Title: Is there a causal relationship between orthostatic hypotension and falling? A meta-analysis of prospective observational studies.

Alphabetical order:

H.J.G. Bilo
K.H. Groenier
L.C. Hartog
K.J.J. van Hateren
N. Kleefstra
G.W.D. Landman
D. Schrijnders

Contact person:

l.c.hartog@isala.nl
Isala, Diabetes Centre
PO Box 10400 NL-8000 GK Zwolle
The Netherlands
Introduction
The prevalence of orthostatic hypotension (OH), defined as a decrease in systolic blood pressure by at least 20 mmHg and/or a decrease in diastolic blood pressure by at least 10 mmHg within 3 min after changing from supine to a standing position, increases with advancing age.[1] The etiology of orthostatic hypotension is multifactorial and caused by a combination of change in baroreceptor sensitivity, autonomic failure, hypovolemia, and medications, for example antihypertensive and antipsychotic drugs.[2 3] Orthostatic hypotension is associated with an increased risk of cardiovascular disease and all-cause mortality, especially in the elderly. [4-7] OH is also thought to be associated with an increased fall risk and especially in frail elderly, orthostatic hypotension and the subsequent increased fall risk potentially leads to severe morbidity.[8-10] Together with the etiology of orthostatic hypotension, the etiology of fall risk is complex and multifactorial and orthostatic hypotension is one out of many risk factors believed to contribute to an increased risk of falling in elderly. Other risk factors for example are the presence of comorbidity like cardiac arrhythmias and polypharmacy. [10-15] Despite the numerous studies that have examined the association between OH and falling, the relationship remains poorly characterized. Two recent systematic reviews showed that OH was a risk factor for falling in elderly, although the absolute attributable risk is not established due to the lack of a meta-analysis. [10 16] Angelousi et al. tried to perform a meta-analysis, but could not perform a meta-analysis for falls considering the low number of studies with available adjusted associations. [16] However, they did not aim to perform a meta-analysis with individual patient data. Furthermore, the number of studies (n=9) is not necessarily a reason for not performing a meta-analysis.
Although most clinicians regard OH as causal factor for falls, it remains to be established whether and to what extent orthostatic hypotension contributes to falling. Despite the lack of evidence for a causal relationship between OH and fall risk, a variety of interventions are currently being investigated and already deployed that target OH.
We aim to investigate whether and to what extent OH contributes to fall risk in a meta-analysis of individual patient data. In case we cannot retrieve all individual
patient data; we aimed, as a secondary goal, to study the same relationship in a meta-analysis, which combines published study results.

**Objectives**
The primary objective is to perform a meta-analysis of studies that provide individual patient data for studying whether and to what extent orthostatic hypotension is associated with falling.
The secondary objective is to perform a meta-analysis of published study results for studying whether and to what extent orthostatic hypotension is independently associated with falling, in case not all individual patient data are provided.

**Protocol**
This protocol was developed in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) recommendations.

**Mandatory eligibility criteria**
Studies in adults with a prospective design regardless of follow-up duration that describes the relationship between orthostatic hypotension and fall incidents.

Studies should have used the 1996 consensus guideline definition of Orthostatic hypotension.[1]

**Data sources and searches**
An electronic search of Medline (via PubMed), Embase, the Cochrane Library (all without date limitation), and the abstracts of the 2012, 2013, and 2014 annual meetings of the International society of hypertension and American Society of Hypertension, through April 2015. Language restriction: English.

Additional studies will be retrieved by hand searching references of original and review articles. Completed but unpublished data will be identified by searching clinical trials registries (www.clinicaltrials.gov, www.clinicaltrialsregister.eu and www.trialregister.nl).

**Search Strategy**
‘Orthostatic hypotension’ OR ‘postural hypotension’ OR ‘orthostatic’ OR ‘MeSH terms orthostatic hypotension’ AND ‘falls’ OR ‘falling’ OR ‘recurrent falls’ OR ‘accidental falls’ OR ‘fall-risk’ OR ‘MeSH terms accidental falls’. Also see appendix for our search strategy.

**Study selection**
Publications retrieved from Medline, Embase, and the Cochrane Library will be imported in Endnote reference management software. After removing duplicate results, two reviewers (LH, DS) will independently screen abstracts and select any abstract that can potentially be relevant. Next, the same two reviewers (LH, DS) independently investigate full texts for eligible studies, extract data and assess quality of each study. Differences in opinion between the two reviewers are to be resolved by consensus with a third reviewer (KH).

**Data collection and data items**
Authors of the selected papers will be contacted and asked whether they are able and willing to share (anonymous) individual patient data, to analyze the primary outcome. In case individual patient data are not provided, the authors will be asked to provide results from adjusted analyses.
In case individual data and additional data are not provided, published data are used; adjusted data are preferred over unadjusted data.
Two reviewers independently extract data, and discrepancies will be resolved by consensus. A data extraction form is designed and the following study characteristics are extracted; author identification, year of publication, National Clinical Trial (NCT) number if applicable, quality assessment (Newcastle-Ottowa Scale), studied population, sample size, compared groups; participants’ baseline characteristics (age, gender, blood pressure, OH, BMI, medication, hypertension, Parkinson); and fall incidents (yes/no).

**Outcome data**
Association of orthostatic hypotension and falling reported as RRs or ORs with corresponding 95% CIs.

**End-point**
The primary end-point will be falling (yes or no).

**Quality assessment**

The quality of each study will be assessed using the Newcastle-Ottawa Scale ([http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)). The scale varies from 1 to 9 stars and each study is evaluated on three broad categories: selection of the study groups; comparability of the groups; and ascertainment of the outcome of interest.

Two reviewers (LH, DS) independently assess quality; differences in opinion are to be resolved by consensus or a third reviewer (KH) when necessary.

Sensitivity analysis will be performed for every outcome described in objectives.

**Analyses**

1) For the primary outcome:
   a. Analyzing all studies that describe the relationship between OH and falling or fall-risk with individual patient data:
      i. Unadjusted
      ii. Adjusted for age and gender
      iii. Adjusted for age, gender, BMI, antihypertensive drugs, systolic blood pressure, poly pharmacy*, DM.

2) For the secondary outcome:
   a. Analyzing all studies with available adjusted data:
      i. All studies that have adjusted for age and gender
      ii. All studies that have adjusted for age, gender, and relevant other variables.

3) Repeating analyses 1 and 2 with subgroups of study quality assessed using the Newcastle-Ottowa Scale; scoring 9 stars versus ≤ 8 stars.

4) Predefined subgroup analysis will be performed on the variables: age, patient group; community-dwelling or nursing home patients, study quality, and specific patients groups; e.g. hypertension, diabetes, Parkinson.
5) Sensitivity analysis will be performed for every outcome described in objectives.

In case of significant heterogeneity across the studies, pooling of data will not be appropriate. If differences in outcome due to clinically important subgroup differences are found, we will not perform an overall meta-analysis.

**Synthesis of results**

**Individual patient data:** continuous variables are presented as mean (+ standard deviation) for normally distributed variables, or as median (interquartile range) for non-normally distributed variables. We will perform both ‘one-stage’ and ‘two-stage’ models. Univariate binary logistic regression analyses and subsequently multivariate binary logistic regression analyses will be performed to assess the association of OH (dichotomous variable) and falling (dichotomous variable). When possible, a cox regression analysis will be performed. Cox proportional hazard modeling will be used to investigate the relation between OH, and falling.

**Published data:**

Odds Ratio’s and Risk Ratio’s between patients with OH compared to patients with no OH and 95% confidence intervals will be calculated with a random effects model. Because of the observational design of all studies heterogeneity can be expected, therefore a random effects model will be used. Significant heterogeneity will be considered to exist if the p value is <0.10. We will use relative risks as a common measure of the association between OH and falling. A Forest-plot will be made so all relative risks and confidence intervals will be visual and to perform the ‘eye-ball’-test.

Subgroup analysis will be performed to explore the possible source of heterogeneity.

Predefined subgroup analysis will be performed on the variables: age, patient group; community-dwelling or nursing home patients, methodological quality study, and specific patients groups; e.g. hypertension, diabetes, Parkinson. Median values of continuous variables will be used as cut-off values for grouping studies.
We will assess publication bias only when at least 10 studies are included in the meta-analysis for the primary outcome with a funnel plot, both visually and formally with Egger’s test. Evidence for publication bias, is defined as an asymmetrical appearance of the funnel plot with a gap in a bottom corner of the graph. When there is an asymmetric funnel-plot we can perform a 'trim-and-fill' analysis.

All analyses will be performed using RevMan 5.1 and SPSS.

Appendix

* Definition poly-pharmacy: ≥ 5 medications used chronically.

Search Strategy

((("hypotension, orthostatic"[MeSH Terms] OR ("hypotension"[All Fields] AND "orthostatic"[All Fields]) OR "orthostatic hypotension"[All Fields] OR ("orthostatic"[All Fields] AND "hypotension"[All Fields]))) OR ("hypotension, orthostatic"[MeSH Terms] OR ("hypotension"[All Fields] AND "orthostatic"[All Fields]) OR "orthostatic hypotension"[All Fields] OR ("postural"[All Fields] AND "hypotension"[All Fields]) OR "postural hypotension"[All Fields]) OR "hypotension, orthostatic"[MeSH Terms]) AND ((("accidental falls"[MeSH Terms] OR ("accidental"[All Fields] AND "falls"[All Fields]) OR "accidental falls"[All Fields] OR "falls"[All Fields]) OR falling[All Fields]) OR (recurrent[All Fields] AND ("accidental falls"[MeSH Terms] OR ("accidental"[All Fields] AND "falls"[All Fields]) OR "accidental falls"[All Fields]) OR "accidental falls"[All Fields] OR "falls"[All Fields])) OR ("accidental falls"[MeSH Terms] OR ("accidental"[All Fields] AND "falls"[All Fields]) OR "accidental falls"[All Fields] OR "falls"[All Fields]) OR fall-risk[All Fields]) OR "accidental falls"[MeSH Terms])
References


