Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies

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Background

Whether orthostatic hypotension (OH) is a risk factor for cardiovascular morbidity and death is uncertain. Currently available evidence derives from non-homogeneous and partly ambiguous studies.

Objective

We aimed at assessing the relationship between OH and death or major adverse cardiac and cerebrovascular events (MACCEs) by integrating results of previous studies.

Methods

We performed a meta-analysis of prospective observational studies reporting on the association between prevalent OH, mortality, and incident MACCE, published from 1966 through 2013. Mantel–Haenszel pooled estimates of relative risk (RR) and 95% confidence intervals (CIs) for all-cause death were assessed as the primary endpoint at the longest follow-up; incident coronary heart disease (CHD), heart failure (HF), and stroke were assessed as secondary endpoints. We also performed post hoc subgroup analyses stratified by age and a meta-regression analysis.

Results

We identified a total of 13 studies, including an overall population of 121 913 patients, with a median follow-up of 6 years. Compared with the absence of OH, the occurrence of OH was associated with a significantly increased risk of all-cause death (RR 1.50; 95% CI 1.24–1.81), incident CHD (RR 1.41; 95% CI 1.22–1.63), HF (RR 2.25; 95% CI 1.52–3.33), and stroke (RR 1.64; 95% CI 1.13–2.37). When analysed according to age, pooled estimates of RR (95% CI) for all-cause death were 1.78 (1.25–2.52) for patients <65 years old, and 1.26 (0.99–1.62) in the older subgroup.

Conclusion

Orthostatic hypotension is associated with a significantly increased risk of all-cause death, incident CHD, HF, and stroke.

Keywords

Orthostatic hypotension • Mortality • Heart failure • Stroke • Coronary artery disease

Introduction

According to the current International Consensus Statement (2011), orthostatic hypotension (OH) is defined as a sustained reduction of systolic blood pressure (SBP) of at least 20 mmHg and/or diastolic blood pressure of at least 10 mmHg, or SBP fall >30 mmHg in hypertensive patients with supine SBP >160 mmHg, when assuming a standing position or during a head-up tilt test of at least 60°. Orthostatic hypotension is a classic manifestation of autonomic nervous system (ANS) failure during orthostasis, and is a frequent finding in the elderly, with a prevalence reported between 6% and 35%. Further, OH prevalence increases with comorbidities, such as neurodegenerative, cardiovascular, metabolic and renal disorders. On a pathophysiological basis, causes of OH may be classified into two main categories according to the presence or absence of structural ANS disease. The structural autonomic impairment involves neurodegenerative processes affecting the ANS, and is traditionally referred to as ‘neurogenic OH’. The relative contribution of structural and confirmed autonomic disease in the overall OH prevalence in populations is less than 10%. A more common functional ANS failure, also known as non-neurogenic OH, includes drug-induced OH and OH occurring in conditions of volume depletion. When the underlying
condition cannot be determined, OH is described as idiopathic, accounting for at least one-third of all symptomatic patients with OH.4,5 The impaired orthostatic response may lead to symptoms of cerebral hypoperfusion and syncopal attacks directly by abrupt or progressive falls in blood pressure, or indirectly, by triggering the vasovagal reflex.4,6 However, the majority of patients with OH are asymptomatic or have few non-specific symptoms, thus accounting for a high rate of underdiagnosis.4,7

Over the last few decades, several epidemiologic studies have found significant associations between prevalent OH and the risk of incident major adverse cardiac and cerebrovascular events (MACCEs) [death, coronary heart disease (CHD), stroke, and heart failure (HF)], although results have not always been consistent.8–13 In general, studies have been small, and only few of them had enough power to attain statistical significance.14–17 To allow an updated and precise quantitative estimate of the relationship between the baseline presence of OH and incident MACCE, we performed a systematic review and meta-analysis of observational epidemiologic studies available in the literature.

Methods
The present meta-analysis was planned, conducted, and reported in accordance with currently available statements for design, analysis, and reporting of meta-analyses of randomized and observational studies.18–20

Search methods for identification of studies
Medline and Embase databases, the Clinical Trials Registry (www.clinicaltrials.gov), as well as abstracts from major cardiological and neurological societies meetings were searched for potentially relevant articles using the search terms ‘orthostatic hypotension’, ‘postural hypotension’, ‘coronary heart disease’, ‘stroke’, ‘mortality’, and ‘heart failure’. We also searched reference lists of all identified articles for additional relevant studies, including hand-searching reviews and previous meta-analyses. This methodological approach21 has been previously validated in our hands.22 Two of the authors (F.R. and M.R.) performed the screening of titles and abstracts, reviewed full-text articles, and determined their eligibility. The search was performed for the period January 1966–December 2013, and was restricted to the English-language literature. Reviewers were not blinded to study authors or outcomes. Divergences were resolved by consensus and/or involving another reviewer. Studies were included for the analysis if they met the following criteria: (i) published as full-length article, (ii) English language, (iii) sample size ≥ 100 OH+ patients, (iv) minimum follow-up period of 6 months, (v) including adult individuals (≥ 18 years), and (vi) reporting all-cause mortality, incident CHD, HF, and/or stroke outcomes for both individuals with and without OH.

Coding, data collection, and quality assessment
Two investigators (F.R. and M.R.) independently abstracted raw data sets related to baseline characteristics of studies, patient populations, and outcomes ascertained from original eligible sources, and collected them by using a standardized prepared data extraction form. Definitions of OH were consistent with the consensus statement,3 with only slightly differences concerning the timing of blood pressure measurements. The endpoints of interest in the overall analysis were ascertained based on the International Classification of Diseases 9th and 10th Revisions (ICD-9 and ICD-10), and the ascertainment of events was accepted as reported. Coronary heart disease was defined as the occurrence of fatal or non-fatal myocardial infarction, a percutaneous coronary intervention, a coronary artery bypass graft, other form of acute or chronic ischemic heart disease, sudden cardiac death or death due to ventricular fibrillation (ICD-9 410–414 and ICD-10 I21-I24, I46, H9, R96). Incident HF was defined as ICD-9 428 or ICD-10 I50. ICD-9 and ICD-10 codes used for coding stroke were 430–438 or I60-I64, respectively. Other details on patients and study designs were abstracted, and internal validity of included observational studies was appraised by means of the Newcastle-Ottawa Scale.23 This scale awards 1 up to 9 stars judging each single study on three main categories, i.e. selection of study group, comparability, and ascertainment of the outcome of interest.

Statistical analysis
Categorical variables were reported as percentages, and continuous variables as means and standard deviation or medians and interquartile range (IQR) as appropriate. From abstracted data the relative risk (RR) was calculated using the Mantel–Haenszel method for each study outcome to allow for pooling of similar outcomes. The average effects for the outcomes and 95% confidence interval (CI) were obtained using a random-effect model. Heterogeneity of the effect across studies was assessed by means of Cochrane Q chi² statistics and I² statistics. Lack of homogeneity was considered for Cochrane Q chi² test P ≤ 0.10 and for I² statistics ≥ 50%. When heterogeneity was judged as significant, the pooled RR was calculated through the analysis of the variance between studies with the ‘method of moments’ or the DerSimonian and Laird method for random effects. The z-statistic was computed for each clinical outcome, and results were considered statistically significant at a P < 0.05. Meta-analysis results are here displayed in classic forest plots with point estimates of the effect size and 95% CIs for each trial and for the studies overall, being the area of squares and diamonds proportional to study’s weight. A jackknife sensitivity analysis was performed, for each endpoint of interest, to evaluate the robustness of the results and the impact of each single study on the summary estimate of effect; pooled estimates were recalculated multiple times, using a random-effects model, each time with removal of a single study from the baseline group. The likelihood of publication bias was assessed using funnel plots by displaying individual study RR with 95% CIs for the endpoints of interest and the Egger regression asymmetry test (P < 0.10 was here considered as indicative of statistically significant publication bias). We also performed the non-parametric ‘trim-and-fill’ procedure that would adjust for funnel plot asymmetry by generating hypothetical missing studies. To investigate possible sources of heterogeneity among studies, post hoc subgroup analyses and an explorative meta-regression analysis using a mixed-effects model to assess the effect of selected variables [sample size, age, sex, body mass index (BMI), diabetes, hypertension, smoking, and follow-up duration] were performed.24 Statistical analysis and graphs were made using the Review Manager (RevMan) software package (version 5.2 for OSx, The Nordic Cochrane Centre, The Cochrane Collaboration, 2008, Copenhagen, Denmark), OpenMetaAnaylst (version for OSx, Brown University School of Public Health Providence, RI, USA) and STATA 11.0 version (STATA, College Station, TX, USA).

Results
Of 1836 citations identified and retrieved, we reviewed 39 potentially relevant articles. Twenty-six of them did not fit with our inclusion criteria (outcome data not reported or too small studies,25–28 or full-text article only available in Chinese language29) and were therefore discarded (Figure 1). We finally included 13 studies, based on 12 unique cohorts from 6 different countries (5 studies from the USA, 2 from Sweden, 2 from Israel, and 1 each from the Netherlands, Finland, and Japan). In total, such studies reported on 12 192 certified
reported deaths, 3584 new-onset HF diagnoses, 2705 CHD-related events, and 1407 cerebrovascular events. The reported prevalence of OH varied between 4.6 and 42.5%. The overall quality of studies was high, with 11 studies scoring 9 stars and 2 studies scoring 7 stars according to the Newcastle-Ottawa Scale. The main characteristics of the included studies are summarized in Table 1.

Orthostatic hypotension and mortality
Of the 12 cohorts included, 10 studies investigated the association between OH and incident risk of all-cause death for a total pooled population of 65 174 patients. The median follow-up was 5 years (IQR 4–9 years). By pooling together the results of selected studies, OH was associated with a significantly increased risk of death (RR 1.50; 95% CI 1.24–1.81) (Figure 2A). When analysed according to age, pooled estimates of RR (and associated 95% CI) for all-cause death were 1.78 (1.25–2.52) for patients <65 years old, and 1.26 (0.99–1.62) for the older subgroup.

Orthostatic hypotension and cardiovascular disease
Orthostatic hypotension and coronary heart disease
The association between OH and CHD-related outcomes was investigated in four studies, for an overall population of 49 512 patients with a median follow-up of 6.4 (IQR 4.7–10.8) years. Only two studies showed a significant association between OH and CHD,30,31 while two others did not.10,11 By pooling the results of such studies with a random-effect model, OH was associated with a significantly higher risk of cerebrovascular events (RR 1.64; 95% CI 1.13–2.37) (Figure 2D).

Assessment of publication bias
Funnel plots for all-cause death, CHD-related events, and HF demonstrated a certain degree of asymmetry. Nonetheless, after adjustments with calculation of hypothetical missing negative studies by means of the Duval and Tweedie’s ‘trim-and-fill’ test,13 the pooled analysis continued to show statistically significant associations between OH and all-cause death (adjusted RR 1.66; 95% CI 1.37–2.00) (Figure 3A), CHD-related events (adjusted RR 1.47; 95% CI 1.28–1.70) (Figure 3B) and HF (adjusted RR 2.72; 95% CI 1.77–4.18) (Figure 3C). Conversely, visual inspection of funnel plot for stroke did not reveal any asymmetry, and—strengthening this finding—we could reasonably exclude publication bias or ‘small study effect’ by the Egger’s test of intercept (stroke intercept = 0.99, P = 0.84). In this case, the non-parametric ‘trim-and-fill’ procedure could not impute any ‘missing’ study (Figure 3D). We could therefore exclude the presence of significant publication bias and consider our results reasonably robust.

Sensitivity analyses
According to Jackknife sensitivity analysis, no single study significantly affected the pooled RRs for each endpoint of interest (Figure 4A–D).

Evaluation of sources of heterogeneity
The tests of heterogeneity between studies for all-cause mortality (cochrane Q P < 0.00001; I² = 93%), HF (cochrane Q P < 0.0001; I² = 85%), and stroke (cochrane Q P < 0.000001; I² = 95%) were significant. Post hoc subgroup analyses performed to explore the source of heterogeneity among studies did not show significant results. Also, to test the influence of study characteristics on the association between OH and risk of all-cause mortality, CHD, HF, and stroke, univariable meta-regression analyses were performed, but failed to reveal any significant association between the magnitude of RR for each endpoint of interest and study-level covariates, i.e. age, sex, BMI, diabetes, and hypertension (Table 2).

Discussion
This meta-analysis provides evidence of a strong association between OH and the subsequent risk of all-cause death and HF, supporting smaller previous studies32,34,35 but also extends current knowledge demonstrating a significant relationship between OH and increased risk of incident CHD-related events and stroke.

In our study, the predictive value of OH for MACCE seemed to be neither influenced by conventional cardiovascular risk factors nor by follow-up duration and gender. Further, in post hoc subgroup analysis, the association between OH and risk of all-cause death was stronger among middle-aged individuals younger than 65 years. The most likely explanation for this finding is that the presence of OH in younger individuals is a sign of more severe disease, probably of a neurodegenerative aetiology, and that in older individuals prevalent...
<table>
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<th>First author (study name) - Year of publication</th>
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<th>Follow-up (years)</th>
<th>Mean age (years)</th>
<th>Male (%)</th>
<th>Diabetes (%)</th>
<th>Hypertension (%)</th>
<th>BMI (kg/m²)</th>
<th>Baseline CHD (%)</th>
<th>OH definition</th>
<th>OH prevalence (%)</th>
<th>Study quality</th>
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<td>18.9</td>
<td>21.4</td>
<td>n.a</td>
<td>n.a</td>
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<td>SBP decline ≥ 20 mmHg from supine to standing (at 1 min)</td>
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<tr>
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<td>12 363</td>
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<td>54</td>
<td>45.3</td>
<td>10.9</td>
<td>32.3</td>
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<td>SBP decline ≥ 20 mmHg or DBP decline ≥ 10 mmHg from supine to standing (within 3 min)</td>
<td>12.1</td>
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OH, orthostatic hypotension; BMI, body mass index; HF, heart failure; ARIC, atherosclerosis risk in communities; MPP, Malmö Preventive Project; CPP, Captopril Prevention Project; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease.
Figure 2 Outcomes of orthostatic hypotension in prospective observational studies. Forest plots with individual and overall estimates of the relative risk on a logarithmic scale and 95% confidence interval for all-cause mortality (A), coronary heart disease (B), heart failure (C), and stroke (D). The solid vertical line in the centre of the graph is the 'line of no effect', that is, a relative risk of 1.0 represented by individuals with orthostatic hypotension (OH+) when compared with individuals without (OH−). A relative risk < 1.0 favours individuals with orthostatic hypotension, whereas one > 1.0 favours individuals without orthostatic hypotension. The vertical interrupted red line indicates the pooled effect estimate. The diamond size is proportional to the study weight in this random-effects model. Black squares indicate weighted point estimates of the effect of each single study.
comorbidities contribute to weaken the magnitude of the effect (dilution effect). Moreover, the exposure time is longer when a disease starts at a younger age. Indeed, because any outcome becomes more frequent with aging, it is not surprising to find a negative interaction on a multiplicative scale. Similar discrepancies had also been observed in the ARIC study and in the Cardiovascular Health Study, where hazard ratios for stroke associated with OH were lower with increasing age. Prospective data of the Swedish Malmö Preventive Project reported a two-fold higher risk of death in individuals with OH younger than 42 years, not supportive of a frailty hypothesis, but rather suggestive of a causal relationship between OH and increased mortality. While qualitatively in agreement with individual previous studies, our analysis supports this hypothesis with statistically significant and robust evidence.

In search for explanations on why prevalent OH predicts negative outcomes, such as death and development of CV disease, several mechanisms can be proposed. Aging, diabetes, hypertension, Parkinson’s disease, and carotid arterial disease are all associated with both OH and increased mortality, and all share the potential to impair or override autonomic mechanisms that regulate blood pressure homeostasis. Baroreflex dysfunction, a marker of ANS imbalance implicated in the pathogenesis of OH, is characterized by enhanced sympathetic activity and withdrawal of parasympathetic control, and has long been recognized as an important mediator of increased cardiovascular morbidity and mortality. In the ATRAMI and the CIBIS II studies, both increased heart rate and diminished vagal activity have been shown to be strong predictors of death.

Orthostatic hypotension is also a condition of impaired haemodynamic homeostasis, where compensatory neuroendocrine mechanisms are intermittently activated. These mechanisms may trigger the activation of other biologic effectors, e.g. platelets or the coagulation cascade, potentially promoting the occurrence of cardio- or cerebrovascular events. Corroborating this hypothesis, hyperactivation of the endothelin system has been observed in patients diagnosed with syncope due to OH. Thus, physiological vasoconstrictors, such as endothelin-1 and vasopressin, may play a role as an adaptive mechanism to hypotension during

Figure 3 Assessment of publication bias. Begg’s funnel plot and Duval and Tweedie’s ‘trim-and-fill’ analysis of studies according to the relative risk of all-cause mortality (A), coronary heart disease-related events (B), heart failure (C), and stroke (D), vs. the standard error of relative risk. The non-parametric ‘trim-and-fill’ procedure imputes hypothetical missing studies, adds them to the analysis, and then re-computes the summary effect size adjusting for funnel plot asymmetry. White circles: observed studies, black circles: imputed missing studies.
**Figure 4** Jackknife sensitivity analysis. To evaluate whether the summary estimate of the effect could have been significantly affected by a single study, pooled estimates for all-cause mortality (A), coronary heart disease-related events (B), heart failure (C), and stroke (D) were recalculated, using a random-effects model, by omitting one study at a time. Each line represents a re-analysis of the data with exclusion of one study at a time to assess the influence of this particular study on the overall result.
orthostasis, but promoting atherothrombosis in the susceptible individuals in the long term. Moreover, wide swings in blood pressure and supine hypertension associated with OH may provoke intermittent ischaemic bouts and increased afterload, leading to permanent end-organ damage such as left ventricular hypertrophy and decreased renal function. Interestingly, among hypertensive individuals, isolated systolic OH is strongly associated with a higher incidence of stroke, whereas isolated diastolic OH seems to be more detrimental for the coronary circulation. In summary, our study does not allow to draw conclusions as to whether OH is a marker of a generally increased risk of death, an intermediate variable in the causal pathway of cardiovascular risk factors, a simple measure of disease severity, or an independent causal mechanism. To this end, a better understanding and classification of OH aetiology, especially in non-neurogenic OH, is needed, as it is not clear whether patients with an overt neurodegenerative disease (neurogenic OH) share the same risks as those without.

Today, an effective therapy against OH is not available. In symptomatic OH, various drugs have been tested, but without convincing data and international consensus on their efficacy. With the increasing evidence that patients with this cardiovascular dysautonomia in addition to manifest debilitating symptoms also have increased CV risk and increased mortality, more efforts should be dedicated in identifying and characterizing patients with OH. For instance, it is not clear whether patients with OH benefit from anti-hypertensive treatments to the same extent as those without. Further, it is uncertain whether such patients might benefit more from specific groups of anti-hypertensive drugs, and whether therapeutic modulation of the ANS might reduce risk. Future studies should aim at answering these questions.

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### Limitations

We acknowledge some limitations of our analysis. The overall number of studies included for the evaluation of secondary endpoints is small to draw definite conclusions for subgroup differences and the meta-regression analysis. The failure to find statistical significance when comparing subgroups, or in the meta-regression, could mean either that the effect—if any—is quite small, or that the analysis had not enough power to detect even a large effect. Thus, our subgroup analysis and the meta-regression for secondary endpoints could not exclude that a given study covariate might be related to the observed effect. In addition, study cohorts included in our meta-analysis mostly consisted of white populations, hence results cannot necessarily be extrapolated to other ethnic groups. Furthermore, OH was assessed within 3 min of taking the upright position, thus not taking into account ‘delayed OH’. Finally, the presence of OH in the various studies was commonly only evaluated at one single time point, so that the persistence of the condition was not accounted for as a possible additional variable explaining the variability of outcomes among studies.

### Conclusions and implications

This meta-analysis supports the hypothesis that OH is an independent predictor of increased mortality and incident cardio- and cerebrovascular disease. Consequently, assessment of OH in future prospective epidemiological studies and high-risk patients should be encouraged. Future randomized trials should also test the hypothesis whether abnormal orthostatic response can modify the study outcome in affected individuals.

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### Conflict of interest

none declared.

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