Systematic Review and Meta-Analysis of the Prevalence of Resistant Hypertension in Treated Hypertensive Populations

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BACKGROUND
Although treatment-resistant hypertension (RH) is a serious burden on population health, there exists uncertainty about its prevalence. Hence, the objectives of this work were to systematically review and critically appraise the literature and to conduct a meta-analysis on the prevalence of RH in treated hypertensive populations.

METHODS
PubMed, Cochrane Library, CRD York databases, and study bibliographies were systematically searched for observational and interventional studies that report disease frequency in adult populations. The pooled prevalence was obtained through random-effect modeling. Furthermore, quality assessment, publication bias diagnostics, meta-regression, subgroup analysis by sex, and sensitivity analysis were performed.

RESULTS
Out of 318 retrieved studies, 20 observational studies and 4 randomized control trials (RCTs) with a total population of 961,035 were included. The random-effect method for observational studies and RCTs yielded RH prevalence ratios of 13.72% (95% confidence interval (CI) = 11.19%–16.24%) and 16.32% (95% CI = 10.68%–21.95%), respectively. Yet, most studies were incapable of ruling out pseudo-resistance caused by white-coat effect, poor medication adherence, and suboptimal dosing. Differences in RH prevalence by sex were negligible. Meta-regression analysis showed that study-level characteristics had no statistically significant influence on RH prevalence. The inclusion of further studies in the sensitivity analysis concurred with the baseline results (13.19%; 95% CI = 10.89%–15.49%).

CONCLUSIONS
Researchers should enhance comparability of future empirical evidence through homogeneous methodologies and comparable baseline populations. This meta-analysis concludes that RH is a frequent phenomenon and further harmonization in terms of RH definition and measurement would be necessary to clearly distinguish true treatment resistance from pseudo-resistance.

Keywords: blood pressure; epidemiology; hypertension; meta-analysis; prevalence; refractory hypertension; resistant hypertension.

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Hypertension is one of the most common chronic diseases worldwide. Its complications, including stroke and heart failure, are leading causes of morbidity and mortality.[1] A reduction in blood pressure (BP) significantly reduces cardiovascular morbidity and mortality. Still, great proportions of the treated hypertensive population cannot achieve long-term BP control (≤140/90 mm Hg).[2] Treatment-resistant hypertension (RH) has been increasingly identified as a reason for uncontrolled BP. RH is associated with end-organ damage and with a rise in cardiovascular risk compared with treatment-responding hypertension.[2,3]

Despite the growing importance of RH from a clinical, public health, and economic viewpoint, currently available treatment options are limited. Promising treatments such as vasopeptidase inhibition with omapatrilat, direct renin inhibition with aliskiren, vaccination, or renal denervation could not convince in clinical trials,[4–6] and big pharmaceutical players have recently announced that they will discontinue drug development for cardiovascular diseases.[7] Funding agencies and pharmaceutical companies need to decide whether to channel research and development resources into other, more promising areas, such as Alzheimer's disease or cancer. To answer the question of whether there is a need to develop new treatment approaches for RH, the true disease prevalence must be known. Until now, however, no robust prevalence estimates exist, with current estimates ranging between 2%[8] and 34%.[9] Hence, the goals of this article are (i) to systematically review and to critically appraise the methodological and study design–related aspects of the literature on RH and (ii) to estimate a pooled prevalence of RH in the treated hypertensive population.

METHODS

Search strategy

The goal of the search was to find observational and interventional studies that report prevalence of RH in treated, essential hypertensive adult patients. A search strategy was implemented using PubMed, CENTRAL, and CRD York,

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as well as Internet search engines (Google Scholar) and study bibliographies for manual searches (28 August 2013). Different query groups were individually created using free-text as well as MeSH-terms (refractory hypertension, resistant hypertension, epidemiology, prevalence, incidence, prognosis) and were finally combined into a single search. No restrictions were imposed on the year of study publication or follow-up period. Articles in English, German, Spanish, French, and Russian language were considered. Full-text published articles and abstracts from peer-reviewed journals only were eligible for inclusion.

Study selection

Three reviewers (D.A., U.W., S.F.) independently screened the search results, excluded irrelevant publications based on title and abstract, obtained full-text versions of potentially appropriate studies, and assessed them for eligibility. Observational and interventional studies that measure the prevalence of RH in a treated, essentially hypertensive population (aged ≥18 years) were included. Inclusion required that articles determine treatment resistance by taking into account both antihypertensive medication regimen and systolic/diastolic BP. Owing to the varying definitions of treatment resistance,[2] the 2 most common definitions were admissible: (i) uncontrolled BP (≥140/90 mm Hg) despite antihypertensive regimen of ≥3 medications of different classes or (ii) uncontrolled BP (≥140/90 mm Hg) despite antihypertensive regimen of ≥3 medications of different classes (including diuretics) or treatment with ≥4 antihypertensive agents of different classes irrespective of BP values (definition of the American Heart Association (AHA)).[10] If an explicit definition of RH was not provided in a particular study, it was still suitable for inclusion if the presentation of its data allowed us to calculate the prevalence of RH according to 1 of the 2 definitions. Publications that examined pregnant individuals or populations exclusively with secondary RH (e.g., in the course of chronic kidney diseases (CKD)) were excluded. Likewise, studies that sampled RH patients only were not applicable. If multiple articles were published from the same population sample, the most informative article was included. Disagreements between the 3 reviewers about inclusion and exclusion were solved by discussion and consensus.

Data extraction and quality assessment

Study authors (D.A., U.W., S.F.) independently extracted data and assessed study quality. Information about the study design, location (countries/region of the study, clinical care setting), methodology (patient recruitment, definition and diagnostic method for RH), population characteristics (sample size, mean age, sex distribution, mean systolic/diastolic BP), and completeness of follow-up were extracted in a standardized form. Whenever studies reported the prevalence of true RH, these figures were preferred to prevalence of apparent RH. In case mean population measures and their respective SDs, such as age, were only presented for subgroups but not for the complete study sample, these values were combined to 1 overall measure for the whole sample. When the original authors did not specify the BP measurement technique (auscultatory or oscillatory method) but referred to a guideline, it was assumed that the technique endorsed in the guideline was applied. Original authors were contacted in the event more detailed information about their publications was needed.

An assessment of the quality of included studies was conducted with a checklist for prevalence studies adapted from Loney *et al*.[11] The quality assessment rests upon 3 conceptual (sampling method, sampling frame, sample size), 2 analytical (method of outcome measurement, analytical bias), and 3 descriptive criteria (description of refusers, confidence intervals/subgroup analysis, description of study population) of the studies.

Data synthesis and statistical analysis

Statistical analysis was executed in R using the meta package. The results are presented in Forest plots. If not indicated otherwise by the original author (e.g., due to weighting of units in the original sample), the prevalence was calculated by dividing the number of individuals with RH by the total number of treated hypertensives. Confidence intervals (95% CIs) were calculated for each prevalence point estimate. The pooling was performed using the random-effect model (REM). Fixed-effects modeling was not applied because it presumes that all studies are functionally equivalent (i.e., all factors (e.g., population age) that could influence RH prevalence are basically identical in all of the studies and, consequently, the difference in prevalences across the studies occurs only due to sampling error).[12] However, as usually is the case, the included studies in this analysis reveal non-negligible differences with respect to their baseline population, BP measurement methods, and definitions of RH. Hence, it is necessary to account for interstudy variability by using REM. In addition to Cochran's Q, T^2 is reported, which is the total amount of true heterogeneity (variance) on the scale of the original effect measure (i.e., in percentage). I^2 statistics were calculated to quantify the share of dispersion across the effects that is due to true heterogeneity rather than due to sampling error.[12] Observational and interventional studies were analyzed separately to avoid pooling of populations that are different by design. Subgroup analysis was applied where evidence suggests impact on RH prevalence, given that the necessary data were retrievable from the primary studies. Because female sex is suspected to be a risk factor of RH,[10] subgroup analyses were performed for studies where RH prevalence by sex could be determined. Additionally, a sensitivity analysis[12] was conducted by including studies with definitions of RH that were similar but not completely identical to the 2 admissible definitions of RH used in this article. Studies that did not clearly distinguish between treated and untreated hypertensive patients were also included into the sensitivity analysis.

Furthermore, a multivariable meta-regression was performed in observational studies to explore whether the following study-related characteristics were potential effect size modifiers: sample size, continent where the study was implemented (North/South America or Europe), type of BP measurement (office or ambulatory 24-hour BP

measurement), clinical setting (primary care, specialty care, primary and specialty care, general population), and operational definition of RH (AHA or alternative definition) that was used in the study. Meta-regression on the 4 RCTs only was not implemented because the small number of trials would not have allowed a meaningful interpretation. Similarly, we refrained from conducting a meta-regression on population-related metrics, such as mean age or BP because aggregation bias is likely to distort results.[12] Publication bias was visualized with funnel plots and tested using the method of Egger *et al.*[12]

RESULTS

Systematic review

The search yielded 318 studies, of which 2 were duplicates. Out of 32 shortlisted articles that examine RH prevalence, 2 were excluded because of secondary hypertension, 1 was excluded because of a lacking definition of RH, another was excluded because no blood pressure values were used to define RH, and 4 were excluded because the treatment status of the sample was not clear. After excluding studies that did not fulfil the inclusion criteria, 20 observational studies and 4 RCTs with overall populations of 870,531 and 95,504, respectively, were included in the meta-analysis (Figure 1).[3,9,13–34] Included studies were published between 1991 and 2013, the majority being conducted on the American continent, mainly in the United States.[13–16,18–20,22,23,25,26,28,30,31,34] Three studies drew their samples from the general population,[20,31,33] 4 drew their samples from primary care clinics,[9,22,29,30] 19 drew their samples from specialty clinics,[3,13,14,19,24,25,27,28,32,34] and 7 drew their samples from primary or specialty care clinics.[15–18,21,23,26] The average age and share of men in the examined samples ranged from 51.2 to 68.4 years and from 27.0% to 77.0%, respectively. Six papers defined RH according to AHA,[9,16–18,20,31] whereas the rest had an alternative definition. Three RCTs had no explicit definition of RH but still allowed us to calculate the prevalence of RH.[15,22,30] The main characteristics of the included studies can be found in Supplementary Table S1.

Although the articles are mostly satisfactory on the descriptive parts, such as study objectives, populations, and primary/secondary outcomes, they reveal deficiencies in analytical and conceptual sections (Supplementary Table S2). Except for 6 studies,[9,15,20,22,30,31] none made power calculations to estimate necessary sample sizes. The majority of articles used office BP monitoring (OBPM).[9,13,15,16,18–24,28–32,34] Auscultatory BP measurement was most frequently used,[13–16,21,24,27–31,34]

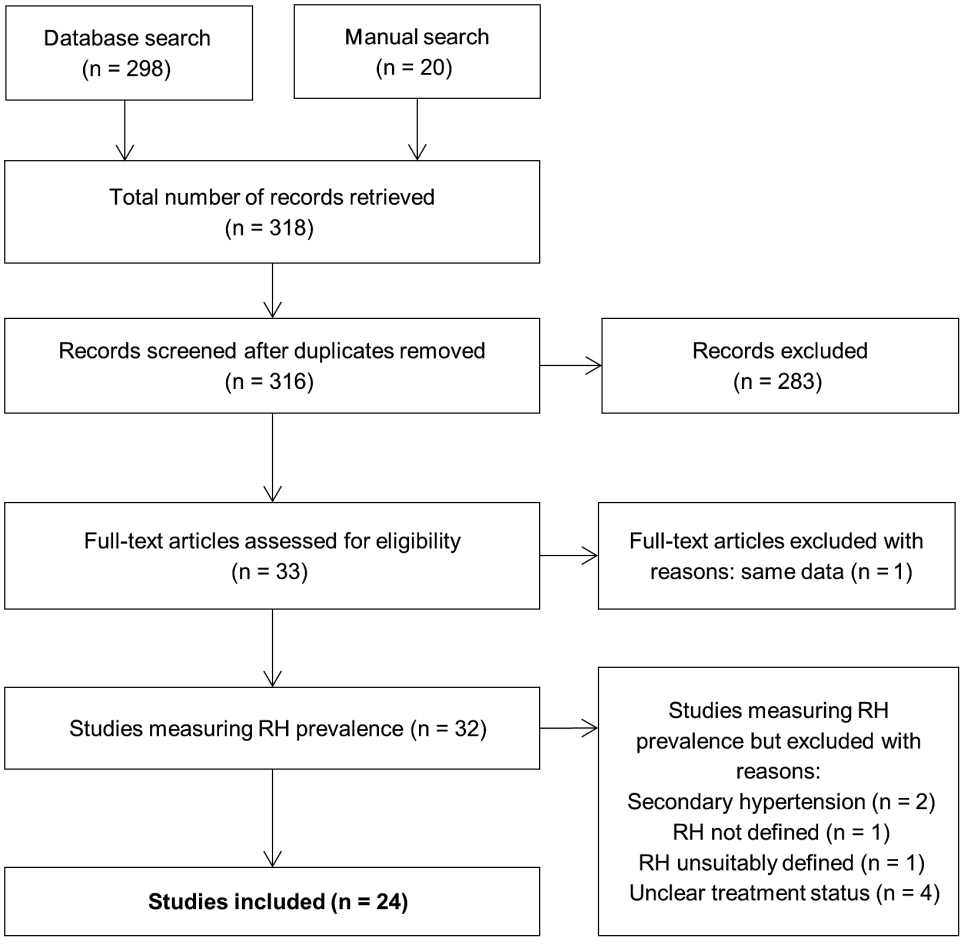

Figure 1. Flow chart for the selection of studies for meta-analysis of resistant hypertension (RH).

followed by the oscillatory method[9,20,25,32,33] or a combination of both.[3,17] Similarly, a substantial number of studies were not able to account for optimal medication dosing and adherence to treatment.[13,14,16–18,20,23,24,26,29,32] People that refused to participate in the survey, were not chosen to participate in the study, or were lost to follow-up were not described in most cases.[3,13,15,17,19,21,23,24,26–29,31–33] Although confidence intervals of the prevalence on RH were never given, all but 5 studies reported results by subgroups or analyzed confounding factors.[22,24,27,28,33] According to the Egger test, no publication bias is present ($P = 0.47$). RH prevalence ratios of the reviewed studies are roughly symmetrically scattered around the pooled estimate of RH prevalence, indicating a well-balanced set of available studies (Supplementary Figure S1). The relatively prominent dispersion of prevalence ratios across the more exact studies (i.e., those with a lower SE) may be explained by differences in study design and methodology.

Prevalence of RH

The results of the included studies show a varying picture of the prevalence of RH, ranging from 5.56%[32] in a French hospital hypertension clinic to 34.32% in high-risk hypertensive individuals in the United Kingdom and Scandinavia.[9] The pooled prevalence of RH across the 20 observational studies amounts to 13.72% (95% CI = 11.19%–16.24%) with the REM (Figure 2). Heterogeneity is statistically significant ($Q = 9{,}438$; $P < 0.0001$), the variance of the pooled prevalence amounts to 0.32% ($T^2 = 0.0032$), and most of the observed dispersion in prevalences is due to this true variance ($I^2 = 99.8\%$). With respect to the 4 RCTs (Figure 3), the pooled prevalence is 16.32%, with equally significant heterogeneity (95% CI = 10.68%–21.95%; $Q = 1{,}455$, $P < 0.0001$; $T^2 = 0.0033$; $I^2 = 99.8\%$).

Subgroup analysis

Nine observational studies allowed us to identify distinct prevalence rates for men and women.[13,14,16,18,23,26,29,31,33] Aside from 2 European studies,[29,33] the remainder of the studies included in the subgroup analysis were conducted on the Northern American continent. Six papers used OBPM,[13,16,18,23,29,31] two used applied ambulatory BP measurement (ABPM),[14,33] and 1 did not provide any information on the BP measurement type.[26] The population of these studies, amounting to 775,003 individuals, had an average age of 60.6 years (age range = 52.4–69), and 48.0% were men. The pooled prevalences barely differed between sex, with 15.32% (95% CI = 12.52%–18.12%; $Q = 1{,}320$, $P < 0.0001$; $T^2 = 0.0016$; I^2=99.4%) in men and 15.64% (95% CI = 13.67%–17.61%; $Q = 488$, $P < 0.0001$; $T^2 = 0.0008$; $I^2 = 98.4\%$) in women.

Multivariable random-effect meta-regression analysis

Overall, the meta-regression on the 20 observational studies explained 46.86% of the true heterogeneity, meaning that roughly half of the between-study dispersion is caused by unobserved covariables. No regressor revealed a statistically significant relationship to the prevalence of RH (Supplementary Table S3). Because statistical significance was not achieved, no further stratification (e.g., by RH definition) was conducted.

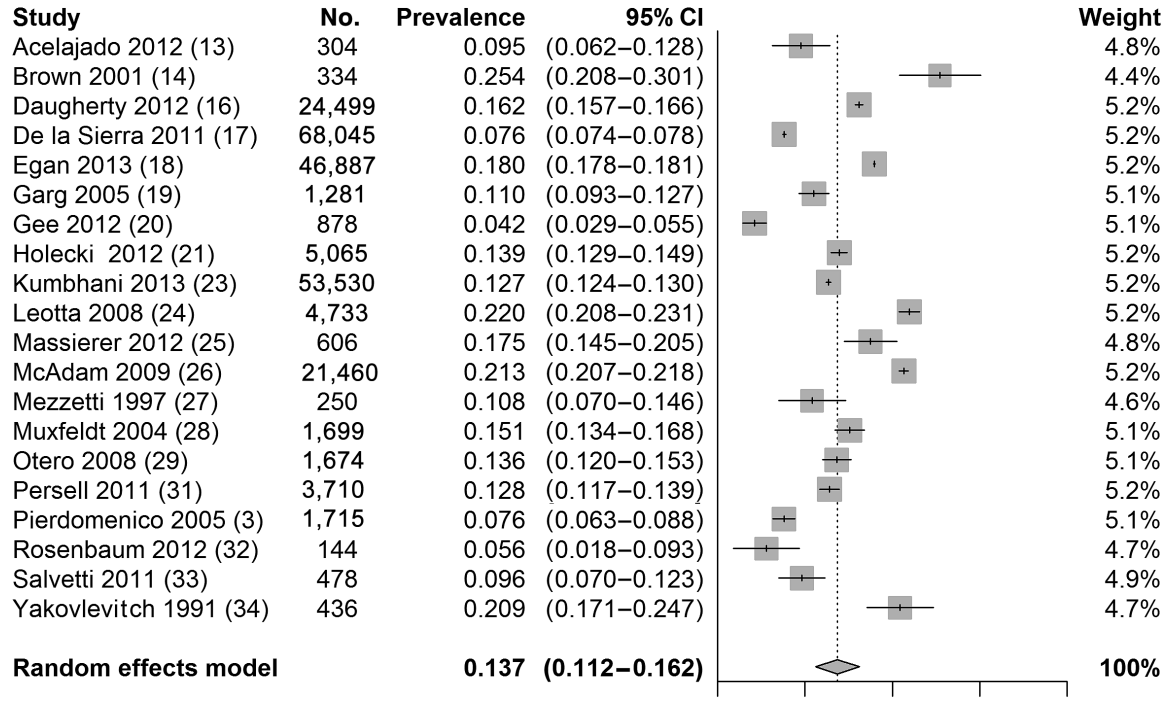

Figure 2. Forest plot for the pooled prevalence of resistant hypertension from 20 observational studies. The effect size (prevalence) of each study is represented by the small, solid vertical line, and its 95% confidence interval (CI) is shown by the solid horizontal line. The dashed vertical line represents the pooled prevalence, and the diamond represents its 95% CI. The size of the shaded squares symbolize the weight each study was assigned in the pooling.

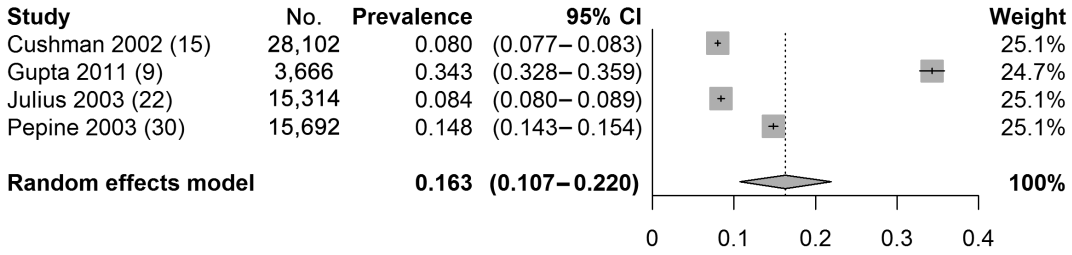

Figure 3. Forest plot for the pooled prevalence of resistant hypertension from 4 randomized control trials (RCTs). The effect size (prevalence) of each study is represented by the small, solid vertical line, and its 95% confidence interval (CI) is shown by the solid horizontal line. The dashed vertical line represents the pooled prevalence, and the diamond represents its 95% CI. The size of the shaded squares symbolize the weight each study was assigned in the pooling.

Sensitivity analysis

In the sensitivity analysis, 4 additional studies were included in the REM pooling.[35–38] In 3 of the studies, it was not clear whether the prevalence was determined on basis of the total hypertensive population or treated hypertensive population.[35,36,38] One study had a definition of RH that was close to but not did conform to the 2 admissible definitions:[37] RH was defined as office systolic BP >160 mm Hg despite antihypertensive regimen of ≥3 medications (including 1 diuretic). Adding these studies to the pooling only negligibly altered the pooled prevalence from 13.72% to 13.19% (95% CI = 10.89%–15.49%; Q = 9,791, $P < 0.0001$; T^2=0.0032; I^2 = 99.8%), indicating the robustness of the main analysis.

DISCUSSION

Our meta-analysis found that prevalence of RH in treated hypertensive populations is 13.72% (95% CI = 11.19%–16.24%) according to 20 observational studies and 16.32% (95% CI = 10.68%–21.95%) according to 4 RCTs. Overall, the prevalence results obtained in this meta-analysis corroborate estimations of the literature. A recent cross-sectional study found that 12.9% of treated hypertensive individuals were treatment-resistant.[39] Sarafidis *et al.* summarize[40] in their review article that the prevalence of true RH in the general hypertensive population, after excluding pseudo-resistance, is approximately 12%–15%. According to a further review,[41] observational studies report a prevalence of 12%–15%, whereas RCTs may obtain higher results. They conclude that prevalence of true RH in treated hypertensive patients lies somewhere between 15% and 30%. In another literature overview,[42] RH prevalence in the United States varies between 8% and 28%, which lies approximately within the range of prevalence ratios identified in our analysis.

The findings in our subgroup analysis do not support the claim that female sex is associated with RH.[10] It may be possible that hidden confounders, such as differences in physiological factors or medication adherence, explain this association.[15] For instance, renal artery stenosis in the course of fibromuscular dysplasia, which a cause of secondary RH, may increase the risk of uncontrolled BP.

Concerning the meta-regression, numerous differences in study-level characteristics across studies, such as diverse sampling frames, might suppress the occurrence of statistically significant results. Relationships that are present within studies do not necessarily hold true across studies and vice versa.

This article sheds light on 4 important aspects in the field of RH. First, the definition of RH was not identical across the studies. Some authors adopted the official AHA definition,[9,16–18,20,31] whereas others used the alternative definition. However, RH prevalence might be biased downwards with the alternative definition. Evidence suggests that RH prevalence can vastly fluctuate according to RH definition: Hayek *et al.* demonstrate that prevalence dropped from 30.9% to 3.4% in the same population when using increasingly stringent interpretations of the AHA definition of RH.[43] To maximize homogeneity of pooled studies, articles, such as that by Alderman *et al.*,[44] which had a strongly divergent definition of RH, were not included. Second, the methodology of studies was heterogeneous. On the one hand, the method of BP measurement differed: although most articles assessed BP in the office, only a few performed ABPM.[3,14,17,25,27,33,36] Evidence recommends ABPM over OBPM, arguing that the former method can detect pseudo-resistance caused by the white-coat effect.[2] Indeed, a study that used ABPM observed the white-coat effect in 1 of 3 individuals with apparent treatment resistance.[17] Consequently, it is possible that OBPM inflates RH prevalence due to unreliable BP measurement methods. On the other hand, medication adherence and optimal dosing could not be observed equally well in all studies. Although all RCTs[9,15,22,30] accounted for dosing and adherence, most of the observational studies failed to monitor these factors (Supplementary Table S2). If measured at all, adherence is based on patient self-reports,[3,13,21,27,34] which are subject to numerous uncertainties. Yet, to provide an RH prevalence estimate that conforms to the AHA definition, nonadherent patients would need to be excluded.[10] It is probable that a substantial part of patients are pseudo-resistant because they are nonadherent to drug therapy or take medications at wrong doses.[45] Reporting RH prevalence without excluding nonadherence and suboptimal dosing will cause artificially augmented RH

prevalence. Third, the 2 abovementioned observations reveal that only a minority of studies actually measure true RH.[3,25,27] The incapacity of ruling out pseudoresistance (i.e., white-coat effect, poor adherence, and wrong dosing) impairs the precision of RH prevalence. Instead of assessing truly resistant hypertension, most of the studies measure apparent resistance, which is bound to higher prevalence figures. Fourth, only a few studies had a near-optimal sampling frame and sampling method for measuring prevalence in an unbiased manner.[18,20,31] Ideally, a prospective survey would select a sufficiently sized random (clustered) sample of participants from the general treated hypertensive population. This would imply hypertensives with forced titration, optimal dosing, and closely monitored adherence from primary, secondary, and tertiary care settings. However, the included studies (i) chose their participants at convenience/by referral,[3,13,14,19,21,24,25,27–29,34,36,37] (ii) were limited to a certain health plan, clinic, or care setting,[3,9,13,14,19,22,24,25,27–30,32,34–38] (iii) focused on elderly, multimorbid, and high-risk patients,[9,15,19,22,23,30] or (iv) were interventional.[3,9,15,22,23,30,37] These factors constitute a source of selection bias and limited external validity. For instance, the higher prevalence derived from the 4 RCTs is likely rooted in the selection of cardiovascular high-risk patients. Although the RCTs provide a good approximation of true RH prevalence because medication adherence and optimal dosing were ensured, the pooled RCT results should not be directly applied without any reservation to the general treated hypertensive population. Completely reconciling the antagonistic effects of different sampling frames/methods and study designs on the prevalence, such as high-risk patients vs. optimal drug dosing/adherence, is not feasible, but this meta-analysis provides the most exact estimates available in the literature. Finally, more effective combination therapies might further reduce the prevalence of RH in the near future. Recent evidence indicates that, in addition to conventional triple therapy, mineralocorticoid receptor antagonists (e.g., spironolactone) might be beneficial for blood pressure control in RH patients.[46] The ongoing PATHWAY trial will show whether spironolactone is the most effective step 4 treatment for RH.[2]

To our best knowledge, this is the first article to determine a pooled prevalence of RH through a systematic review and meta-analysis. This study's generalizability is strengthened by a large number of included studies from various countries and care settings, as well as by a very large and diverse baseline population. A subgroup analysis by sex was conducted, and heterogeneity was investigated by meta-regression. The robustness of our results was demonstrated in the sensitivity analysis.\

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

DISCLOSURE

The authors declared no conflict of interest.

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