid remediable aldosteronism; PA, primary aldosteronism.

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 ($P < .001$) (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.

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 ($P < .001$), 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.

To clarify the prediction of the random effect logistic regression model, we provide a table with examples how

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)	<.001
Region	United States vs Europe	4.88 (2.07–11.57)	.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)	.004
Study objective	Prevalence PA vs other	1.71 (0.81–3.62)	.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)	<.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)	.02
	ARR vs other	0.75 (0.39–1.43)	
	No screening vs ARR	4.36 (1.52–12.54)	

Abbreviations: ARR, aldosterone to renin ratio; CI, confidence interval; HT, hypertension; OR, odds ratio; PA, primary aldosteronism.

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

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%). Although 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, 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 United States also showed 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 cutoff 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 cutoffs 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.

Because 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. 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 under or 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 in all hypertensive patients should be performed, in both primary care and referral centers, with all untested patients being accounted for.

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