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The Prevalence of Nonadherence in Patients With Resistant Hypertension: A Systematic Review Protocol

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Abstract

Background: Resistant hypertension, usually defined as blood pressure remaining above goal despite the concurrent use of 3 or more antihypertensive agents of different classes, is common (about 10% prevalence) and known to be a risk factor for cardiovascular events. These patients also undergo more screening intensity for secondary hypertension. However, not all patients with apparent treatment-resistant hypertension have true resistant hypertension, with some of them being nonadherent to prescribed pharmacotherapy. The prevalence of nonadherence varies from about 5% to 80% in the published literature. However, the relative contributions of intentional and nonintentional nonadherence are not well described. Nonintentional nonadherence refers to occasional forgetfulness and/or carelessness and can sometimes be related to an inability to follow instructions, because of either cognitive or physical limitations. Intentional nonadherence refers to an active process in which a patient may choose to alter the prescribed medication regimen by discontinuing medications, skipping doses, or modifying doses or dosing intervals.

Objective: Our objective is to establish the overall prevalence of nonadherence in the apparent treatment-resistant hypertension population and evaluate the relative contributions of nonintentional and intentional nonadherence subtypes.

Design: We will conduct a systematic review and meta-analysis.

Setting: We will include observational studies and randomized controlled trials where adherence to antihypertensive medications is measured using a test of adherence, either direct or indirect.

Patients: We will include adult human participants aged 18 years or older with a diagnosis of resistant hypertension.

Measurements: Data extracted from individual studies will include title, first author, design, country, publication year, funding body, method of assessing adherence to antihypertensive medication, prevalence of medication nonadherence, definition of resistant hypertension, sample size, sex, mean age, and coexistent comorbidities.

Methods: A librarian will search the databases Medline, EMBASE, Cochrane, CINAHL, and Web of Science for studies meeting criteria for inclusion. Two reviewers will independently screen the titles and abstracts retrieved and assess the methodological quality of eligible full-text articles using the Cochrane Risk of Bias tool for clinical trials and the Newcastle-Ottawa Scale for observational studies. Summary estimates of prevalence will be generated using pooled analysis using the random-effects method. Subgroup analyses, sensitivity analyses, and evaluation of publication bias will also be performed.

Results: The outcomes of interest are the pooled prevalence of nonadherence to antihypertensive medication in apparent treatment-resistant hypertension and the prevalence of nonadherence based on different methods of assessing nonadherence (indirect vs direct), which will allow us to estimate the relative proportion of unintentional and intentional nonadherence subtypes in the overall phenomenon of medication nonadherence.

Limitations: Possible limitations of this study include the finding of severe heterogeneity, the limitations of the literature search, publication bias, and the lack of granular data in the published studies for a study-level meta-analysis.

Conclusions: This systematic review will provide a synthesis of current evidence on the prevalence of medication nonadherence in apparent treatment-resistant hypertension and on the relative contributions of nonintentional and intentional nonadherence subtypes. These findings will provide clinicians with a better understanding of the factors underlying treatment-resistant hypertension and will serve as a strong research base to guide future research on interventions to address medication nonadherence as well as the nonintentional and intentional subtypes.

Trial registration: This protocol has been registered with PROSPERO. We will add registration details once available.

Abrégé

Contexte: On définit généralement l'hypertension réfractaire comme une valeur de pression artérielle qui demeure au-dessus de la valeur cible, et ce, malgré l'administration concomitante d'au moins trois agents antihypertenseurs de classes différentes. L'hypertension réfractaire est fréquente (prévalence d'environ 10 %) et constitue un facteur de risque d'événements cardiovasculaires. Les patients atteints d'hypertension réfractaire font également l'objet d'un dépistage plus intensif de l'hypertension secondaire. Cependant, tous les cas apparents d'hypertension résistante au traitement ne constituent pas nécessairement des cas d'hypertension réfractaire. Certains résultent plutôt d'une inobservance de la pharmacothérapie prescrite. La littérature rapporte une prévalence d'environ 5 à 80 % de l'inobservance du traitement, mais les contributions relatives de l'inobservance intentionnelle et non intentionnelle ne sont pas clairement établies. L'inobservance non intentionnelle fait référence aux oublis occasionnels ou à la négligence, qui peuvent être liés à l'incapacité de suivre des instructions en raison de limitations physiques ou cognitives. L'inobservance intentionnelle désigne quant à elle un processus actif où le patient choisit consciemment de modifier la posologie de sa médication, soit en interrompant le traitement, en sautant des doses ou en modifiant les doses ou les intervalles posologiques.

Objectifs: Nous souhaitons mesurer la prévalence globale de l'inobservance au traitement parmi les cas apparents d'hypertension réfractaire et établir la contribution relative des sous-types intentionnel et non intentionnel d'inobservance.

Type d'étude: Nous procéderons à une revue systématique et à une méta-analyse de la documentation pertinente.

Cadre: L'étude inclura les études observationnelles et les essais contrôlés à répartition aléatoire traitant d'une mesure de l'observance du traitement antihypertenseur au moyen d'un test d'observance direct ou indirect.

Sujets: Seront inclus tous les patients adultes ayant reçu un diagnostic d'hypertension réfractaire.

Mesures: Les données suivantes seront extraites de chaque étude : le titre de l'article, le nom de l'auteur principal, la méthodologie et le lieu de l'étude, l'année de publication, l'organisme ayant financé les travaux, la méthode employée pour la mesure de l'observance, la prévalence de l'inobservance, la définition d'hypertension réfractaire, la taille de l'échantillon, ainsi que le sexe, l'âge moyen et les comorbidités des patients.

Méthodologie: Un bibliothécaire fera une présélection des études répondant aux critères d'inclusion dans les bases de données Medline, EMBASE, Cochrane, CINAHL et Web of Science. Les titres et résumés des articles retenus seront révisés de façon indépendante par deux examinateurs qui évalueront également la qualité méthodologique des articles complets à l'aide de l'outil Cochrane sur le risque de biais (essais cliniques) et de l'échelle de Newcastle-Ottawa (études observationnelles). Des estimations sommaires de la prévalence seront générées par l'analyse de l'ensemble des données par une méthode à effets aléatoires. Nous procéderons également à des analyses de sous-groupes, à des analyses de sensibilité, de même qu'à l'évaluation des biais de publication.

Résultats: Le principal résultat attendu est la combinaison de la prévalence de l'inobservance du traitement antihypertenseur dans les cas d'hypertension réfractaire apparente et de la prévalence de l'inobservance selon la méthode employée pour la mesurer (indirecte ou directe). Ce résultat nous permettra d'estimer la proportion des sous-types (inobservance intentionnelle et non intentionnelle) dans l'ensemble des cas répertoriés d'inobservance au traitement.

Limites: Les résultats pourraient être limités par une importante hétérogénéité, des facteurs limitant la recherche documentaire, des biais de publication et le manque de données agrégées dans les études publiées pour procéder à une méta-analyse au niveau de l'étude.

Conclusion: Cette revue systématique constituera une synthèse des données probantes sur la prévalence de l'inobservance au traitement dans les cas apparents d'hypertension réfractaire et sur les contributions relatives des sous-types intentionnel et non intentionnel d'inobservance. Ces résultats permettront aux cliniciens de mieux comprendre les facteurs sous-tendant l'hypertension réfractaire. Ils serviront également de base solide pour orienter les recherches futures sur des interventions visant à aborder l'inobservance au traitement médicamenteux et ses sous-types intentionnel et non intentionnel.

Keywords

resistant hypertension, apparent treatment-resistant hypertension, pseudoresistant hypertension, adherence, nonintentional nonadherence, intentional nonadherence, compliance, antihypertensive drugs, systematic review

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Background

Resistant hypertension is defined by the American Heart Association/European Society of Hypertension/European Society of Cardiology (AHA/ESH/ESC) as blood pressure (BP) remaining above goal despite the concurrent use of 3 or more antihypertensive agents of different classes, with one of the classes being a diuretic and all of the medications being prescribed at optimal dose amounts, or with controlled BP, but requiring 4 or more medications.[1,2] It is common, with an estimated prevalence of about 10%, and known to be a risk factor for cardiovascular events.[3] Furthermore, patients with resistant hypertension are often part of high-risk groups with multiple cardiovascular comorbidities as well as vulnerable or disadvantaged populations. Hence, these patients undergo higher screening intensity for secondary hypertension. However, not all patients with apparent treatment-resistant hypertension have true resistant hypertension. Some of them may in fact be on an inadequate BP-lowering medication regimen, a phenomenon sometimes referred to as therapeutic inertia.[4] Others may suffer from white-coat hypertension, in which office BPs are persistently elevated, whereas home BPs are within the normal range.[5] Importantly, some of them may be nonadherent to prescribed pharmacotherapy.[6,7] There are several ways of assessing medication nonadherence in hypertensive patients and other patient populations. These can be broadly divided into indirect and direct methods. Indirect methods include questionnaires, self-reports, pill counts, rates of prescription refills, assessment of the patient's response, and measurement of physiological markers such as BP and heart rate (HR), medication event monitoring systems, and patient diaries. Direct methods include directly observed therapy and measurement of the levels of BP-lowering drugs in physiologic fluids such as blood and urine.[6] The long-term prevalence of nonadherence in chronic diseases is about 50%.[8] However, this varied from 3% to 86% in individual studies in apparent treatment-resistant hypertension patients from a recent systematic review.[9] 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% (directly observed therapy) and 49% (physical test, ie, blood or urine assay). Although they were not grouped in this fashion, the former are indirect measures and the latter are the more accurate direct measures. Increased awareness of these methods is important because only the direct measures can identify the phenotype of "intentional" nonadherence. Nonintentional nonadherence refers to occasional forgetfulness and/or carelessness and can sometimes be related to an inability to follow instructions because of either cognitive or physical limitations. It can be identified with pill counts or pharmacy refill data.[6,8] It can be managed using reminders, pill packs, and other interventions. Intentional nonadherence refers to an active process in which a patient may choose to alter the prescribed medication regimen by discontinuing medications entirely, skipping doses, or modifying doses or dosing intervals, however still continuing to refill prescriptions.[7] Underlying health beliefs and certain demographic factors and comorbid conditions have been associated in the past with intentional nonadherence in other settings.[10,11] Intentional nonadherence thus evades detection by indirect measures, such as pill counts of pharmacy refill reports. It requires more intensive measures (such as therapeutic drug monitoring or directly observed therapy) to diagnose.[6,7,12] Interventions to address intentional nonadherence are also not well studied. Our research questions are the following:

Research Question 1: What is the overall prevalence of nonadherence in the apparent treatment-resistant hypertension population?
Research Question 2: What are the relative contributions of adherence with direct and indirect measures of adherence?

In principle, the difference between the indirect and direct measures may help us estimate the level of intentional nonadherence in this setting.

Methods

Study Design

This systematic review aims to evaluate the overall prevalence of medication nonadherence in the apparent treatment-resistant hypertension population and to determine the variation in nonadherence based on direct and indirect measures. It adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[13] using the Cochrane Risk of Bias tool and the Newcastle-Ottawa Scale to qualitatively evaluate the studies included in the systematic review.[14,15] This protocol is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2015 checklist (see Supplemental Material).

Eligibility Criteria

Types of studies. We will include observational studies, including cross-sectional, retrospective, and prospective studies, as well as randomized controlled trials (RCTs).

Patient population. We will include studies conducted on adult human participants aged 18 years or older with a diagnosis of resistant hypertension.

Intervention. We will include studies where adherence to BP-lowering medications is measured using a test of adherence, either direct (such as therapeutic drug monitoring or directly

Table 1. Medline Search Strategy-Ovid Interface.

Medline search strategy—Ovid interface
1. Hypertension/dt and (resistant or uncontrolled or refractory).tw.
2. ((or uncontrolled or refractory) adj3 (hypertens* or blood pressure or bp)).tw.
3. ATRH.tw.
4. resistant hypertension.kw.
5. or/1-4
6. Medication Adherence/ or Patient Compliance/
7. (adheren* or nonadheren* or complian* or noncomplian*).tw,kf.
8. 6 or 7
9. 5 and 8
10. exp Cohort Studies/
11. (cohort or retrospective* or prospective*).tw,kf.
12. Cross-Sectional Studies/
13. (cross-sectional or prevalence).tw,kw.
14. randomized controlled trial.pt.
15. controlled clinical trial.pt.
16. randomi?ed.ab.
17. placebo.ab.
18. clinical trials as topic.sh.
19. randomly.ab.
20. trial.ti.
21. or/10-20
22. 9 and 21
23. (infant/ or child/) not adult/
24. 22 not 23

observed therapy) or indirect (eg, pill counts or pharmacy refill data).

Language. We will only include studies published in the English language. Studies published in other languages will be included if a full-text version is available in English.

Information sources and search strategy. The specific search strategies will be created by a librarian with expertise in systematic review searching. These search strategies will then be reviewed by an independent second librarian, in accordance with the Peer Review of Electronic Search Strategies (PRESS) standard.[16] The databases Medline (Ovid Interface, 1946 through April 2, 2019), EMBASE Classic+EMBASE (1947 through April 2, 2019), Cochrane (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials), CINAHL, and Web of Science will be searched. The search terms will be adapted for the different databases. The Medline search strategy is included in Table 1.

Study Records

Data management and selection process. Titles and abstracts of studies identified through the various database searches will be uploaded to Covidence, an Internet-based software program that facilitates collaboration among reviewers during the study selection process.[17] Two reviewers (G.B. and J.V.I.) will independently screen the titles and abstracts retrieved after the literature search to evaluate whether they meet the predefined inclusion criteria. Conflicts arising after the title and abstract screening step will be resolved through discussion between the 2 reviewers until a consensus is reached. Full-text articles for the studies meeting the inclusion criteria will be retrieved and screened by the same 2 reviewers to select studies to be included in the systematic review. Should the reviewers be unable to retrieve the full-text version of a study after thorough searching using different databases and search strategies, or should a full-text version be unavailable, the study will be excluded from the systematic review. Again, conflicts arising after this step of the screening process will be resolved through discussion between the 2 reviewers to reach consensus. The reasons for excluding trials will be recorded, both after title and abstract screening and after full-text screening. Reviewers will not be blinded to the authors or journals when screening articles.

Data collection process. A data extraction template will be created by the principal investigator (S.H.), in collaboration with one of the reviewers (G.B.), in Microsoft Excel. Data will be extracted independently and in duplicate from each eligible study by 2 reviewers (G.B. and J.V.I.). Any disagreements between the 2 independent reviewers (G.B. and J.V.I.) will be resolved through discussion until a consensus is reached. Reviewers will not be blinded to the authors or journals during this process.

Data items. Data extracted from the full text of studies included in this systematic review will include the following: (1) title, (2) first author, (3) study design, (4) country where the study was performed, (5) publication year, (6) funding body, (7) method of assessing adherence to antihypertensive medication (direct or indirect with specific method, including different methods used concurrently or sequentially within a single study), (8) prevalence of adherence or nonadherence to antihypertensive medications, and (9) definitions of resistant hypertension (including number of medications prescribed needed to meet definition, level of BP needed to meet definition, and way of measuring BP [office BP, home BP, or ambulatory BP monitoring] as well as inclusion or exclusion of secondary causes of hypertension).

In addition, demographic data extracted from each group (adherent vs nonadherent) in each included study will include the following: (1) sample size, (2) sex (percentage of men and women), (3) mean age (years), and (4) coexistent comorbidities (coronary artery disease, diabetes, previous cardiovascular disease, chronic kidney disease, obesity, dyslipidemia, depression).

Outcomes and prioritization. The primary outcome of interest is the pooled prevalence of nonadherence to antihypertensive medication in apparent treatment-resistant hypertension, expressed in percentages.

The secondary outcome of interest is the prevalence of nonadherence, expressed in percentages, based on different methods of assessing nonadherence (indirect vs direct), which will allow us to estimate the relative proportion of unintentional and intentional nonadherence subtypes in the overall phenomenon of medication nonadherence.

Quality assessment of individual studies. We will evaluate the study quality and the presence of potential bias within individual studies included in this systematic review at both the outcome and study levels. The methodological quality of eligible full-text articles will independently be assessed by 2 reviewers (G.B. and J.V.I.) using the Cochrane Risk of Bias tool[14] (for RCTs) and the Newcastle-Ottawa Scale[15] (for observational studies). The Cochrane Risk of Bias tool includes the following domains: Selection Bias, Performance Bias, Detection Bias, Attrition Bias, Reporting Bias, and Other Bias. The Newcastle-Ottawa Scale includes the following domains: Selection, Comparability, Exposure, and Outcome. Disagreements will be resolved through discussion until consensus is reached.

Data synthesis. In the absence of significant heterogeneity, defined as less than 80%, a pooled estimate of the prevalence of nonadherence will be generated. The summary prevalence will be estimated using the random-effects modeling as described by DerSimonian and Laird.[18] We have chosen 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 will use the Cochran Q statistic test and the I^2 statistic. All analyses will be conducted using the Comprehensive Meta-Analysis V2 software (Version 2.2; Biostat, Englewood, New Jersey).

Subgroup analyses will be used to explore possible sources of heterogeneity, based on the type of test used to measure adherence (direct vs indirect, specific test, concurrent or sequential use of different tests within a single study), study design, and definition of resistant hypertension. We will conduct univariate meta-regression to assess moderator variables which are continuous in nature. The subgroup analyses and meta-regression will also be assessed as a method of resolving any statistical heterogeneity, if present. Sensitivity analyses will be conducted by excluding 1 study at a time and observing change in pooled estimate (with a $>10\%$ change being considered significant).

We will follow the Meta-analysis of observational studies in epidemiology (MOOSE) guidelines while performing quantitative synthesis and reporting of the observational studies.[19]

Should meta-analysis not be feasible due to significant heterogeneity between the individual studies, we will perform a qualitative narrative synthesis. This will summarize the key characteristics of the studies included as outlined in the data items section as well as the methodological quality of the studies included as assessed as outlined in the quality assessment section.

Assessment of publication bias. Visual examination of funnel plots for asymmetry and Egger statistic will be used to assess for the presence of publication bias across included studies.[20]

Discussion

The purpose of this systematic review is to summarize the available literature on the prevalence of nonadherence to antihypertensives in the apparent treatment-resistant hypertension population and to determine the difference between nonadherence with direct and indirect measures.

The issue of medication nonadherence in patients with apparent treatment-resistant hypertension has previously been assessed in a study by Durand et al.[9] Although it is true that the methodology and primary outcome of our study resemble the ones encountered in the Durand et al systematic review and meta-analysis, there are a few important differences to highlight. Two years have passed since this review, and we believe more studies have been published since which will help provide an updated estimate.[21] There was substantial statistical heterogeneity in the review, which may also be present in the current study we are planning, and we will attempt to resolve this using meta-regression and subgroup analyses. In addition, this review also did not group studies by direct or indirect methods of measurement. Arguably, these are qualitatively useful and discrete subsets and may assist in furthering our understanding of the heterogeneous entity of nonadherence a little bit deeper. Possible limitations of the planned study include the finding of severe heterogeneity which may not be resolved by the analytic plan, the limitations of the literature search (attenuated by our use of an information specialist), publication bias, and the potential lack of granular data in the published studies for a study-level meta-analysis.

The findings of this systematic review will be useful to many clinicians to better assess the contribution of medication nonadherence to the problem of resistant hypertension. In addition, this systematic review will alert clinicians to the possibility of medication nonadherence in patients with apparent treatment-resistant hypertension as well as to the varying accuracy of different measures of nonadherence and will help prevent nonadherent patients from often undergoing invasive tests to screen for secondary causes of hypertension. It will also prevent this patient population from being unnecessarily referred for more invasive treatments. This will allow nonadherent patients with apparent

treatment-resistant hypertension to receive care more tailored to their specific needs and avoid the potential side effects and complications of these more advanced investigations. This systematic review will also provide a basis for future research on strategies to better address the different factors that contribute to medication nonadherence in this setting.

List of Abbreviations

AHA, American Heart Association; BP, blood pressure; ESC, European Society of Cardiology; ESH, European Society of Hypertension; HR, heart rate; RCTs, randomized controlled trials; PRESS, Peer Review of Electronic Search Strategies.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Author Contributions

S.H. developed the initial design; A.(S.)D. developed the search strategy with contribution from S.H.; G.B. wrote the initial draft of the manuscript; all authors read and approved the final manuscript.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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