The Prevalence of Non-Adherence in Patients with Resistant Hypertension: a Systematic Review and Meta-Analysis

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Brief Summary

Resistant hypertension is known to be a risk factor for cardiovascular events. These patients also undergo higher screening intensity for secondary hypertension. However, not all patients with apparent treatment resistant hypertension have true resistant hypertension, with some of them being non-adherent to prescribed pharmacotherapy. This systematic review aims to establish the overall prevalence of non-adherence in the apparent treatment resistant hypertension population and assess the relative contributions of non-adherence assessed with direct and indirect measures.

ABSTRACT

Background: Resistant hypertension is quite prevalent and a risk factor for cardiovascular events. Patients with suspected resistant hypertension undergo more screening intensity for secondary hypertension, despite some of them being non-adherent to prescribed pharmacotherapy. The prevalence of non-adherence in this setting varies from about 5 to 80% in the published literature. Apart from the wide range, the relation between method of assessment and prevalence is not well established. Our objective was to establish the overall prevalence of non-adherence in the apparent treatment resistant hypertension population, explore causes of heterogeneity, and evaluate the effect of the method of assessment on the estimate of non-adherence.

Methods: We performed a systematic review and meta-analysis. MEDLINE, EMBASE Classic+EMBASE, Cochrane, CINAHL, and Web of Science were searched for relevant articles. Details about the method of adherence assessment were extracted from each included article and grouped into direct and indirect. Pooled analysis was performed using the random effects model and heterogeneity was explored with metaregression and subgroup analyses.

Results: The literature search yielded 1428 studies, of which 36 were included. The pooled prevalence of non-adherence was 35% (95% confidence interval 25 – 46 %). For indirect methods of adherence assessment, it was 25% (95% CI 15 – 39 %), whereas for direct methods of assessment, it was 44% (95% CI 32 – 57 %). Metaregression suggested gender, age, and time of publication as potential factors contributing to the heterogeneity.

Conclusions: Non-adherence to pharmacotherapy is quite common in resistant hypertension, with the prevalence varying with the methods of assessment.

INTRODUCTION

Resistant hypertension (RH) is defined as blood pressure (BP) remaining above target despite the concurrent use of three or more antihypertensive agents of different classes, with one of the classes preferably being a diuretic and all of the medications being prescribed at optimal doses[1,2,3]. RH is common, with an estimated prevalence of about 10 to 30 %, and known to be a risk factor for cardiovascular events[4]. Furthermore, patients with RH are often part of high-risk groups with multiple cardiovascular comorbidities as well as vulnerable or disadvantaged populations. These patients undergo higher screening intensity for secondary hypertension. However, not all patients with apparent treatment RH have true RH. Apart from white coat hypertension and suboptimal prescribed drug doses and combinations, some individuals with apparent treatment RH may be non-adherent to the prescribed pharmacotherapy[5,6].

There are several ways of assessing medication non-adherence, which can be broadly divided into indirect and direct methods. Indirect methods include questionnaires, self-reports, pill counts, rates of prescription refills, medication event monitoring systems (MEMS), and patient diaries. Direct methods include BP response to directly observed therapy (DOT) and measurement of the levels of BP-lowering drugs in physiologic fluids such as blood and urine[5]. The long term prevalence of non-adherence in chronic diseases is reported at about 50%[7]. However, this varied from 3 to 86% in individual studies in apparent treatment RH patients from a recent systematic review[8]. Interestingly, the pooled prevalence in this review varied based on the method of adherence measurement, from a low of 13% (similar estimate from self-report and physician interview) and 19% (prescription refill) to a high of 45% (DOT) and 49% (physical test, i.e. blood or urine assay). Though they were not grouped in this fashion, the former are indirect measures and the latter are direct measures. Apart from potentially different accuracy, these methods may capture different facets of non-adherence which might require different management strategies. As an example, pill counts and pharmacy refill data might identify occasional forgetfulness and/or carelessness, which can sometimes be related to an inability to follow instructions, either because of cognitive or physical limitations[5,7]. It can be managed using reminders, pill packs, and other interventions. In other settings, a patient may choose to alter the prescribed medication regimen, either by discontinuing medications entirely, skipping doses, or modifying doses or dosing intervals, however still continuing to refill prescriptions[6]. Underlying health beliefs and certain demographic factors and comorbid conditions may be associated with this, which would evade detection by indirect measures[9,10]. It requires more intensive measures (such as therapeutic drug monitoring (TDM) or DOT) to diagnose[5,6,11]. Interventions to address this form of non-adherence are also not well studied.

In the present study, we report on the overall prevalence of non-adherence in the apparent treatment RH population and what are the relative contributions of non-

adherence based on different methods of assessment, with an emphasis on attempting to explain the heterogeneity of the data.

METHODS

This systematic review and meta-analysis has been conducted and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[12]. It is registered with the International Prospective Register of Systematic Reviews database (registration number: CRD42020137944). The study protocol has also been published separately[13].

Search Strategy

The databases MEDLINE (Ovid Interface, 1946 through April 02, 2019), EMBASE Classic+EMBASE (1947 through April 02, 2019), Cochrane (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials), Cumulative Index of Nursing and Allied Health Literature (CINAHL), and Web of Science were searched for relevant articles for this systematic review and meta-analysis. The search was designed by an information specialist (AD) and the search terms were adapted for the different databases. The MEDLINE search strategy is included in the supplementary appendix, table 1. Additional relevant records were identified through review of references of selected articles and from suggestions from experts in the field.

Inclusion Criteria

We included observational studies, including cross sectional, retrospective, and prospective studies, as well as randomized controlled trials (RCTs) done on adult human participants aged 18 years or older with a diagnosis of RH, either uncontrolled on three or more drugs, or controlled with four or more drugs[1,2,3]. We only included studies where adherence to blood pressure lowering medications was measured using a test of adherence, either direct (such as TDM or DOT) or indirect (for example pill counts or pharmacy refill data). Only studies published in the English language were included. Studies published in other languages were included if a full-text version was available in English.

Study Selection

Titles and abstracts of studies identified through the various database searches were uploaded to Covidence, an Internet based software program that facilitates collaboration among reviewers during the study selection process[14]. Two reviewers (GB and JVI) independently screened the titles and abstracts retrieved after the literature search to evaluate whether they met the pre-defined inclusion criteria. Conflicts between reviewers were resolved through discussion between the two reviewers until a consensus was reached. Full-text articles for the studies meeting inclusion criteria were retrieved and screened by the same two reviewers in order to select studies to be included in the systematic review. The reasons for excluding trials were recorded, both after title and abstract screening

and after full-text screening. Reviewers were not blinded to the authors or journals when screening articles.

Data Extraction

We extracted key elements of study design, definitions of RH used, demographic characteristics, comorbidities, and data on adherence from the included studies. For adherence, details about the method of assessment were extracted and grouped into direct (eg urine or plasma assay or TDM, DOT) and indirect (eg pill counts, questionnaires, adherence scales). For studies that reported more than one method of assessment, the highest value was used for the pooled analysis. Additionally, for studies that reported both direct and indirect methods, these were compared in a separate meta-analysis. All data was extracted in duplicate by two reviewers (GB and JVI).

Quality and Risk of Bias Assessment

The study quality and the presence of potential bias within individual studies included in this systematic review were evaluated at both the outcome and study levels. The methodological quality of eligible full-text articles was independently assessed by two reviewers (GB and JVI) using the Newcastle-Ottawa scale[15]. The Newcastle-Ottawa scale includes the following domains: selection, comparability (not applicable to the studies included in this systematic review and meta-analysis), exposure (not applicable to the studies included in this systematic review and meta-analysis), and outcome. Disagreements were resolved through discussion until consensus was reached.

Data Synthesis and Statistical Analysis

A pooled estimate of the prevalence of non-adherence was generated. The summary prevalence was estimated using the random effects modeling as described by DerSimonian-Laird[16]. We chose the random effects method because of its conservative summary estimate and because it incorporates between- and within-study variance. To assess heterogeneity of the event frequencies across studies, we used the Cochran's Q-statistic test and the I^2 statistic. All analyses were conducted using the Comprehensive Metaanalysis V2 software (Version 2.2, Biostat, Englewood NJ). Subgroup analyses were used to explore possible sources of heterogeneity, based on type of test used to measure adherence (grouped as direct versus indirect), study design, and definition of RH. We conducted univariate metaregression to assess moderator variables which are continuous in nature. The subgroup analyses and metaregression were also assessed as a method of resolving any statistical heterogeneity. Sensitivity analyses were conducted by excluding one study at a time and observing change in pooled estimate (with a > 10% change being considered significant). Publication bias was assessed by visual examination of the funnel plot and the Duval and Tweedie's trim and fill method[17,18].

RESULTS

Literature Search

The figure 1 shows a flow diagram of the systematic review process. The initial database search identified 2770 articles and 13 additional records were identified through other sources. After removal of duplicates, 1428 titles and abstracts were screened. 1218 articles were excluded at this stage and therefore 210 full-text articles were assessed for eligibility. 174 of these were excluded, with the most common reasons for exclusion being absence of RH as defined above and ineligible study design, such as case reports, reviews, or editorials. Therefore, 36 full-text articles were eligible for inclusion in this systematic review and meta-analysis. A summary of the included articles is included in Legend for **Figures and Tables**

Table 1 Study Characteristics

Table 2 Population Characteristics

Figure 1 Flow Diagram for Literature Search and Selection

Figure 2 Forest Plot

Supplementary Appendix

Supplementary Table 1 MEDLINE Search Strategy – Ovid Interface

Supplementary Table 2 Quality Assessment

Supplementary Figure 1 Regression of Mean Age on Logit Event Rate

Supplementary Figure 2 Regression of Proportion of Men on Logit Event Rate

Supplementary Figure 3 Supplemental Figure 3: Regression of Publication date on Logit Event Rate

Supplementary Figure 4 Regression of Sample Size on Logit Event Rate

Supplementary Figure 5 Regression of Sample Size excluding one study on Logit Event Rate with Exclusion of One Large Study

Table 1 and Table 2, which describe the study and population characteristics.

Study Characteristics

36 studies were included in this systematic review. Of these, 21 were conducted in Europe, 11 in North America, and 4 in South America. The majority of the included studies were observational, with 15 prospective cohort studies, 11 cross-sectional studies, and 6 retrospective cohort studies. 3 of the included studies were RCTs and 1 was a pre-post intervention study.

The total number of participants included was 69,912. One study[19] accounted for the vast majority of these. The median sample size was 83, with a range from 18 to 60,327. The proportion of patients with comorbidities, such as diabetes, chronic kidney disease (CKD), congestive heart failure (CHF), and cerebrovascular disease (CVD), was inconsistently reported in the individual studies.

Definition of Resistant Hypertension

The definition of RH as well as the thresholds used to define non-adherence to prescribed pharmacotherapy varied between studies. 32 studies used office BP for defining RH and only 3 used ambulatory blood pressure monitoring (ABPM). One study used both methods. Antihypertensive regimens were not consistently reported and it often was not specified whether patients were on an optimized regimen. The most common threshold for diagnosis of RH was systolic blood pressure (SBP) ≥ 140 and/or diastolic blood pressure (DBP) ≥ 90. Patients with secondary forms of hypertension as well as white-coat hypertension were not consistently excluded, as is apparent from the low use of ABPM for diagnosis of RH.

Assessment of Adherence

18 studies assessed non-adherence using direct methods, 12 with indirect methods, and 6 with both direct and indirect methods, either concurrently or sequentially (see Table 1). DOT was used in 5 studies, plasma and/or urine assays in 19, MEMS in 2, non-standardized questionnaires in 4, standardized questionnaires such as the Morisky Medication Adherence Scale (MMAS) and the Medication Adherence Report Scale (MARS) in 8, prescription refill in 2, Proportion of Days Covered (PDC) in 3, and pill counts in 2 (see Table 1).

Prevalence of Non-Adherence

The pooled prevalence of non-adherence to antihypertensive pharmacotherapy was 35% (95% confidence interval [CI] 25 to 46%) as shown in figure 2. The prevalence of non-adherence varied across studies, with values ranging from 3.3%[20] to 86.1%[21], leading to a high degree of statistical heterogeneity ($I^2 = 99$, $p < 0.001$).

Subgroup Analyses and Metaregression

Using indirect methods of adherence assessment, the pooled prevalence of non-adherence was 25% (95% CI 15 – 39%, I^2 = 99), whereas with direct methods of assessment, it was 44% (95% CI 32 – 57%, I^2 = 89). The prevalence of non-adherence was higher in the subgroup of studies where ABPM was required for definition of RH (61%, 95% CI 27 – 86%, I^2 = 89), compared to the subgroup of studies which defined RH based on office BP (32%, 95% CI 22 – 44%, I^2 =99). Lastly, there was no difference in the prevalence of adherence in retrospective studies (38%, 95% CI 16 – 66%, I^2 = 94) or prospective studies (34%, 95% CI 24 – 47%, I^2 = 99). Excluding one study did not change the overall pooled estimate by > 10% (range 34 – 36%, compared to 35% with all studies). The subgroup analyses did not resolve the heterogeneity, which remained high.

With univariate metaregression (supplementary appendix, figures 1 to 5), there was an association of higher prevalence of non-adherence with younger age (slope coefficient 0.20, p < 0.001), higher proportion of men (slope coefficient 0.08, p < 0.001), and with more recent studies (slope coefficient 0.04, p < 0.001). An association of larger sample size with lower prevalence of non-adherence was also seen (slope coefficient 0.003, p < 0.001), which was driven by one large study with a sample size of 60,327 and a non-adherence prevalence of 11%. Exclusion of this study resulted in the association no longer being significant (slope coefficient 0.0001, p = 0.40).

Six studies reported both direct and indirect methods of assessment[22,23,24,25,26,27]. In a pooled analysis, the odds of detecting non-adherence were higher with direct methods (summary odds ratio 1.95, 95% CI 1.31 to 1.95, p = 0.001), though with significant statistical heterogeneity (I^2 = 98).

Quality Assessment and Publication Bias

The overall quality of the studies was fair, with a median of 4 stars (range 3 to 5). A large proportion of studies rated high on the representativeness subsection of the selection domain of the Newcastle-Ottawa scale. However, they rated poorly on the subsection demonstration that the outcome of interest, in this case non-adherence to antihypertensive medications, was not present at start of study. They rated mostly high on the assessment of outcome, length of follow-up, and adequacy of follow-up subsections of the outcome domain of the scale (see supplementary appendix, table 2).

There was no evidence of publication bias from visual examination of the funnel plot and no additional studies were imputed using the Duval and Tweedie's trim and fill method (see supplementary appendix, figure 6).

DISCUSSION

In this systematic review, we report a high degree of non-adherence prevalence in patients with apparent treatment RH, at 35%. However, there was significant heterogeneity identified among the studies, with a range of non-adherence from

3% to 86%. Studies using direct methods reported a higher degree of non-adherence, at 44%, compared to indirect methods, at 25%. The study level metaregression reveals younger age, male sex, and more recent publication date as being associated with higher rates of non-adherence.

Though non-adherence has always been part of the evaluation for RH, the extent of non-adherence, approximately at 1 in 3 patients in this systematic review, is so high, that an accurate assessment of adherence is essential before the patient is labeled as RH. Instead of investigations for secondary hypertension, consuming valuable healthcare resources, more attention needs to be focused on assessment and management of non-adherence in these patients. Additionally, non-adherence in most clinical settings is assessed by patient questionnaire, pharmacy filling data, or pill counts. As we demonstrate, these indirect methods of adherence provide a lower estimate compared to direct methods of assessment of non-adherence, such as TDM or DOT. Unfortunately, both TDM and DOT are mostly research tools and not available or funded in routine clinical practice. We hope this systematic review elevates their status for more routine use, especially in the setting of RH, where the high prevalence of non-adherence makes these tools more valuable and possibly cost effective.

A previous systematic review[8] also reports on a high degree of non-adherence in this population, though with 24 studies, compared to 36 in the present study. Additionally, we believe grouping assessment methods into direct and indirect methods provides a more accurate picture of the non-adherence phenotype. Additionally, in the present study, the exploration of heterogeneity provides more insight into the fact that patients of a younger age and men might have a higher non-adherence phenotype. We also report the trend for higher rates of non-adherence in the recently published studies. It is not quite clear whether this is because of ascertainment bias or more accurate assessment of non-adherence. Regardless, pill counts and pharmacy filling data may be necessary, but are far from sufficient for assessment of adherence.

The dichotomy of direct and indirect assessment of adherence does not necessarily mean that one is more accurate than the other. Indirect assessment of non-adherence with pill counts and pharmacy filling data may provide more insight into the occasional forgetfulness or missed doses in a patient who is otherwise engaged with the medication regimen. Direct methods of non-adherence provide pharmacokinetic and pharmacodynamic data, however in a cross-sectional manner. We would posit that these two broad techniques are complementary in the complete diagnosis of non-adherence.

The assessment of non-adherence is merely the first step in adequate blood pressure control. Management of non-adherence requires further exploration of the reasons of non-adherence and taking steps accordingly. Much of the focus has been on patient aids, such as reminders and smart pill bottles, and these would be useful for the unintentional non-adherence phenotype. For patients who

are otherwise disengaged in the medication and therapy plan, further exploration of their motives and beliefs is necessary. The diagnosis of non-adherence is but the initial step in this process.

Possible limitations of this study include the finding of severe heterogeneity, which has not been completely resolved by the analytic plan, the limitations of the literature search), and the potential lack of granular data in the published studies for a patient-level meta-analysis. However, there was no publication bias seen in the analysis and an information specialist was used for the literature search, attenuating these issues.

CONCLUSIONS

In patients with apparent treatment RH, standard indirect measures of assessing adherence can miss a substantial proportion of patients who are non-adherent to prescribed pharmacotherapy.

This systematic review and meta-analysis also provides a basis for future research on strategies to better address the different factors that contribute to medication non-adherence in this setting.

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DISCLOSURES

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LIST OF ABBREVIATIONS

ABPM: Ambulatory Blood Pressure Monitoring

BP: Blood Pressure

CHF: Congestive Heart Failure

CI: Confidence Interval

CINHAL: Cumulative Index of Nursing and Allied Health Literature

CKD: Chronic Kidney Disease

CVD: Cerebrovascular Disease

DBP: Diastolic Blood Pressure

DOT: Directly Observed Therapy

HR: Heart Rate

MARS: Medication Adherence Report Scale

MEMS: Medication Event Monitoring System

MMAS: Morisky Medication Adherence Scale

PDC: Proportion of Days Covered

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCTs: Randomized Controlled Trials

RH: Resistant Hypertension

SBP: Systolic Blood Pressure

TDM: Therapeutic Drug Monitoring

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Legend for Figures and Tables

Supplementary Appendix

Table 1: Study Characteristics

Study (Year of Publication)	Country	Design	BP Measurement Setting	Definition of RH	Adherence Measurement
Avataneo (2018)[22]	Italy	Cross-sectional	Office	SBP>=140 or DBP>=90[1*]	Plasma assay + questionnaire
Azizi (2016)[28]	France	RCT	Office	SBP>=140 or DBP>=90[1*]	Urine assay + MMAS-8
Beaussier (2015)[29]	France	RCT	Office	SBP>=140 or DBP>=90[1*]	Plasma and urine assays + questionnaire and pill counts
Brinker (2014)[11]	USA	Retrospective cohort	Office	SBP>=140 or DBP>=90[1*,2]	Plasma assay
Bunker (2011)[30]	UK	Prospective cohort	Office	SBP>=140 or DBP>=90[1*]	Directly Observed Therapy
Burnier (2011)[31]	Switzerland	Prospective cohort	Office	SBP>=140 or DBP>=90[1*]	Medication Event Monitoring System
Ceral (2011)[32]	Czech Republic	Retrospective cohort	Office	SBP>=150 or DBP>=95[1]	Plasma assay
Corrêa (2016)[23]	Brazil	Cross-sectional	Office	SBP>=140 or DBP>=90[1*,2]	Urine assay + MMAS-8
Daugherty (2012)[33]	USA	Prospective cohort	Office	SBP>=140 or DBP>=90[1*,2]	Proportion of Days Covered
de Jager (2018)[34]	Netherlands	RCT	Ambulatory	Daytime SBP>=135[1]	Plasma assay
de Jesus (2016)[35]	Brazil	Cross-sectional	Office	SBP>=140 or DBP>=90[1*]	MMAS-4
de Souza (2009)[36]	Brazil	Prospective cohort	Office	SBP>=140 or DBP>=90[1*]	MMAS-4 and pill counts
Durand (2018)[24]	Ireland	Cross-sectional	Office	SBP>=140 or DBP>=90[1*]	Urine assay + MARS, MMAS-8 and prescription refill
Elmula (2013)[37]	Norway	Prospective cohort	Office	SBP>=140 or DBP>=90[1*]	Directly Observed Therapy
Ewen (2015)[38]	Germany	Prospective cohort	Office	SBP>=140 or DBP>=90[1*]	Plasma and urine assays
Ewen (2015)[39]	Germany	Prospective cohort	Office	SBP>=140 or DBP>=90[1*]	Plasma and urine assays
Florczak (2015)[21]	Poland	Prospective cohort	Ambulatory	Daytime SBP>=140[2]	Plasma assay
Garg (2005)[40]	USA	Retrospective cohort	Office	SBP>=140 or DBP>=90[1*]	Questionnaire
Grigoryan (2013)[41]	USA	Prospective cohort	Office	SBP>=135 or DBP>=85 (>=125/75 if diabetic)[1]	Medication Event Monitoring System
Hameed (2015)[42]	UK	Retrospective cohort	Office	SBP>=140 or DBP>=90[1]	Directly Observed Therapy
Hayes (2018)[43]	Ireland	Cross-sectional	Office	SBP>=140 or DBP>=90[1*,2]	Prescription refill
Heimark (2016)[44]	Norway	Prospective cohort	Office	SBP>=140 or DBP>=90[1*]	Directly Observed Therapy
Irvin (2012)[45]	USA	Prospective cohort	Office	SBP>=140 or DBP>= 90 (>=130/80 if diabetic/CKD)[1*,2]	MMAS-4
Jung (2013)[46]	Germany	Cross-sectional	Office and ambulatory	Office SBP>=140 or DBP>=90 or ABPM >=130/80[2]	Urine assay
Kociánová (2017)[47]	Czech Republic	Cross-sectional	Office	SBP>=140 or DBP>=90[1*,2]	Plasma assay
Massierer (2012)[48]	Brazil	Cross-sectional	Office	SBP>=140 or DBP>=90[1*]	MMAS-4
Pandey (2015)[25]	USA	Retrospective cohort	Office	SBP>=140 or DBP>=90[1*,2]	Plasma assay + MMAS-8
Porter (2014)[20]	USA	Pre-post intervention	Office	SBP>=140 or DBP>=90 (>=130/80 if diabetic)[1]	Proportion of Days Covered
Pucci (2017)[49]	UK	Cross-sectional	Office	SBP>=140 or DBP>=90[1*]	Urine assay
Rosa (2014)[50]	Czech Republic	Cross-sectional	Office	SBP>=140 or DBP>=90[1*]	Plasma assay
Ruzicka (2019)[26]	Canada	Prospective cohort	Ambulatory	Daytime SBP>=135[1]	Directly Observed Therapy
Schmieder (2016)[51]	Germany	Prospective cohort	Office	SBP>=140 or DBP>=90[1*]	Urine assay
Sim (2013)[19]	USA	Prospective cohort	Office	SBP>=140 or DBP>=90[1,2]	Proportion of Days Covered
Štrauch (inpatient) (2013)[27]	Czech Republic	Cross-sectional	Office	SBP>=140 or DBP>=90 (>=130/80 if diabetic/CKD)[1]	Plasma assay
Štrauch (outpatient) (2013)[27]	Czech Republic	Cross-sectional	Office	SBP>=140 or DBP>=90 (>=130/80 if diabetic/CKD)[1]	Plasma assay
Velasco (2015)[52]	USA	Prospective cohort	Office	SBP>=140 or DBP>=90[1,2]	Plasma assay
Yakovlevitch (1991)[53]	USA	Retrospective cohort	Office	SBP>140 or DBP>90 if <= 50, SBP>150 if 51 to 60 or SBP>160 if > 60[1]	Questionnaire

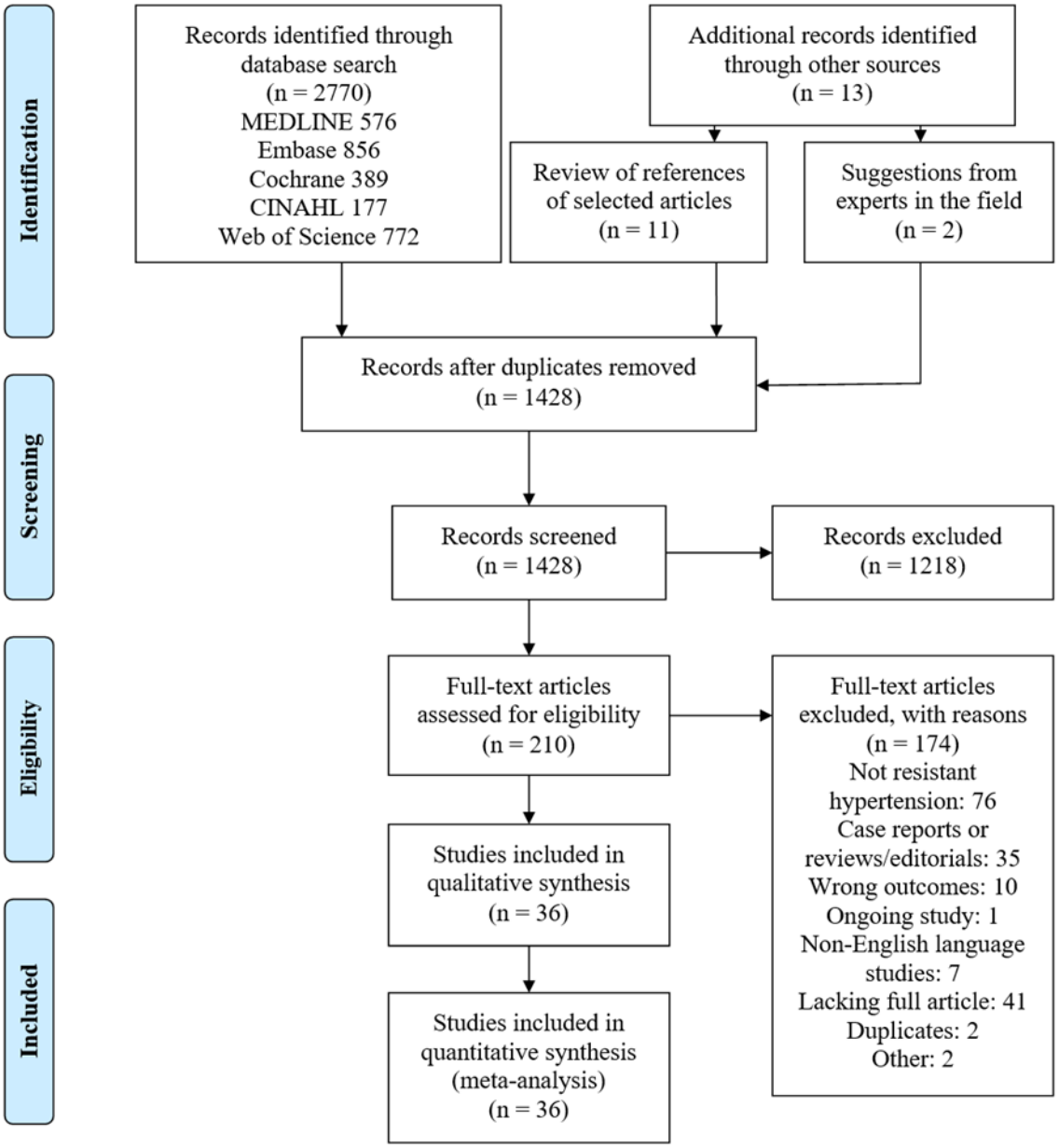
ABPM: Ambulatory Blood Pressure Monitoring; CKD: Chronic Kidney Disease; DBP: Diastolic Blood Pressure; M:Male; MARS :Medication Adherence Report Scale; MMAS: Morisky Medication Adherence Scale; RCT: Randomized Controlled Trial; RH: Resistant Hypertension; SBP: Systolic Blood Pressure; 1: On 3+ anti-hypertensives; 1* On 3+ anti-hypertensives including 1 diuretic; 2: On 4+ anti-hypertensives

Table 2: Population Characteristics

Study (Year of Publication)	Sample Size	Sex (% M)	Mean Age (years ± standard deviation)
Avataneo (2018)[22]	50	58	56 ± 7
Azizi (2016)[28]	85	NR	NR
Beaussier (2015)[29]	164	55	55 ± 10
Brinker (2014)[11]	56	NR	NR
Bunker (2011)[30]	37	35	57
Burnier (2011)[31]	41	76	50.5
Ceral (2011)[32]	84	59.5	55 ± 11
Corrêa (2016)[23]	21	43	NR
Daugherty (2012)[33]	3550	49	60
de Jager (2018)[34]	98	42	63 ± 11
de Jesus (2016)[35]	96	43.8	53.9 ± 9.9
de Souza (2009)[36]	44	27.3	48.6 ± 9.0
Durand (2018)[24]	204	57.8	70 ± 11
Elmula (2013)[37]	18	89	54
Ewen (2015)[38]	27	60	61.9 ± 9.9
Ewen (2015)[39]	100	67	62.7 ± 10.6
Florczak (2015)[21]	36	64	52.5 ± 9.1
Garg (2005)[40]	141	45	57 ± 13
Grigoryan (2013)[41]	69	NR	NR
Hameed (2015)[42]	48	47.9	62 ± 11
Hayes (2018)[43]	646	53.7	71.1 ± 12.2
Heimark (2016)[44]	83	78	58.3 ± 10.0
Irvin (2012)[45]	2654	48.2	67.4 ± 8.7
Jung (2013)[46]	76	57.9	58
Kociánová (2017)[47]	106	56	56,8
Massierer (2012)[48]	106	27	57.3 ± 10.6
Pandey (2015)[25]	47	53	52.5 ± 2
Porter (2014)[20]	60	96.7	62 ± 6.18
Pucci (2017)[49]	131	NR	NR
Rosa (2014)[50]	72	NR	55.5 ± 10.5
Ruzicka (2019)[26]	48	66.7	62.1 ± 13.1
Schmieder (2016)[51]	79	72	60.4 ± 10
Sim (2013)[19]	60327	48	69 ± 11
Štrauch (inpatient) (2013)[27]	176	58,5	52 ± 11
Štrauch (outpatient) (2013)[27]	163	56,4	54 ± 12
Velasco (2015)[52]	78	NR	NR
Yakovlevitch (1991)[53]	91	42	57 ± 14

M – Male; NR – Not Reported

Figure 1: Flow Diagram for Literature Search and Selection



Study	Year	Event rate	Lower limit	Upper limit
Yakovlevitch	1991	0.10	0.05	0.18
Burnier	2001	0.07	0.02	0.20
Garg	2005	0.16	0.11	0.23
de Souza	2009	0.36	0.24	0.51
Ceral	2011	0.66	0.55	0.75
Daugherty	2012	0.42	0.41	0.44
Irvin	2012	0.08	0.07	0.09
Massierer	2012	0.20	0.13	0.29
Elmula	2013	0.17	0.06	0.41
Grigoryan	2013	0.29	0.20	0.41
Jung	2013	0.53	0.41	0.64
Sim	2013	0.07	0.07	0.07
Strauch	2013	0.47	0.42	0.52
Brinker	2014	0.54	0.41	0.66
Porter	2014	0.03	0.01	0.12
Rosa	2014	0.38	0.27	0.49
Beaussier	2015	0.18	0.13	0.25
Ewen 1	2015	0.56	0.37	0.73
Ewen 2	2015	0.48	0.38	0.58
Florczak	2015	0.86	0.71	0.94
Pandey	2015	0.51	0.37	0.65
Velasco	2015	0.55	0.44	0.66
Azizi	2016	0.52	0.41	0.62
Hameed	2016	0.50	0.36	0.64
Heimark	2016	0.32	0.23	0.43
Schmieder	2016	0.44	0.34	0.55
Bunker	2017	0.62	0.46	0.76
de Jager	2017	0.68	0.58	0.77
Kociánová	2017	0.45	0.35	0.54
Pucci	2017	0.16	0.11	0.23
Avataneo	2018	0.42	0.29	0.56
Corrêa	2018	0.57	0.36	0.76
de Jesus	2018	0.69	0.59	0.77
Durand	2018	0.26	0.20	0.32
Hayes	2019	0.16	0.14	0.19
Ruzicka	2019	0.29	0.18	0.43
Summary Prevalence		0.35	0.25	0.46

Heterogeneity
Q 5641, I^2 99, P <0.0001