Preventive Medicine 85 (2016) 90–97

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Review

Orthostatic hypotension and the risk of incidental cardiovascular diseases: A meta-analysis of prospective cohort studies

Wei Xin [a], Shuhua Mi [a,*], Zhiqin Lin [b], Hui Wang [b], Wei Wei [c]

[a] Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, No. 2 Anzhen Road, Chaoyang District, Beijing 100029, China
[b] Department of Cardiovascular Medicine, Affiliated Hospital of Guiyang Medical College, Guizhou, China
[c] Department of Pathophysiology, Medical School of Nankai University, Tianjin, China

ARTICLE INFO

Available online 26 January 2016

Keywords:
Orthostatic hypotension
Coronary heart disease
Stroke
Risk factors
Meta-analysis

ABSTRACT

Objective. To quantitatively estimate the prospective associations between orthostatic hypotension (OH) and cardiovascular diseases, including coronary heart disease (CHD) and stroke.

Methods. Relevant prospective cohort studies were identified by searching of Medline and Embase databases. We applied fixed or random effect model to estimate the overall effects depending on the heterogeneity among the included studies.

Results. Eight published articles from 7 cohorts, consisting of 64,782 participants, were included. During a mean follow-up of 15.2 years, 5719 CHD events and 3657 stroke events occurred. The overall results of the meta-analysis indicated that OH was associated with significant increased risk for incident CHD (adjusted hazard ratio [HR]: 1.32, 95% confidence interval [CI]: 1.12–1.56) and stroke (HR: 1.19, 95% CI 1.08–1.30), which were independent of conventional risk factors. Stratified analyses by ages suggested that the associations between OH and CHD and stroke were significant for both the middle-aged and the old participants.

Conclusion. Presence of OH was independently related to significantly increased risk for incidence of CHD and stroke. Further, studies regarding the mechanisms and potential treatments for OH may be important for understanding whether the associations between OH and cardiovascular diseases are causative.

Contents

Introduction

Orthostatic hypotension (OH) is currently considered as the failure of cardiovascular reflexes to maintain blood pressure on standing

* Corresponding author. Fax: +86 10 64451254.
E-mail address: mishuhuaaz@163.com (S. Mi).

http://dx.doi.org/10.1016/j.ypmed.2016.01.007
0091-7435/

from a supine position (Freeman et al., 2011). The prevalence of OH varied according to the different populations studied and tended to increase with age and the prevalence of comorbidities such as hypertension, diabetes mellitus (DM), cardiovascular (CV) disorders, and neurodegenerative diseases (Benvenuto and Krakoff, 2011; Fedorowski and Melander, 2013). A previous study showed that OH is not uncommon in hospitalized patients in the United States (36 per 100,000 patients), particularly in the elderly population (Shibao et al., 2007). Meanwhile, cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality in most of the countries all over the world (Go et al., 2013). Therefore, early identification of possible risk factors for CVDs is not only of significance to understand the novel pathophysiologic mechanisms of the diseases, but also critical for the development of preventative and therapeutic strategies against CVDs. Although individuals with OH are often asymptomatic (Rutan et al., 1992), it has been repeatedly observed that these subjects are likely to have some conventional conditions which may contribute to CVDs, including aging, hypertension, DM, metabolic disorders and possibly, higher body mass index (BMI) (Benvenuto and Krakoff, 2011; Fedorowski and Melander, 2013). Indeed, recent meta-analyses have shown that OH was related to an increased risk of heart failure (Xin et al., 2013a) and all-cause mortality (Xin et al., 2013b), and evidence from several epidemiological studies indicated that subjects with OH were associated with increased risk of future CV events (Eigenbrodt et al., 2000; Fedorowski et al., 2010; Lin et al., 2011; Rose et al., 2000; Verwoert et al., 2008), although the results of these studies are not always consistent (Alagiakrishnan et al., 2013; Casiglia et al., 2013; Fedorowski et al., 2013). Therefore, in this study, we performed a meta-analysis to summarize the current evidence regarding the association between OH and CVDs, and tried to establish an overall quantitative estimate of the prospective association between presence of OH and the incidental CVDs, including coronary heart disease (CHD) and stroke. Moreover, we tried to explore whether publication biases were significant among these studies, and to clarify which subgroups of subjects with OH are particularly at higher risk for incidental CVDs.

Methods

We followed the previously proposed MOOSE (Stroup et al., 2000) (Meta-analysis of Observational Studies in Epidemiology) and Cochrane's Handbook guidelines (Higgins and Green, 2011) during the design, implementation, analysis, and reporting for this study.

Literature searching

Pubmed and Embase databases were searched for relevant records, using the terms “orthostatic hypotension”, “postural hypotension” in combination with “cardiovascular diseases”, “coronary disease”, “myocardial ischemia”, “myocardial infarction”, “coronary restenosis”, “cerebrovascular disorders” and “stroke”. We limited the searching within studies in humans without restriction of languages. Reference lists of original and review articles were also screened using a manual approach for potential relevant studies. The final literature search was conducted on January 31th, 2014.

Study selection

Studies were included for analysis if they agreed with all of the following criteria: 1) published as full-length article in any language; 2) reported as prospective cohort studies (without restrictions of sample size and follow-up duration); 3) included adult population (aged over 18); 4) OH was identified at baseline as exposure of interest, and defined as a reduction in systolic BP ≥ 20 mm Hg or a reduction in diastolic BP ≥ 10 mm Hg within 3 min from supine to standing, which is in consistent with a previously published international consensus criteria (Kaufmann, 1996); 5) CHD or stroke events were recorded during follow-up; and 6) outcome data were reported as the multivariable-adjusted hazard ratio (HR) or risk ratio, and their corresponding 95% confidence intervals (CI) for CHD or stroke incidence as compared with individuals with OH at baseline to those without OH.

Data extraction and quality assessment

Two authors (WX and ZL) independently performed processed of literature searching, data extraction, and quality evaluation according to the inclusion criteria. Discrepancies were resolved by discussion. Extracted data include: 1) general information: year of publication and the location of the study; 2) baseline characteristics of the study population: source of the population, numbers of the participants, age, gender, mean BMI, proportions of participants with hypertension and DM; 3) definition and prevalence of OH at baseline; 4) follow-up data: follow-up duration, numbers of cases for each outcome, and variables that were adjusted for multivariable analysis; and 5) outcome data: HRs and 95% CIs for the associations between OH and CHD and stroke.

The quality of each study was evaluated using the Newcastle–Ottawa scale (Wells et al., 2010). This scale ranges from 1 to 9 stars and scores each study on the basis of three aspects: selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest.

Statistical analysis and data synthesis

Hazard ratio (HR) was used as a common measure of the associations between OH and the risk of incidental CHD and stroke across studies. HRs and corresponding standard errors, derived from 95% CIs or p values, were logarithmically transformed in order to stabilize variance and normalize the distribution (Higgins and Green, 2011). We applied the Cochrane's Q test (Higgins and Green, 2011) and I^2 test (Higgins and Thompson, 2002) to assess heterogeneity among studies. A significant heterogeneity was defined by a $p \geq 0.10$ at Q statistic and by $I^2 > 30\%$. However, if $I^2 < 40\%$, a not important heterogeneity might be considered among the included studies. If significant heterogeneity was detected, we used random-effect model to obtain a pooled estimate of effect, and the fixed-effect model was applied in the absence of heterogeneity. Sensitivity analyses, by removing each study individually at a time, were conducted to evaluate the robustness of our results. Univariate meta-regression and subgroup analyses were applied to evaluate the potential impacts of baseline characteristics of the participants (age, gender, mean BMI, proportions of the participants with hypertension and DM, and the prevalence of OH) and the studies (follow-up, event rates and study quality) on the overall effects. The median values of continuous variables were determined as cut-off values for grouping studies. Potential publication bias was assessed by funnel plots with the Egger regression asymmetry test (Egger et al., 1997). We used RevMan (version 5.1; Cochrane Collaboration, Oxford, UK) and STATA software (Version 12.0; Stata Corporation, College Station, TX) for the meta-analysis and statistics.

Results

Literature search results

The study searching process is shown in Fig. 1. Overall, the database searching identified 744 citations from Pubmed and Embase, of which the majority was excluded after initial screening of abstracts and titles, mainly based on the facts that they were not relevant studies, or the study design or article types did not meet the purpose of current analysis. After full-text review of 21 papers, eight papers were finally included in our meta-analysis.

Study characteristics and quality

Of note, our study included 8 papers (Alagiakrishnan et al., 2013; Casiglia et al., 2013; Eigenbrodt et al., 2000; Fedorowski et al., 2010; Fedorowski et al., 2013; Lin et al., 2011; Rose et al., 2000; Verwoert et al., 2008) based on 7 cohort studies, and 2 of the papers reported CHD and stroke outcomes separately based on the same cohort study (Eigenbrodt et al., 2000; Rose et al., 2000). Overall, 7 cohort studies with 64,782 participants, who were all free of CHD or stroke at baseline, were included in our meta-analysis. Six of the cohorts included general population (Alagiakrishnan et al., 2013; Casiglia et al., 2013; Eigenbrodt et al., 2000; Fedorowski et al., 2010; Lin et al., 2011; Rose et al., 2000; Verwoert et al., 2008), while the other one included hypertensive patients (Fedorowski et al., 2013). During a mean follow-up duration