Original Article

Medication adherence among patients with apparent treatment-resistant hypertension: systematic review and meta-analysis

Hannah Durand[a], Peter Hayes[b], Eimear C. Morrissey[a], John Newell[c,d], Monica Casey[b], Andrew W. Murphy[b,e], and Gerard J. Molloy[a]

Objectives: Medication nonadherence is a known behavioural contributor to poor blood pressure (BP) control that puts patients with hypertension at elevated cardiovascular risk. Studies of medication adherence for apparent treatment-resistant hypertension (aTRH) vary significantly with respect to design, methods, and setting, and, as a result, have produced highly variable figures describing the prevalence of nonadherence. This review aimed to describe the prevalence and potential moderators of medication nonadherence estimates for aTRH.

Methods: Systematic review and random effects meta-analysis.

Results: From an initial discovery of 921 studies, we identified 24 studies that measured medication adherence for patients with uncontrolled BP despite being prescribed three or more antihypertensive medications of different classes. By using a random effects model, the pooled prevalence of nonadherence was 31.2% (95% confidence interval = 20.2–44.7, $I^2 = 99.50$) with nonadherence rates ranging from 3.3 to 86.1%. The strongest contributor to variance in nonadherence rates was the method of adherence assessment used. Studies that relied on self-report measures of adherence and/or pharmacy data reported lower levels of nonadherence than studies using more objective methods, such as liquid chromatography–mass spectrometry in single time-point bioassays or directly observed therapy.

Conclusion: Findings indicate that medication nonadherence is a significant problem among aTRH patients. Identifying the most accurate and clinically feasible adherence assessment methods is necessary to reduce BP and cardiovascular morbidity, facilitate early behavioural intervention, prevent unnecessary diagnostic testing, and limit sometimes unnecessary and expensive BP lowering procedures.

Registration number : CRD42016028121.

Keywords: hypertension, medication adherence, meta-analysis, resistant hypertension, systematic review

Abbreviations: ABPM, ambulatory blood pressure monitor; AHA, American Heart Association; aTRH, apparent treatment-resistant hypertension; BP, blood pressure; CHD, coronary heart disease; DOT, directly observed therapy; ESC, European Society of Cardiology; ESH, European Society of Hypertension; MEDAL, Medication Adherence Across the Lifespan; MEMS, medication event monitoring system; MPR, medication possession ratio; PRISM, Preferred Reporting Items for Systematic reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; RCT, randomized controlled trial; REM, random effects model; RH, resistant hypertension

INTRODUCTION

Medication nonadherence is a known behavioural contributor to poor blood pressure (BP) control that puts patients with hypertension at elevated cardiovascular risk [1,2]. The term apparent treatment-resistant hypertension (aTRH) is used to describe patients who appear to have resistant hypertension, that is, patients whose BP remains above goal despite concurrent use of three or more antihypertensive agents of different classes, one of which should ideally be a diuretic and all of which should be prescribed at optimal dose amounts, or patients whose BP is controlled but require four or more medications to do so [3,4], and for whom causes of pseudoresistance (i.e. nonadherence, the white-coat effect, measurement error) have not been excluded. aTRH is common among treated hypertensive patients, with prevalence estimates of more than 10% consistently reported [5]. Patients with aTRH are at increased cardiovascular risk relative to those whose BP is controlled by three or fewer medications, and 50% more likely to experience an adverse

Journal of Hypertension 2017, 35:000–000

[a]MEDAL (Medication Adherence Across the Lifespan) Group, School of Psychology, [b]Discipline of General Practice, School of Medicine, [c]School of Mathematics, Statistics & Applied Mathematics, National University of Ireland, [d]Biostatistics Unit, Health Research Board Clinical Research Facility, Galway and [e]Health Research Board Primary Care Clinical Trials Network, Dublin, Ireland

Correspondence to Hannah Durand, MSc, G050 AMBE, MEDAL (Medication Adherence Across the Lifespan) Group, School of Psychology, National University of Ireland, Galway, Ireland. Tel: +353 91 492803; e-mail: h.durand1@nuigalway.ie

Received 3 May 2017 **Revised** 23 June 2017 **Accepted** 6 July 2017

DOI:10.1097/HJH.0000000000001502

cardiovascular event than patients with controlled hypertension [6].

It is not certain what proportion of aTRH can be attributed to nonadherence to antihypertensive medications. Studies of medication adherence for aTRH vary significantly with respect to design, methods, and setting, and, as a result, have produced highly variable nonadherence estimates. Two recent narrative reviews have reported highly variable estimates of nonadherence for aTRH (e.g. 23.0–66.0% [7]; 7.0–65.5% [8]); however, these only report on three common studies, and do not report how or why individual studies were selected for review and therefore, may provide an arbitrary selection of the available evidence. There has been no systematic investigation of the prevalence of nonadherence estimates for aTRH, or statistical moderators of these estimates. This review aimed to systematically determine the prevalence of medication nonadherence among patients with aTRH.

METHODS

The current systematic review and meta-analysis has been conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9]. The review is registered with the International Prospective Register of Systematic Reviews database (registration number: CRD42016028121).

Search strategy

Electronic databases PsycINFO, PubMed, Embase, Web of Science, and CINAHL were searched for research articles published from the start of the databases until December 2015. The following search string was used: 'medication' AND ('adheren∗' OR 'nonadheren∗' OR 'nonadheren∗' OR 'complian∗' OR 'noncomplian∗' OR 'noncomplian∗') AND ('resistant' OR 'uncontrolled') AND 'hypertension'. References of selected articles and review articles were checked to identify additional relevant articles.

Inclusion and exclusion criteria

Articles were considered relevant if they reported original research and if their study population consisted of patients with aTRH. Prevalence of medication nonadherence had to be reported as an outcome. Articles were excluded if they were review or expert opinion articles, case studies, or contained secondary analyses on data already included in this review. Where dual or duplicate publication was identified, the article with the most completely reported data was included. Intervention studies with appropriately reported baseline adherence data were also included.

Study selection

Titles and abstracts were screened for inclusion by two independent reviewers (H.D. and E.C.M.). Full texts were also evaluated by two independent reviewers (H.D. and P.H.). In the case of disagreement between reviewers, a third reviewer acted as an adjudicator (A.W.M. or G.J.M., depending on the nature of the expertise required to resolve the disagreement). Articles were retained if they contained studies exploring nonadherence to antihypertensive medication in aTRH, were published in English, and were available in full text by January 2016. Owing to the varying definitions of treatment resistance [10], the following common definitions were acceptable: first, uncontrolled BP (≥140/90 mmHg) despite antihypertensive regimen of at least three medications of different classes (including one diuretic) or treatment with at least four antihypertensive agents of different classes irrespective of BP control status [definition of the American Heart Association (AHA) [3], the European Society of Hypertension (ESH), and the European Society of Cardiology (ESC) [4]]; second, uncontrolled BP (≥140/90 mmHg) despite antihypertensive regimen of at least three medications of different classes; or third, definitions deemed more stringent than first or second.

Data extraction

From each included study two reviewers (H.D. and P.H.) independently extracted the following information: country of publication, study setting, design, sample size, definition of resistant hypertension, number of medications, definition of nonadherence, proportion of nonadherent patients, and factors associated with nonadherence, if reported. Several methods of measuring nonadherence have been reported; these were grouped into categories: case note evaluation/physician interview, self-report scale, physical test (urine/blood), pill count/prescription refill data, medication possession ratio (MPR), electronic monitors [medication event monitoring system (MEMS)], directly observed therapy (DOT), or combination of measures (e.g. self-report scale and physical test).

Quality and risk of bias assessment

Given the diversity of study designs included in this review, an assessment of the quality of studies was conducted with reference to criteria outlined by Sanderson *et al.* [11] in their review of quality and risk of bias assessment tools for observational studies.

Data synthesis and statistical analysis

Statistical analysis was conducted by using the 'metaprop' function in R [12,13]. Results are presented in forest plots. Nonadherence estimates were calculated by dividing the number of patients meeting each study's definition of nonadherence out of the total number of enrolled patients. When only percentages were reported, they were converted into absolute numbers. Confidence intervals [95% confidence intervals (CIs)] were calculated for each prevalence point estimate. A random effects model (REM) was used to calculate a pooled summary estimate of nonadherence, as the assumptions of fixed-effects modelling were not deemed tenable in this context [14]. I^2 statistics were calculated to quantify the share of dispersion across the effects that are due to true heterogeneity rather than sampling error [14]. Egger's test was used to detect publication bias [15]. A leave-one-out sensitivity analysis was performed by iteratively removing one study at a time to confirm that findings were not driven by any single study. Subgroup analysis was applied to detect moderator variables in which evidence suggests potential impact on nonadherence

estimates, provided that necessary data were retrievable from the primary studies. Subgroup analyses examined: type of adherence measure (categorized above), study setting (primary care, general hospital, or specialist hypertension referral clinic), and definition of resistant hypertension (AHA/ESH/ESC versus 'other') as potential moderator variables (Table 1).

RESULTS

Description of studies

Literature search

A PRISMA flow diagram outlining the systematic review process is provided (Fig. 1). The initial literature search resulted in the identification of 921 unique articles, after 800 duplicates were removed. Of these, 891 were rejected after reviewing the abstracts. Of the remaining 30 articles, six were excluded in the full-text screening phase. Therefore, 24 fully extracted primary studies were available for meta-analysis. One included article [16] described two distinct study populations (i.e. inpatients and outpatients). These were treated as separate observations in the meta-analysis. No additional articles that met our inclusion criteria were identified through a reference list search. Refer to Table 1 for a summary of included articles.

Study characteristics

Twelve studies took place in Europe [16–27], 10 in the United States [28–37], and two elsewhere [38,39]. The majority of studies were retrospective or cross-sectional cohort studies. Two randomized controlled trials and one prepost intervention study were also included [25,30,32].

Patient characteristics

The pooled participant sample was 68 313; however, one study [35] accounted for over 60 000 of these. The number of patients included ranged from 18 [21] to 60 327 [35]. Mean age and sex distribution were similar across studies; however, these were inconsistently reported. BP measurements, both SBP and DBP, were also inconsistently reported; those studies that did report these figures often broke BP down by subgroups or time points. The medications assessed were often not reported; those that were reported varied between studies.

Quality and risk of bias

A summary of the critical appraisal is presented in Fig. 2. Egger's test for publication bias was significant ($Z = 7.28$, $df = 23$, $P = 0.02$).

Summary of the evidence

Overall, the studies included varied considerably with respect to design, methods, and setting. Of particular interest, the definitions of resistant hypertension and adherence varied significantly. Details of antihypertensive regimens are generally not reported, even for studies that use physical tests of urine or blood to measure adherence. Patients were often not reported to be on optimal hypertensive therapy, and the methodology of drug dosage assessment is typically not reported. For physical tests, timing of sampling after drug intake is not clearly defined. Furthermore, influence of preanalytical factors (procedures that occur prior to sample analysis that may produce erroneous results, e.g. patient identification, physical sample collection, sample preparation, and handling, etc.) and pharmacokinetics on the level of drugs detected were not discussed. For the majority of studies, patient consent for adherence assessment was not adequately explained. No study provided information about patient agreement with the medication regimen. No study distinguished between under-use and over-use of medications.

Prevalence of nonadherence

The prevalence of nonadherence varied between the studies, ranging from 3.3 [32] to 86.1% [20]. The lowest estimate of nonadherence was measured by MPR; the highest was measured by using a physical test of urine.

The pooled prevalence of nonadherence was 31.2% (95% CI = 20.2–44.7) with the REM. This analysis revealed significant heterogeneity across studies ($I^2 = 99.50$, $P < 0.001$). To evaluate the robustness of the association results, we performed a leave-one-out sensitivity analysis by iteratively removing one study at a time and recalculating the pooled prevalence estimate. The pooled estimate remained stable, indicating that results were not driven by any single study.

No study examined the consequences of nonadherence for aTRH; however, several studies examined differences in BP between adherent and nonadherent groups [16,18,22–24,31,34,36,37]. Only six studies examined determinants of nonadherence beyond baseline BP [16,24,31,34,36,37]; these suggested that age, sex, race, income, and other socioeconomic indicators, and heart rate were all associated with nonadherence to antihypertensive therapy.

Subgroup analyses

All studies provided sufficient information to perform subgroup analysis by type of adherence measure, study setting, and definition of resistant hypertension. There was no significant association between adherence measures and study settings ($\chi^2 = 18.67$, $P = 0.18$, $V = 0.62$), adherence measure and definition of resistant hypertension ($\chi^2 = 8.67$, $P = 0.28$, $V = 0.60$), or study setting and definition of resistant hypertension ($\chi^2 = 1.07$, $P = 0.59$, $V = 0.21$).

Adherence measures: Seven types of adherence measures were employed across studies. The most common measure was a physical test [16–18,20,22–24,34,37], typically assessed by using liquid chromatography–mass spectrometry in either blood or urine. Studies using this type of measure defined nonadherence as at least one drug below detectable levels; all differentiated between partial and complete nonadherence. Three studies used DOT [19,21,26] (i.e., witnessed taking of drugs in a clinic setting followed by ambulatory BP monitoring with a drop in BP suggesting nonadherence); three used a combination of self-report and objective measures [25,31,38]; two used MEMS [27,30]; two used physician interview [29,33]; two used prescription refill data [28,35]; two used self-report scales only [36,39]; and one used MPR (i.e. the number of doses of a given medication taken over a specified time

TABLE 1. Summary of articles reporting on medication nonadherence for apparent treatment-resistant hypertension

Reference	Design	Setting	Sample	Definition of RH	Ave. no. of medications	Adherence measure	Nonadherence definition	*N* nonadherent (%)	Influencing factors
Beaussier *et al.* [25]	Prospective randomized parallel-group open-blinded endpoint trial	General Hospital Paris, France	164	SBP ≥ 140 or DBP ≥ 90 on ≥3 meds incl. 1 diuretic	/	Combination: Physical test (plasma) Physical test (urine) Patient interview Pill count Sum of 4 items (max. score = 4)	Score < 2	30 (18.3)	/
Brinker *et al.* [37]	Retrospective cohort	General Hospital Texas, USA	56	AHA/ESH/ESC	5.3 ± 0.7 (nonadherent) 4.2 ± 0.4 (adherent)	TDM	Levels of ≥1 medication below minimal detection limit	30 (53.6) Undetectable levels of ≥1 med: $n = 12$ (21.4) Undetectable levels of all meds: $n = 18$ (32.2)	Younger age Higher DBP Higher heart rate
Bunker *et al.* [26]	Prospective cohort	Referral Clinic London, UK	37	SBP ≥ 140 or DBP ≥ 90 on ≥3 meds incl. 1 diuretic	5 (3–7)	DOT	Clinically significant reduction in BP following witnessed drug taking	23 (62.2)	/
Burnier *et al.* [27]	Prospective cohort	General Hospital Lausanne, Switzerland	41	SBP ≥ 140 or DBP ≥ 90 on ≥3 drugs on two consecutive clinic visits 1-month apart	/	MEMS	<80% days covered	3 (7.0)	/
Ceral *et al.* [24]	Retrospective cohort	Referral clinic, Prague, Czech Republic	84	SBP ≥ 150 or DBP ≥ 95 on ≥3 drugs	5.0 ± 1.2	Physical test (serum)	Levels of ≥1 medication below minimal detection limit	55 (65.5)	Younger age Higher BP Higher heart rate
Daugherty *et al.* [6,28]	Prospective cohort	Large Population Database (primary care) CA & CO, USA	3548	AHA/ESH/ESC	/	Pharmacy data	<80% days covered	1504 (42.4)	/
de Souza *et al.* [38]	Prospective cohort	Referral Clinic Sao Paulo, Brazil	44	SBP ≥ 140 or DBP ≥ 90 on ≥3 meds incl. 1 diuretic on two consecutive clinic visits	5.4 ± 1.1	Combination: Pill count Self-report (MMAS-4)	<80% days covered Score <4	Pill count: 16 (36.4) MMAS-4: 28 (63.6)	/
Elmula *et al.* [21]		Referral Clinic Oslo, Norway	18	SBP > 140 on ≥3 meds incl. 1 diuretic at maximum or highest tolerated dose	5 (3–7)	DOT	Clinically significant reduction in BP following witnessed drug taking	3 (16.7)	/
Ewen *et al.* [22]	Prospective cohort	General Hospital Germany	27	SBP > 140 on ≥3 meds incl. 1 diuretic at maximum or highest tolerated dose	5.0 ± 1.6	Physical test (plasma and/or urine)	Levels of ≥1 medication below minimal detection limit	15 (55.6) Undetectable levels of ≥1 med: $n = 15$ (55.6) Undetectable levels of all meds: $n = 0$	No sig. differences

TABLE 1 (*Continued*)

Reference	Design	Setting	Sample	Definition of RH	Ave. no. of medications	Adherence measure	Nonadherence definition	*N* nonadherent (%)	Influencing factors
Ewen *et al.* [23]	Prospective cohort	General Hospital Germany	100	SBP > 140 on ≥3 meds incl. 1 diuretic at maximum or highest tolerated dose	5.2 ± 1.4	Physical test (plasma and/or urine)	Levels of ≥1 medication below minimal detection limit	48 (48.0) Undetectable levels of ≥1 med: $n = 46$ (46.0) Undetectable levels of all meds: $n = 2$ (2.0)	No sig. differences
Florczak *et al.* [20]	Prospective cohort	General Hospital Warsaw, Poland	36	SBP > 140 on ≥4 meds	5.3 ± 1.4	Physical test (serum)	Levels of ≥1 medication below minimal detection limit	31 (86.1) Undetectable levels of ≥1 med: $n = 26$ (72.2) Undetectable levels of all meds: $n = 5$ (13.9)	/
Garg *et al.* [29]	Retrospective cohort	Referral Clinic Illinois, USA	141	SBP ≥ 140 or DBP ≥ 90 on ≥3 meds	3.7 ± 0.9	MD interview	Physician determines the patient is nonadherent (not taking meds as prescribed or stopping meds without physician's direction)	23 (16.0)	/
Grigoryan *et al.* [30]	Prospective cohort	Primary care Texas, USA	69	SBP ≥ 135 or DBP ≥ 85 (≥125/75 if diabetic) on ≥3 meds	/	MEMS	<80% days covered	20 (29.0)	/
Hameed *et al.* [19]	Retrospective cohort	Referral Clinic Birmingham, UK	48	SBP ≥ 140 or DBP ≥ 90 on ≥3 meds	5 (4–5)	DOT	Clinically significant reduction in BP following witnessed drug taking	24 (50.0)	/
Irvin *et al.* [36]	Prospective cohort	Large population database (primary care) USA	2654	AHA/ESH/ESC	/	Self-report (MMAS-4)	Score ≥ 2	215 (8.1)	Black race Lower education Income < $20 000 p/a Depressive symptoms History of CHD Comorbidities
Jung *et al.* [18]	Cross-sectional	Referral Clinic Frankfurt, Germany	76	Office BP ≥ 140/90 or ABPM ≥ 130/80 on ≥4 meds	5 (IQR 4–6)	Physical test (urine)	Levels of ≥1 medication below minimal detection limit	40 (52.6) Undetectable levels of ≥1 med: $n = 28$ (36.8) Undetectable levels of all meds: $n = 12$ (15.8)	Higher BP Higher heart rate
Massierer *et al.* [39]	Cross-sectional	Referral Clinic Brazil	106	SBP ≥ 140 or DBP ≥ 90 on ≥3 meds in right doses incl. 1 diuretic	/	Self-report (MMAS-4)	Score ≥ 3	21 (19.8)	/
Pandey *et al.* [31]	Retrospective cohort	Referral Clinic Texas, USA	47	AHA/ESH/ESC	/	Combination: TDM MMAS-8	Levels of ≥1 medication below minimal detection limit	24 (51.0)	Younger age Female sex Higher heart rate
Porter *et al.* [32]	Prepost intervention	Referral Clinic North Carolina, USA	60	SBP ≥ 140 or DBP ≥ 90 (≥130/80 if diabetic) on ≥3 meds	3.8 ± 1.2	MPR	<80% days covered	2 (3.3)	/

TABLE 1 (*Continued*)

Reference	Design	Setting	Sample	Definition of RH	Ave. no. of medications	Adherence measure	Nonadherence definition	*N* nonadherent (%)	Influencing factors
Rosa *et al.* [17]	Cross-sectional	Referral Clinic Prague, Czech Republic	122	SBP $\geq$ 140 or DBP $\geq$ 90 on $\geq$3 meds in maximum doses incl. 1 diuretic	/	Physical test (blood)	Levels of $\geq$1 medication below minimal detection limit	27 (22.1) Undetectable levels of $\geq$1 med: $n = 10$ (8.2) Undetectable levels of all meds: $n = 17$ (13.9)	/
Sim *et al.* [35]	Prospective cohort	Large Population Database (primary care) California, USA	60327	AHA/ESH/ESC	/	Pharmacy data	<80% days covered	4223 (7.0)	/
Štrauch *et al.* [16]	Cross-sectional	Referral Clinic Prague, Czech Republic	339 176 inpatient 163 outpatient	AHA/ESH/ESC	Inpatient: 2.5 $\pm$ 1.4 Outpatient: 5.2 $\pm$ 1.3	Physical test (blood)	Levels of $\geq$1 medication below minimal detection limit	Inpatient: Undetectable levels of $\geq$1 med: $n = 18$ (10.0): Undetectable levels of all meds: $n = 16$ (9.0) Outpatient: Undetectable levels of $\geq$1 med: $n = 39$ (24.0) Undetectable levels of all meds: $n = 37$ (23.0)	Nonworking status Lower education Younger age
Velasco *et al.* [34]	Prospective cohort	Referral Clinic Texas, USA	78	AHA/ESH/ESC	4.4	TDM	Levels of $\geq$1 medication below minimal detection limit	43 (55.1)	Younger age Higher DBP Higher heart rate Female sex
Yakovlevitch and Black [33]	Retrospective cohort	Referral Clinic	91	SBP $\geq$ 140 or DBP $\geq$ 90 on $\geq$3 meds	/	MD interview	Patients admitted not taking medications according to the prescribed schedule and/or stopping medications without consulting a physician	9 (9.9)	/

ABPM, ambulatory blood pressure monitor; AHA, American Heart Association; BP, blood pressure; CHD, coronary heart disease; DOT, directly observed therapy; ESC, European Society of Cardiology; ESH, European Society of Hypertension; MEMS, medication event monitoring system; MPR, medication possession ratio; RH, resistant hypertension.

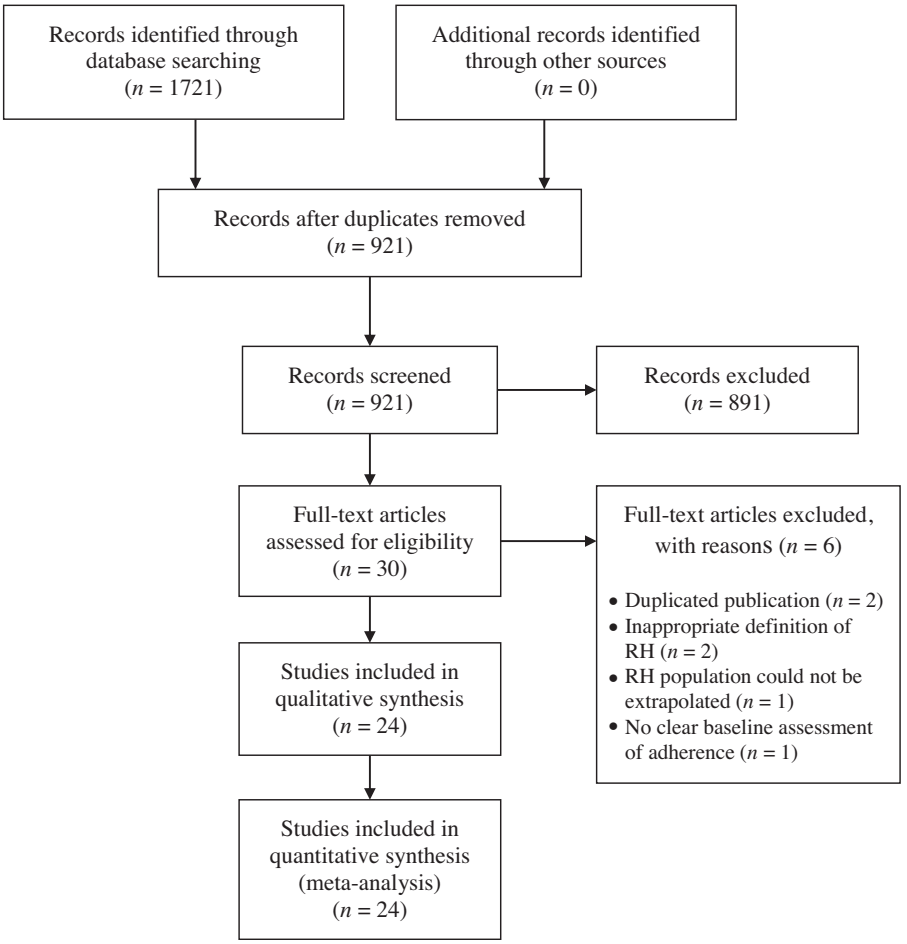

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram.

period, divided by the number of days in the same time period) [32] to measure adherence. Studies using MEMS or refill data generally defined nonadherence as more than 80% of doses collected. Each study's operational definition of nonadherence is described in Table 1.

The highest pooled nonadherence estimates were observed for physical tests (47.9%, $k = 9$) and DOT (44.6%, $k = 3$). The lowest estimate was observed for the MPR study (3.3%). The pooled nonadherence estimate for combination measures was 33.4% ($k = 3$). Refer to Fig. 3 for forest plot.

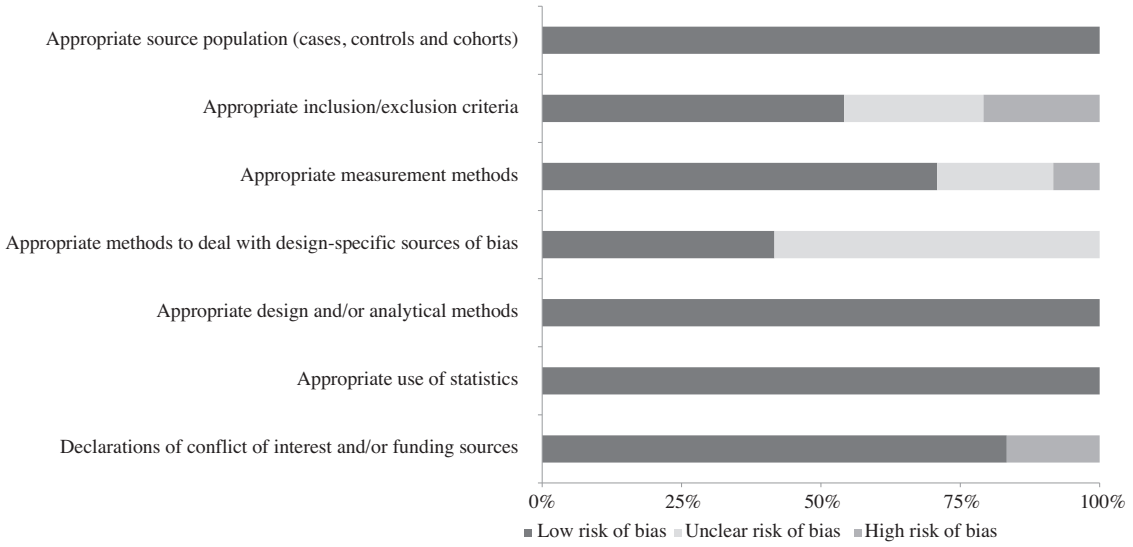

FIGURE 2 Risk of bias graph.

Given the diversity of measures, and the discrepancies between the nonadherence estimates they produced, we performed a sensitivity analysis excluding studies that used less reliable and/or valid measures of adherence (i.e. self-report and MPR). With these measures excluded, the summary estimate of nonadherence remained stable at 31.1% (95% CI = 24.9–38.1, $k = 21$) and between-study heterogeneity remained significant ($I^2 = 99.56$, $P < 0.001$). Furthermore, we conducted a separate analysis by using direct measures of adherence only (i.e. DOT, physical tests, and combination measures). As expected, the summary estimate for these measures was higher than the overall estimate (45.7% nonadherence, 95% CI = 36.1–55.1, $k = 15$) and heterogeneity remained significant ($I^2 = 90.22$, $P < 0.001$).

Study setting: Four studies were set in primary care [18,28,30,35], 10 in general hospitals [20–23,25,27,32,36],

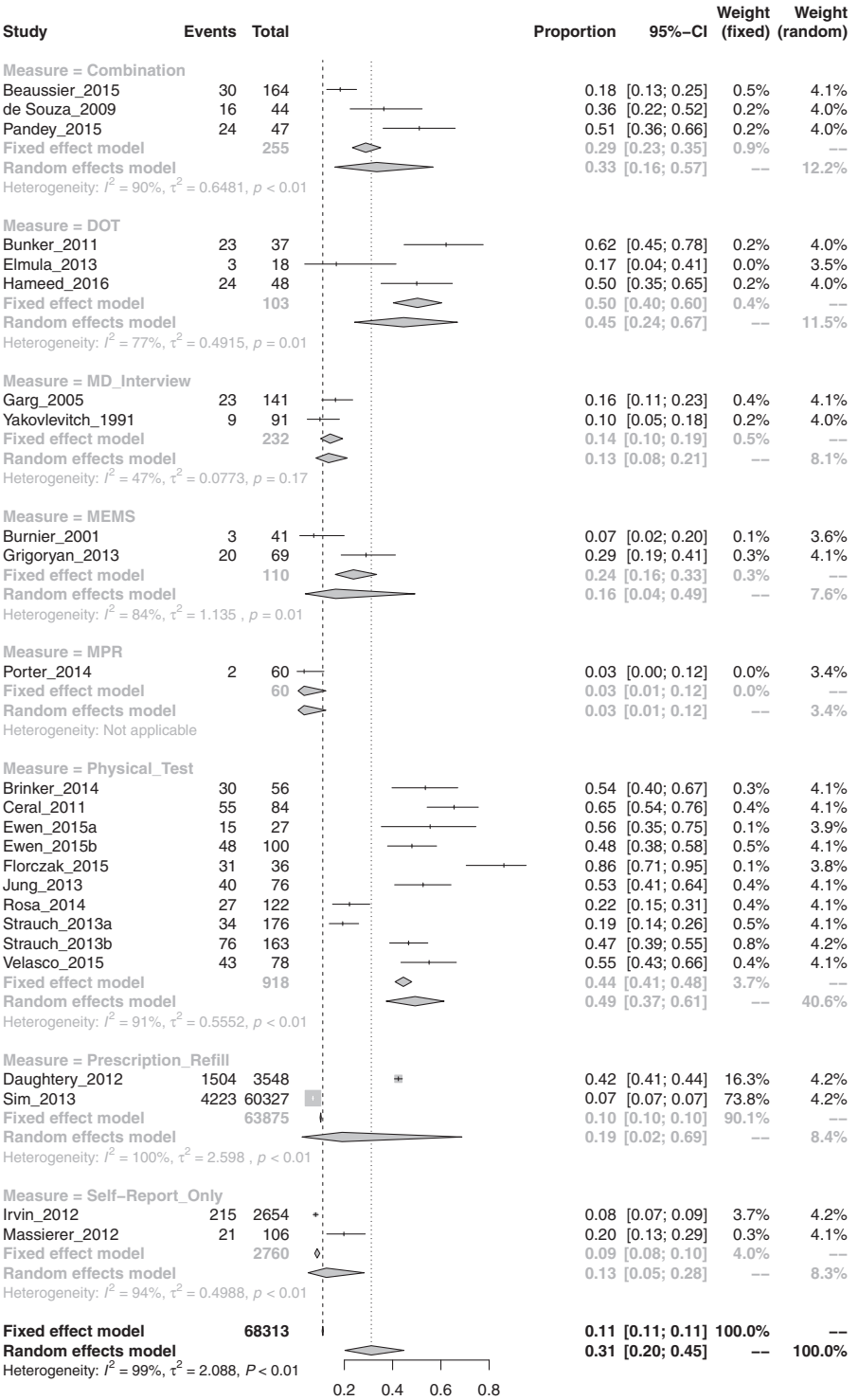

FIGURE 3 Forest plot for subgroup analysis of medication nonadherence estimates by adherence measure.

and 10 in referral clinics [16,17,19,24,26,33,34,38–40]. The lowest estimates were observed for studies set in primary care (25.8%, $k=4$); the highest for studies set in referral clinics (34.1%, $k=11$). The estimate for studies set in general hospitals was 29.2% ($k=9$). Refer to Fig. 4 for forest plot.

Definition of resistant hypertension: Seven studies adhered to the AHA/ESH/ESC definition of resistant hypertension [16,28,31,34–37]. There was no significant difference between pooled estimates for studies that used the AHA/ESH/ESC definition (30.5%, 95% CI = 13.7–54.9, $I^2=99.83$, $k=7$) and studies that used other definitions (32.1%, 95% CI = 22.5–43.5, $I^2=91.96$, $k=17$).

DISCUSSION

These findings suggest that, depending how adherence is measured, approximately 31% of cases of aTRH may be potentially explained by poor adherence. In the studies using objective indicators such as bioassays, we estimated that this nonadherence figure is closer to 50%. Although there are numerous caveats to this analysis, these findings from a broad range of studies from throughout the world suggest that a substantial proportion of those currently diagnosed with and treated for resistant hypertension may not have the condition. Therefore, it is likely that treatment intensification in those with hypertension who

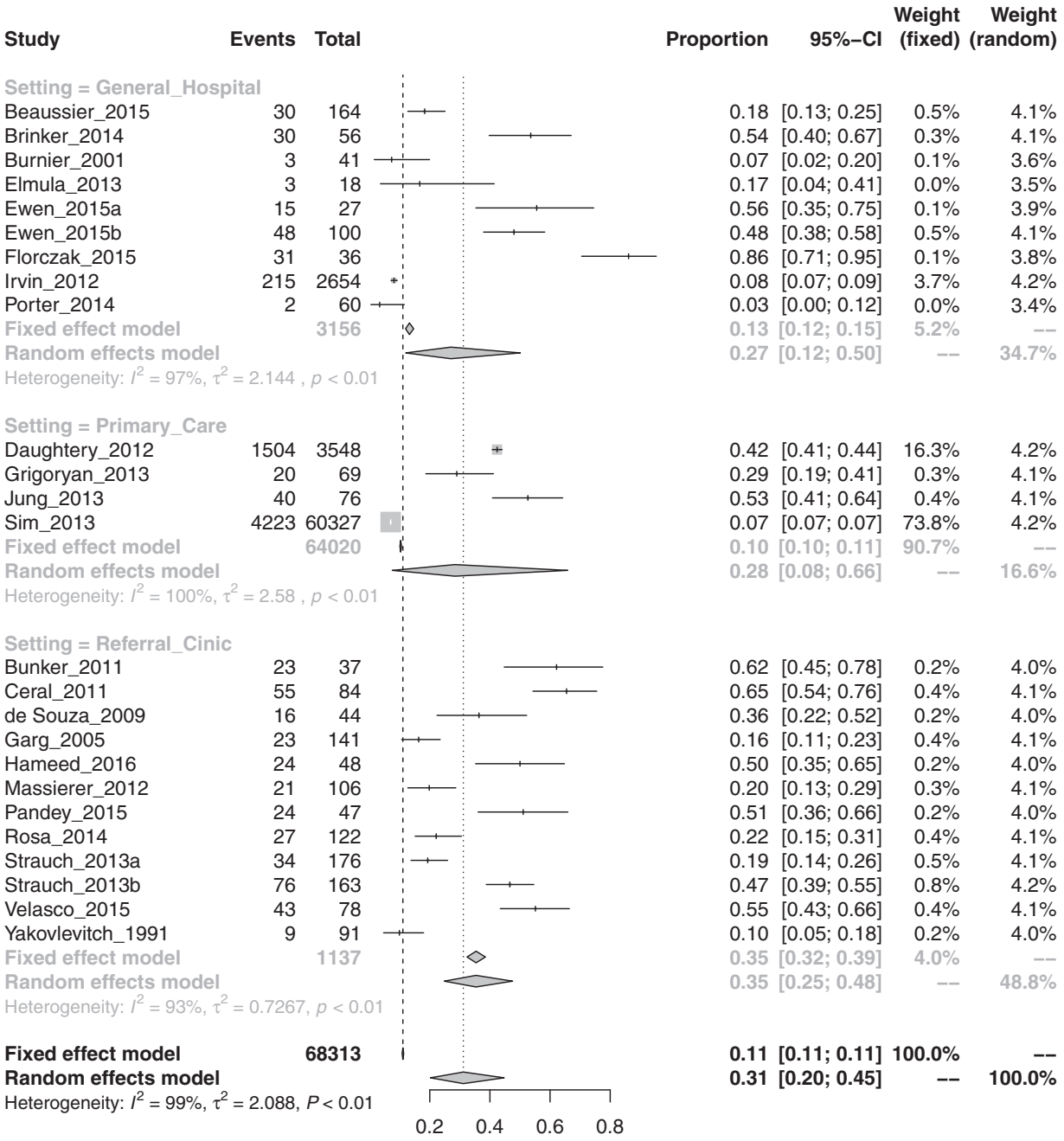

FIGURE 4 Forest plot for subgroup analysis of medication nonadherence estimates by study setting.

appear not to be responding to treatment may be frequently unwarranted where nonadherence has not been assessed.

Adherence is recognized as a key factor in the effectiveness of antihypertensive medication; however, unreliability of adherence assessment has limited its use in clinical practice [41]. A diverse range of adherence assessment methods were used across studies, and the type of measure used to assess adherence had a significant impact on nonadherence estimates. Physical tests of urine or blood were by far the most common, with nine studies using this method as the sole assessment, and three additional studies using physical tests in conjunction with self-report measures. Direct measures, that is, physical tests and DOT, yielded the highest estimates, whereas MPR and pharmacy data yielded the lowest estimates. Although different measures yield highly variable estimates of nonadherence, each measure provides important information that can contribute to our understanding of nonadherence in different ways. For example, although MEMS have been touted by some as a gold standard, the measure recorded is not a direct confirmation that a pill has been taken but merely that the container has been opened; as such, they tell us nothing about those who intentionally modify or skip doses. Although physical tests can confirm that a patient has swallowed their medication, these measurements give only a single snapshot of behaviour and so daily-life adherence between visits may be underestimated or overestimated. Furthermore, certain pharmacokinetic considerations must be made when interpreting results of these tests for different antihypertensive agents. In addition, although self-report measures are subject to a host of biases, they have the potential to elucidate reasons for nonadherence (e.g. illness perceptions, treatment-related beliefs, or cognitive deficits) in a way that more objective measures cannot. Therefore, it is unlikely that there will be a single-gold standard measure that will not make some trade-off on reliability or validity. Significantly, studies that used a combination of physical and self-report measures yielded an estimate closest to the total summary estimate, perhaps suggesting that a combination of objective and subjective measures is the best way to accurately determine nonadherence.

The definition of resistant hypertension varied substantially between studies. Although this was not a significant moderator of nonadherence estimates, this selective observance of the established definition of resistant hypertension should be considered. The most frequent way in which individual study definitions of resistant hypertension differed from that put forward by the AHA/ESH/ESC was the exclusion of patients who required four or more antihypertensive agents to achieve BP control. Exclusion of this important subgroup of aTRH patients has limited the conclusions we can draw regarding the impact of nonadherence for aTRH; in fact, it may be that the proportion of resistant hypertension accounted for by nonadherence would have been higher had these patients been more consistently accounted for within these studies.

The current review identified that certain study-level characteristics moderate nonadherence estimates. However, only six of the included studies examined potential patient-level predictors of nonadherence, and none of these looked beyond basic demographic factors such as age, sex, race, or indicators of socioeconomic status. Though some research has examined patient-level factors affecting nonadherence in hypertension (e.g. [42]), to date the aTRH literature has largely neglected intensive study of nonadherent patients. The primary focus of these studies has been to identify patients whose hypertension is truly resistant to pharmacological treatment. Though this is a critical movement within the study of hypertension, it is insufficient to identify nonadherence among aTRH patients without intention to intervene. Patients who are nonadherent to their antihypertensive medications may not be truly resistant; they are, however, still at elevated cardiovascular risk relative to those whose BP is under control. Little attention has been paid to patient-level factors that affect nonadherence for aTRH patients; this is an important limitation of the literature that merits consideration. Investigation of potential predictors of nonadherence for aTRH, using well established theoretical frameworks and a diversity of measures of adherence, is necessary to inform the development of behaviour-change strategies to promote optimal adherence [43–45], decrease risk of adverse cardiovascular events, and reduce unnecessary prescribing and economic burden on the healthcare system.

In addition to the measurement challenges, there are several additional limitations to be considered. The study of medication adherence for aTRH is increasing rapidly; as such, this review is somewhat limited by the exclusion of articles published after January 2016. However, given that the majority of studies included in this meta-analysis were published within the last 5 years, we can tentatively assume that these are methodologically consistent with more recently published articles that might have been included. The majority of studies we included were descriptive in nature; it has been argued that study bias may be even more confounding for observational studies, and so assessing risk of bias for this type of review is critical. However, there are fewer well established tools available for assessing quality and risk of bias for observational studies, as compared with tools for assessing randomized control trials. For this reason, we used broad criteria identified in a systematic review by Sanderson *et al.* [11]; however, given that a variety of study designs were included, applying the same assessment criteria to all studies proved difficult. Furthermore, given the broad inclusion criteria, the vastly different ways of measuring adherence behaviour, and that aTRH as a condition remains poorly defined in the literature, it is unsurprising that the studies included were significantly heterogeneous and that certain subgroups were considerably small [particularly for MPR, medical doctor (MD) interview, and MEMS]. However, to forgo the meta-analysis because of heterogeneity in this instance fails to address the question of how exactly to synthesize this data in a meaningful and useful way [46].

Limitations notwithstanding, this review had several important strengths. The systematic approach taken ensures that the existing body of literature has been accurately represented, and the statistical techniques employed attempt to explain the considerable variability within this literature. Furthermore, the review was conducted by a multidisciplinary team that included behavioural scientists

and clinicians involved in the care of people with aTRH. This wealth of methodological and clinical knowledge allowed for a diversity of views to be represented during the review process, and has resulted in a review with important implications not only for health science but also clinical practice.

The current study represents the first attempt to systematically synthesize the disparate range of studies that have estimated the prevalence of nonadherence in aTRH. The findings provide an imprecise estimate of nonadherence for this condition. The current evidence suggests that a substantial proportion of people receiving pharmacological treatment for hypertension may not be adherent and therefore, may be inappropriately classified as having aTRH. Given the considerable economic cost of treating hypertension, greater effort must be made to predict nonadherence, and intervene with those who choose or simply forget to take their antihypertensive medication.

ACKNOWLEDGEMENTS

The research is supported by the Health Research Board Patient-Oriented Research Award (Ref: HRA-POR-2014-615).

Conflicts of interest

A.W.M. and the Discipline of General Practice at NUI Galway have received unrestricted funding from Menarini, MSD Ireland and Novartis. The authors have no other conflicts of interest to declare.

REFERENCES

1. Mazzaglia G, Ambrosioni E, Alacqua M, Filippi A, Sessa E, Immordino V, *et al*. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. *Circulation* 2009; 120:1598–1605.
2. Pittman DG, Tao Z, Chen W, Stettin GD. Antihypertensive medication adherence and subsequent healthcare utilization and costs. *Am J Manag Care* 2010; 16:568–576.
3. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, *et al*. Resistant hypertension: diagnosis, evaluation, and treatment a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Hypertension* 2008; 51:1403–1419.
4. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, *et al*. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Blood Press* 2013; 22: 193–278.
5. Achelrod D, Wenzel U, Frey S. Systematic review and meta-analysis of the prevalence of resistant hypertension in treated hypertensive populations. *Am J Hypertens* 2014; 28:355–361.
6. Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, *et al*. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation* 2012; 125:1635–1642.
7. Berra E, Azizi M, Capron A, Høieggen A, Rabbia F, Kjeldsen SE, *et al*. Evaluation of adherence should become an integral part of assessment of patients with apparently treatment-resistant hypertension. *Hypertension* 2016; 68:297–306.
8. Hyman DJ, Pavlik V. Medication adherence and resistant hypertension. *J Hum Hypertens* 2015; 29:213–218.
9. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151:264–269.
10. Myat A, Redwood SR, Qureshi AC, Spertus JA, Williams B. Resistant hypertension. *BMJ* 2012; 345:e7473.
11. Sanderson S, Tatt ID, Higgins JPT. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. *Int J Epidemiol* 2007; 36:666–676.
12. Schwarzer G. Meta: an R package for meta-analysis. *R News* 2007; 7: 40–45.
13. R Core Team. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2013; Available at: http://www.R-project.org/ [Accessed October 2016].
14. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. *Introduction to meta-analysis*. Chichester, UK: Wiley; 2009.
15. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315:629–634.
16. Štrauch B, Petrák O, Zelinka T, Rosa J, Šomlóová Z, Indra T, *et al*. Precise assessment of noncompliance with the antihypertensive therapy in patients with resistant hypertension using toxicological serum analysis. *J Hypertens* 2013; 31:2455–2461.
17. Rosa J, Zelinka T, Petrák O, Štrauch B, Šomlóová Z, Indra T, *et al*. Importance of thorough investigation of resistant hypertension before renal denervation: should compliance to treatment be evaluated systematically. *J Hum Hypertens* 2014; 28:684–688.
18. Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, Toennes SW. Resistant hypertension? Assessment of adherence by toxicological urine analysis. *J Hypertens* 2013; 31:766–774.
19. Hameed MA, Tebbit L, Jacques N, Thomas M, Dasgupta I. Nonadherence to antihypertensive medication is very common among resistant hypertensives: results of a directly observed therapy clinic. *J Hum Hypertens* 2016; 30:83–89.
20. Florczak E, Tokarczyk B, Warchoł-Celińska E, Szwench-Pietrasz E, Prejbisz A, Gosk M, *et al*. Assessment of adherence to treatment in patients with resistant hypertension using toxicological serum analysis. *Pol Arch Med Wewn* 2015; 125:65–72.
21. Elmula FEMF, Hoffmann P, Fossum E, Brekke M, Gjønnæss E, Hjørnholm U, *et al*. Renal sympathetic denervation in patients with treatment-resistant hypertension after witnessed intake of medication before qualifying ambulatory blood pressure. *Hypertension* 2013; 62:526–532.
22. Ewen S, Cremers B, Meyer MR, Donazzan L, Kindermann I, Ukena C, *et al*. Blood pressure changes after catheter-based renal denervation are related to reductions in total peripheral resistance. *J Hypertens* 2015; 33:2519–2525.
23. Ewen S, Meyer MR, Cremers B, Laufs U, Helfer AG, Linz D, *et al*. Blood pressure reductions following catheter-based renal denervation are not related to improvements in adherence to antihypertensive drugs measured by urine/plasma toxicological analysis. *Clin Res Cardiol* 2015; 104:1097–1105.
24. Ceral J, Habrdova V, Vorisek V, Bima M, Pelouch R, Solar M. Difficult-to-control arterial hypertension or uncooperative patients? The assessment of serum antihypertensive drug levels to differentiate nonresponsiveness from nonadherence to recommended therapy. *Hypertens Res* 2011; 34:87–90.
25. Beaussier H, Boutouyrie P, Bobrie G, Frank M, Laurent S, Coudoré F, Azizi M. True antihypertensive efficacy of sequential nephron blockade in patients with resistant hypertension and confirmed medication adherence. *J Hypertens* 2015; 33:2526–2533.
26. Bunker J, Callister W, Chang C-L, Sever P. How common is true resistant hypertension? *J Hum Hypertens* 2011; 25:137–140.
27. Burnier M, Schneider MP, Chioléro A, Stubi CLF, Brunner HR. Electronic compliance monitoring in resistant hypertension: the basis for rational therapeutic decisions. *J Hypertens* 2001; 19:335–341.
28. Daugherty SL, Powers JD, Magid DJ, Masoudi FA, Margolis KL, O'Connor PJ, *et al*. The association between medication adherence and treatment intensification with blood pressure control in resistant hypertension. *Hypertension* 2012; 60:303–309.
29. Garg JP, Elliott WJ, Folker A, Izhar M, Black HR, Service RUH. Resistant hypertension revisited: a comparison of two university-based cohorts. *Am J Hypertens* 2005; 18:619–626.
30. Grigoryan L, Pavlik VN, Hyman DJ. Characteristics, drug combinations and dosages of primary care patients with uncontrolled ambulatory blood pressure and high medication adherence. *J Am Soc Hypertens* 2013; 7:471–476.

31. Pandey A, Raza F, Velasco A, Brinker S, Ayers C, Das SR, *et al.* Comparison of Morisky Medication Adherence Scale with therapeutic drug monitoring in apparent treatment-resistant hypertension. *J Am Soc Hypertens* 2015; 9:420–426.e2.
32. Porter AK, Taylor SR, Yabut AH, Al-Achi A. Impact of a pill box clinic to improve systolic blood pressure in veterans with uncontrolled hypertension taking 3 or more antihypertensive medications. *J Manag Care Pharm* 2014; 20:905–911.
33. Yakovlevitch M, Black HR. Resistant hypertension in a tertiary care clinic. *Arch Intern Med* 1991; 151:1786–1792.
34. Velasco A, Chung O, Raza F, Pandey A, Brinker S, Arbique D, *et al.* Cost-effectiveness of therapeutic drug monitoring in diagnosing primary aldosteronism in patients with resistant hypertension. *J Clin Hypertens* 2015; 17:713–719.
35. Sim JJ, Bhandari SK, Shi J, Liu ILA, Calhoun DA, McGlynn EA, *et al.* Characteristics of resistant hypertension in a large, ethnically diverse hypertension population of an integrated health system. Mayo Clinic Proceedings: Elsevier; 2013. pp. 1099–1107.
36. Irvin MR, Shimbo D, Mann DM, Reynolds K, Krousel-Wood M, Limdi NA, *et al.* Prevalence and correlates of low medication adherence in apparent treatment-resistant hypertension. *J Clin Hypertens* 2012; 14:694–700.
37. Brinker S, Pandey A, Ayers C, Price A, Raheja P, Arbique D, *et al.* Therapeutic drug monitoring facilitates blood pressure control in resistant hypertension. *J Am Coll Cardiol* 2014; 63:834–835.
38. de Souza WA, Sabha M, De Faveri Favero F, Bergsten-Mendes G, Yugar-Toledo JC, Moreno H. Intensive monitoring of adherence to treatment helps to identify 'true' resistant hypertension. *J Clin Hypertens* 2009; 11:183–191.
39. Massierer D, Oliveira ACT, Steinhorst AM, Gus M, Ascoli AM, Gonçalves SC, *et al.* Prevalence of resistant hypertension in nonelderly adults: prospective study in a clinical setting. *Arq Bras Cardiol* 2012; 99: 630–635.
40. Garg AX, Hackam D, Tonelli M. Systematic review and meta-analysis: when one study is just not enough. *Clin J Am Soc Nephrol* 2008; 3: 253–260.
41. Hamdidouche I, Jullien V, Boutouyrie P, Billaud E, Azizi M, Laurent S. Drug adherence in hypertension: From methodological issues to cardiovascular outcomes. *J Hypertens* 2017; 35:1133–1144.
42. Kurdi AI, Chen L-C, Elliott RA. Exploring factors associated with patients' adherence to antihypertensive drugs among people with primary hypertension in the United Kingdom. *J Hypertens* 2017; [Epub ahead of print].
43. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, *et al.* Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2014;CD000011.
44. Morrissey EC, Durand H, Nieuwlaat R, Navarro T, Haynes RB, Walsh JC, Molloy GJ. Effectiveness and content analysis of interventions to enhance medication adherence in hypertension: a systematic review and meta-analysis protocol. *Syst Rev* 2016; 5:1–7.
45. Morrissey EC, Durand H, Nieuwlaat R, Navarro T, Haynes RB, Walsh JC, Molloy GJ. Effectiveness and content analysis of interventions to enhance medication adherence and blood pressure control in hypertension: a systematic review and meta-analysis. *Psychol Health* 2017;1–38; [Epub ahead of print].
46. Lau J, Ioannidis JPA, Schmid CH. Summing up evidence: one answer is not always enough. *Lancet* 1998; 351:123–127.

Reviewers' Summary Evaluations

Reviewer 2

This manuscript provides a comprehensive assessment of the importance of medication nonadherence as a contributor to apparent treatment-resistant hypertension. Using data from 24 studies that measured medication adherence for patients with uncontrolled hypertension, despite being prescribed ≥ 3 antihypertensive medications of different classes, the authors conclude that about one-third of such patients are nonadherent to prescribed medications and objective measures of drug or drug metabolite in blood or urine are the most reliable method of assessment. The authors emphasize that a thorough knowledge of potential predictors of nonadherence to antihypertensive therapy is needed in order to inform the development of behavioral strategies to improve adherence and therefore improve BP control and cardiovascular disease outcomes.

Reviewer 3

Strengths

1. State-of-the art methodology
2. Multidisciplinary approach, with behavioral scientists, physicians, and biostatisticians
3. Well focused objective: patients with apparent treatment-resistant hypertension
4. Large number of studies ($n = 24$)

Weaknesses

1. In a rapidly growing field, it is a pity that the authors put, as an upper limit for publication, January 2016, which means that several papers published after January 2016 have not been taken into account
2. Only one study on medication possession ratio (MPR), and two studies on MD interview, electronic monitory (MEMS) or prescription refill