CHAPTER 5

Is orthostatic hypotension related to falling?
A meta-analysis of individual patient data of prospective observational studies

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ABSTRACT

Background: Orthostatic hypotension (OH) is one out of many risk factors believed to contribute to an increased fall risk in elderly subjects but it is unclear whether an independent association between OH and falling exists.

Purpose: To perform an individual patient data (IPD) meta-analysis of prospective observational studies investigating the relationship between OH and falling.

Materials and Methods: MEDLINE, EMBASE, the Cochrane Library, and the abstracts of annual meetings of selected hypertension societies were searched. Both one-stage (analysing all IPD from all studies simultaneously) and two-stage (analysing IPD per study, and then pooling the results) methods were used, and both logistic and cox regression analyses were performed. The study protocol was published on PROSPERO (2015:CRD42015019178).

Results: From the 34 selected abstracts, 6 studies were included. IPD were provided in 1022 patients from 3 cohorts and were included in the IPD meta-analysis. The hazard ratio (HR) in the one-stage cox proportional hazard model was 1.52 (95% Confidence Interval (CI) 1.23-1.88).

No significant relationship between OH and falling was found in the one-stage logistic regression analysis (Odds Ratio (OR) 1.21 (95% CI 0.87-1.68) and the two-stage logistic and cox regression analyses.

Conclusions: This IPD meta-analysis of prospective observational studies showed a clear and significant relationship between OH and time to first fall incident. Although the ORs of falling was not significantly different for patients with and without OH, the width of the 95% CI does not exclude a relevant clinical association between OH and falling.
INTRODUCTION

The prevalence of orthostatic hypotension (OH), defined as a decrease in systolic blood pressure by at least 20 mmHg or a decrease in diastolic blood pressure by at least 10 mmHg within 3 minutes after changing to standing position, increases with advancing age [1]. OH is associated with cardiovascular disease and all-cause mortality, especially in elderly subjects [2-5]. Furthermore, OH is presumed to be associated with an increased fall risk. Especially in frail elderly, OH and the subsequent increased risk of falling are considered to potentially lead to severe morbidity [6-11]. Equivalent to the aetiology of OH, fall risk is a complex and multifactorial phenomenon and OH is one out of many risk factors believed to contribute to an increased fall risk in elderly subjects [7, 8, 12].

Previous studies on the relationship between OH and fall risk were mostly performed in nursing homes and reported a positive association [9, 13, 14]. These results cannot be directly extrapolated to home dwelling elderly subjects. Two recent systematic reviews described the relationship between OH and falling in old age, although the absolute attributive risk could not established due to few included patients [7, 8].

It remains unclear whether there is an independent association between OH and falling. Therefore, we aimed to investigate whether OH contributes to falling in a meta-analysis of individual patient data (IPD). When individual patient data could not be retrieved, a secondary analysis was pre-planned that aimed to perform a meta-analysis of published study results.

MATERIALS AND METHODS

Protocol

The prespecified objectives, eligibility criteria, quality assessment and main analyses were published on PROSPERO (2015:CRD42015019178). PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations were followed throughout the design, implementation, analysis and reporting of this study [15].

A study was considered eligible if it was a prospective study that used the 1996 consensus guideline definition of OH [1], included adults subjects, and described the relationship between OH and fall incidents.

Data Sources and Searches

An electronic search of MEDLINE (Pubmed), EMBASE, the Cochrane Library, and the abstracts of the 2012, 2013, and 2014 annual meetings of the International society of hypertension and American Society of Hypertension, was performed on 14 April 2015 and updated on 12 February 2016. The search was restricted to the English-language literature.
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Additional studies were retrieved by hand searching references of selected articles. Clinical trials registries (www.clinicaltrials.gov, www.clinicaltrialsregister.eu and www.trialregister.nl) were searched for unpublished data. The following search terms were used: ‘Orthostatic hypotension’ OR ‘postural hypotension’ OR ‘orthostatic’ OR ‘Medical Subject Heading (MeSH) terms orthostatic hypotension’ AND ‘falls’ OR ‘falling’ OR ‘recurrent falls’ OR ‘accidental falls’ OR ‘fall-risk’ OR ‘MeSH terms accidental falls’. The complete search query is available in Appendix 1.

Study Selection
Publications retrieved from MEDLINE, EMBASE, and the Cochrane library were imported in Endnote reference management software. Duplicates were removed and, two reviewers (LH, DS) independently screened abstracts. For abstract selection and full-text selection inclusion criteria were used. The same two reviewers (LH, DS) extracted data and assessed the quality of each study. Differences in opinion between reviewers were resolved by consensus with a third reviewer (KH). Two reviewers (LH, DS) independently searched the trial registers.

Data Collection and Data Items
From each study, data were extracted concerning; authors, year of publication, national clinical trial (NCT) number (if applicable), studied population, sample size, participants’ baseline characteristics (age, gender, blood pressure, OH, body mass index (BMI), medication, hypertension, Parkinson’s disease); and fall incidents (yes/no).

Objective
The primary objective was to investigate whether OH contributes to falling in a meta-analysis of IPD. When individual patient data could not be retrieved, a secondary analysis was pre-planned that aimed to perform a meta-analysis of published study results.

Missing Data and Multiple Reports
Authors of the selected papers were contacted and asked whether they were willing to share (anonymous) individual patient data. Initially, the first author was contacted by email or telephone (repeatedly in case of no response). The other authors were contacted when the first author did not respond. In case individual patient data were not provided, published data were used.

Risk-of-Bias Assessment
The quality of each study was assessed using the Newcastle-Ottowa Scale (NOS) [16]. On a 9-point scale, the NOS evaluates the quality of observational studies on three broad...
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categories: selection of the study groups (maximum of 4 stars); comparability of the groups (maximum of 2 stars); and ascertainment of the outcome of interest (maximum of 3 stars). Two reviewers (LH, DS) independently assessed quality; differences in opinion were resolved by consensus with a third reviewer (KH).

Statistical Analysis
IPD analyses were performed using one-stage and two-stage methods [17-19]. In a one-stage method, analyses are performed with all IPD from all studies simultaneously, just as they belong to a single trial. In a two-stage method analyses are first performed for all individual studies separately and then pooled into a meta-analysis for estimating the overall effect [20]. Both one-stage and two-stage methods were used.

Univariate binary logistic regression analyses and subsequently multivariate binary logistic regression analyses were performed to assess the association of OH and falling (yes/no). A cox proportional hazard modelling was used to investigate the relation between OH and the first fall incident. Three different predefined models were used. In model 1, unadjusted analyses were performed. In model 2, only age and gender were taken into account as possible confounders. Model 3 was adjusted for age, gender, BMI, use of antihypertensive medication, systolic blood pressure (SBP), diabetes mellitus (DM), and the total number of drugs. Logistic regression and cox proportional hazard analyses were performed in both one-stage and two-stage methods. Odds ratios (OR) and hazard ratios (HR) between patients with OH compared to patients without OH and 95% confidence intervals (CI) were calculated. Because of the observational design of all studies heterogeneity was expected, therefore initially a random effects model was used. In case of no significant heterogeneity, a fixed effect model was also applied. Heterogeneity was considered relevant if the p value was <0.10.

Logistic regression and cox proportional hazard analyses were performed using SPSS, version 22. Pooling of results and analyses regarding heterogeneity were performed with RevMan 5.3.

Sensitivity and subgroup analyses
In case of significant heterogeneity, sensitivity analyses were planned to explore the possible source of heterogeneity. In the one-stage method, predefined subgroup analyses were planned and registered at PROSPERO regarding the following variables: age, patient group, community dwelling or nursing home patients, study quality, and specific patients groups; e.g. hypertension, DM, and Parkinson. The predefined subgroup analyses were only performed in case of an adequate number of patients to justify the subgroup analyses. In
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the two-stage method, subgroup and meta-regression analyses were considered with 10 or more included studies [21].

Ethical approval and Clinical Trial registration
This study was performed in accordance with the Declaration of Helsinki. According to Dutch guidelines this study did not fall under the scope of the Medical Research Involving Human Subjects Act, and therefore this study did not need a formal approval of an accredited medical ethics committee. All data were analysed anonymously. The eligibility criteria, outcomes, and analyses were pre-specified and published on PROSPERO (2015: CRD42015019178).

RESULTS

Search results
In total, 34 abstracts [10, 11, 13, 22-52] were selected for full-text evaluation, 6 of these were included in the meta-analysis (Figure 1) [10, 11, 13, 23, 39, 41]. The authors of these studies were contacted for sharing IPD. IPD were provided from 3 studies [10, 11, 23]. The authors of one study did not reply to several attempts to make email (or telephone) contact [39], one was not able to participate in the study without giving a specific reason [41], and one could not provide individual patient data because data were no longer available [13]. Also, results as published could not be used from these studies because only HRs or ORs of subgroup analyses were published instead of results of the total study group regarding OH and falling. In addition, different endpoints were described and therefore these published results could not be included into the current meta-analysis.

Study characteristics
The characteristics of the 6 selected prospective cohort studies are shown in table 1. The baseline characteristics of the 3 included studies are shown in table 2. The follow-up period in all included studies was approximately 1 year.

The participants of the three studies included in the IPD meta-analysis were all community-dwelling elderly [10, 11, 23]. The sample size of the cohorts ranged from 70 to 736 subjects. The median (interquartile range) age was 77 years (73-81). The prevalence of OH ranged from 11% to 82 % and the prevalence of one or more fall incidents ranged from 51% to 62%. OH was measured in all 3 studies from supine to standing position. Fall incidents were retrieved by fall calendars [10], monthly questionnaires [11], or fall diaries [23].
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**Figure 1.** Flowchart.

**Risk-of-Bias Assessment**

The three studies all scored 6 out of 9 stars, meaning that the overall quality of the included studies was moderate [10, 11, 23] (table 1). Because all studies had an equal NOS score, no subgroup analysis was performed regarding study quality. See appendix table 1 for the detailed NOS score of the 3 included studies in the IPD meta-analysis.
Table 1. Characteristics of the selected prospective cohort studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Total</th>
<th>Follow-up (months)</th>
<th>Mean Age (SD)</th>
<th>Female N (%)</th>
<th>Study quality (NOS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allan et al. [23]</td>
<td>UK</td>
<td>179</td>
<td>12</td>
<td>76 (7)</td>
<td>73 (41%)</td>
<td>6 stars</td>
</tr>
<tr>
<td>Gangavati et al. [10]</td>
<td>USA</td>
<td>722</td>
<td>12</td>
<td>78 (5)</td>
<td>462 (64%)</td>
<td>6 stars</td>
</tr>
<tr>
<td>Heitterachi et al. [11]</td>
<td>Australia</td>
<td>70</td>
<td>12</td>
<td>77 (6)</td>
<td>56 (80%)</td>
<td>6 stars</td>
</tr>
<tr>
<td>Maurer et al. [41]</td>
<td>USA</td>
<td>111</td>
<td>9</td>
<td>88 (7)</td>
<td>91 (82%)</td>
<td>8 stars</td>
</tr>
<tr>
<td>Luukinen et al. [39]</td>
<td>Finland</td>
<td>1016</td>
<td>12</td>
<td>76 (5)</td>
<td>620 (61%)</td>
<td>7 stars</td>
</tr>
<tr>
<td>Ooi et al. [13]</td>
<td>USA</td>
<td>844</td>
<td>14</td>
<td>Not reported</td>
<td>677 (80%)</td>
<td>7 stars</td>
</tr>
</tbody>
</table>

NOS: Newcastle-Ottawa Scale: on a 9-point scale, the NOS evaluates the quality of observational studies on three broad categories: selection of the study groups (maximum of 4 stars); comparability of the groups (maximum of 2 stars); and ascertainment of the outcome of interest (maximum of 3 stars).

Table 2. Baseline table of individual patient data.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td>282 (28)</td>
<td>178 (82)</td>
<td>83 (11)</td>
</tr>
<tr>
<td>Falling</td>
<td>621 (61)</td>
<td>129 (60)</td>
<td>456 (62)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>77 (73-81)</td>
<td>76 (71-81)</td>
<td>77 (74-82)</td>
</tr>
<tr>
<td>Female Gender</td>
<td>602 (58)</td>
<td>85 (38)</td>
<td>461 (63)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>27 (24-29)</td>
<td>25 (23-28)</td>
<td>27 (24-30)</td>
</tr>
<tr>
<td>DM, DM vs control</td>
<td>177 (17)</td>
<td>18 (8)</td>
<td>149 (20)</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>624 (61)</td>
<td>75 (33)</td>
<td>519 (71)</td>
</tr>
<tr>
<td>Number of medication</td>
<td>10 (4-13)</td>
<td>4 (2-6)</td>
<td>10 (7-14)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>129 (119-143)</td>
<td>135 (121-149)</td>
<td>131 (119-140)</td>
</tr>
</tbody>
</table>

Data are means (± SD), medians (interquartile range) or n (%). OH: orthostatic hypotension, DM: Diabetes mellitus.


Effect of OH on falling; one-stage method (table 3)
No significant relationship between OH and falling was found in the one-stage logistic regression analysis.

Table 3. Adjusted odds ratios and Hazard ratios for the effect of orthostatic hypotension on the risk of falling with individual patient data (one-stage method). The odds ratios can be interpreted as a measure of the association of OH to falling (the dependent variables). Hazard ratios refer to time to first fall incident.

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(3 studies)</td>
<td>(2 studies)</td>
</tr>
<tr>
<td>OH (model 1)</td>
<td>0.92 (0.69-1.21)</td>
<td>1.30 (1.08-1.57)</td>
</tr>
<tr>
<td></td>
<td>(n=1022)</td>
<td>(n=952)</td>
</tr>
<tr>
<td>OH (model 2)</td>
<td>0.94 (0.70-1.24)</td>
<td>1.30 (1.08-1.57)</td>
</tr>
<tr>
<td></td>
<td>(n=1022)</td>
<td>(n=952)</td>
</tr>
<tr>
<td>OH (model 3)</td>
<td>1.21 (0.87-1.68)</td>
<td>1.52 (1.23-1.88)</td>
</tr>
<tr>
<td></td>
<td>(n=954)</td>
<td>(n=884)</td>
</tr>
</tbody>
</table>


From the three studies, two studies [10, 23] collected data on the time to first fall incident. These two studies could be used in the Cox analyses regarding the relationship between OH and first fall incident. A significant relationship was observed in the Cox regression analysis, HR 1.52 (95%CI 1.23-1.88). The chance of a first fall incident was 52% higher for patients with OH compared to those without. Figure 2 shows the cumulative proportion of first fall incident for patients with and without OH.

![Cumulative proportion of first fall incident](image)

**Figure 2.** Cumulative proportion of first fall incident (survival curve).
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Post-hoc logistic regression analyses were performed with IPD of the same two studies as used in the Cox regression analysis; results did not relevantly change (model 1: OR 0.87 (95% CI 0.65-1.16), model 2: OR 0.89 (95% CI 0.66-1.20), and model 3: OR 1.17 (95% CI 0.83-1.65)).

**Effect of OH on falling; two-stage method**

For the two-stage method, ORs and HRs were analysed for each individual study separately and then pooled in the meta-analysis. No significant relationships were seen between OH and falling, in both the logistic and Cox regression analyses (figures 3 and 4).

As no heterogeneity ($I^2 = 0\%$) was observed, also a fixed effect model was applied. When pooling the odds ratios, no significant relationship was seen between OH and falling, with both the random and fixed effect models. The unadjusted and adjusted ORs of the fixed effect models were 0.95 (95% CI 0.66-1.36; $I^2 = 0\%$) and 0.98 (95% CI 0.66-1.44; $I^2 = 0\%$; $p = 0.40$), respectively (Fig 3).

A Cox regression analysis was only performed for 2 studies [10, 23] because Heitterachi et al. did not report the time to first fall incident in their study [11]. No significant relationship between OH and time to first fall incident was seen. The pooled unadjusted and fully adjusted HRs were 0.95 (95% CI 0.74-1.22; $I^2 = 0\%$; $p = 0.70$) and 1.02 (95% CI 0.77-1.34; $I^2 = 0\%$; $p = 0.98$), respectively (Fig 4).

Sensitivity analyses in both the logistic and Cox regression analysis were not performed because no heterogeneity was present.

**Subgroup analyses**

In the one-stage method, only subgroup analyses regarding hypertension and diabetes status were performed. The three studies were comparable with respect to age, patient group, community dwelling or nursing home patients, and study quality. Subgroup analyses would not provide additional information and was thus not performed. A subgroup analysis on the covariate Parkinson’s disease could not be performed due to a low number of patients with Parkinson’s disease.

No significant relation was seen between OH and falling within the logistic regression analysis stratified to hypertension and diabetes (Appendix table 2). When stratified according to diabetes status within the cox regression analysis, a significant relation was seen within non-diabetic patients in all three models; unadjusted HR 1.29 (95% CI 1.05-1.59), age- and gender adjusted HR 1.29 (95% CI 1.05-1.58), and fully adjusted HR 1.53 (95% CI 1.21-1.93). The stratified analysis regarding to hypertension did not relevantly change the results (Appendix table 2). Interaction between diabetes and OH, and hypertension and OH, was analysed and no interaction was seen, $p=0.53$ and $p=0.86$, respectively. In the two-stage method no subgroup or meta-regression analyses were performed because of the low number of studies included.
Figure 3. Forrest Plot of the adjusted odds ratios for the effect of orthostatic hypotension on the risk of falling with individual patient data for each study (two-stage method). Adjusted for age, gender, BMI, diabetes mellitus, antihypertensive medication, number of medication, and mean systolic blood pressure.

Figure 4. Forrest Plot of the adjusted hazard ratios for the effect of orthostatic hypotension on the risk of falling with individual patient data for each study (two-stage method). Adjusted for age, gender, BMI, diabetes mellitus, antihypertensive medication, number of medication, and mean systolic blood pressure.
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DISCUSSION

The one-stage meta-analysis showed a clear and significant relationship between OH and time to first fall incident. Although the odds ratio of falling was not significantly different for patients with and without OH, the width of the 95% confidence interval does not exclude a relevant clinical association. The results of the two-stage method, in which the results of the separate studies are pooled together, showed no significant relationship between OH and falling.

In the predefined protocol published on PROSPERO no preference was expressed about using logistic regression or cox proportional hazard analysis. Since both analyses can be useful to investigate the relationship between a causal factor and an outcome, both were used. While in the cox proportional hazard analysis the time to the first fall incident is the outcome measure from which the influence of OH on a fall incident is investigated, the ORs resulting from a logistic regression analysis only present cross-sectional information about this relationship after a (arbitrarily) fixed period of time. In the present meta-analysis, patients with OH had a 52% higher hazard on the first fall incident compared to patients without OH at any time during the follow-up period. Since patients can experience recurrent fall incidents over a longer period of time, a time to event analysis such as the cox regression analysis has a distinctive advantage over a binary logistic regression. In different studies OH seems to be related to recurrent falling in elderly patient [13, 32]. All things considered, the cox proportional hazard analysis provided more clinical relevant information in the present meta-analysis [53, 54].

In an IPD meta-analysis both one-stage and two-stage methods can be used. Although both types of analyses use similar IPD, the choice of a one- or two-stage method could result in different conclusions [19]. In the present meta-analysis this phenomenon was seen, HRs were different in one- and two-stage method, leading to different results. Debray et al. described differences between one- and two-stage methods and preferred the one-stage method, particularly in a meta-analysis with only a few studies [19]. Therefore, the conclusion in the present study is mainly based on the one-stage analyses.

This study is the first to aggregate results from observational studies into one IPD meta-analysis. In the prospective studies inconsistent results regarding the relationship between OH and fall incidents were reported [10, 11, 13, 23, 39, 41]. Furthermore, all studies had important limitations. Firstly, only in 1 out of the 6 selected studies the results for the total study population were reported [41]. The other selected studies mainly presented the results of subgroups
or described different endpoints regarding the relationship between OH and fall incidents [10, 13, 23, 39, 41]. Maurer and colleagues described no relation of OH and time to first fall incident in nursing home residents [41]. Only HRs of systolic or diastolic blood pressure decrease at different time-points were presented. In the study of Gangavati et al. a significant relationship was only seen within a subgroup of participants with systolic OH at 1 minute [10] and Allan et al. described only symptomatic OH as a significant predictor of falls in patients with dementia [23]. Besides, Luukinen et al. described the relationship of OH and falling in the subgroup recurrent fallers [39]; no significant association between OH and recurrent falling was seen. However, Ooi et al. reported that OH was an independent risk factor for recurrent falls [13].

Secondly, 2 out of 6 studies did not adjust for important confounders [11, 41]. Heiterrachi et al., described an increased risk of falls in older people with a decrease in systolic blood pressure > 20 mmHg [11], but no confounders were taken into account. Maurer et al. did also not adjust for any confounders; a post-hoc analysis was performed in which was adjusted for available medications only [41].

Thirdly, 2 out of the 6 selected studies did not use the International consensus definition of OH when analysing results [10, 41]. Maurer et al. and Gangavati et al. only described HRs at 1 minute or 3 minutes after standing separately, while the International consensus definition includes a decrease of blood pressure within 3 minutes [1].

In addition, many previous studies investigated the relationship between OH and falling only with retrospective fall data [24, 55, 56], leading to several forms of bias, such as confounding or recall bias [55]. Considering the results of all above-mentioned studies together, none of the studies showed a clear relationship between OH and falling. Several reviews described a theoretical relationship [7, 12], but could not perform a meta-analysis considering the low number of studies [8]. By using IPD, we were able to investigate the relationship between OH and falling in a meta-analysis and adjust for the most important confounders.

Strengths and Limitations

Despite the small number of studies, the current study is the only study, to the best of our knowledge that used the consensus definition of OH, which included a representative group of elderly, and adjusted for important confounders. No heterogeneity was observed and follow-up of all included studies was sufficient.

We acknowledge several limitations of our analysis. Firstly, only a small number of studies, and a limited number of patients were included in the meta-analysis. Unfortunately, one study did not report the time to first fall incident [11] and therefore the Cox regression analysis was only performed on two out of three studies [10, 23]. In addition, both results of the one-stage and two-stage methods showed wide confidence intervals that indicate additional information is needed for more precise estimates [21].
Another important limitation is the lack of subgroup and meta-regression analyses. Because of the limited number of studies included into the meta-analysis no subgroup or meta-regression analyses could be performed. A subgroup analysis according to Parkinson’s disease or dementia would have been useful since both could have influenced the relationship with falling [23]. Subgroup analyses of dementia were not performed because it was not prespecified and only one [23] of the three studies included patients with dementia or Parkinson’s disease. For the other two studies no data regarding dementia or Parkinson’s disease were available [10, 11]. In addition, subgroup analysis regarding study quality was preferred. However, all three included studies scored equal, allowing no subgroup analysis. Furthermore, OH was assessed within 3 min of postural change, thus not taking into account ‘delayed OH’. Also, we did not perform an analysis regarding recurrent falling. Only falling (yes/no) or time to first fall incident were analysed. Finally, both one and two-stage IPD was performed, leading to different results. It is known that one or two-stage IPD occasionally could lead to different conclusions [19].

CONCLUSIONS

This IPD meta-analysis of prospective observational studies showed a significant relationship between OH and time to first fall incident. However, since the small number of prospective studies included in present meta-analysis, more of these studies are needed for a more precise estimate of the relationship between OH and falling.
REFERENCES


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SUPPLEMENTAL DATA

Appendix 1: Search Strategy


Appendix Table 1. Newcastle-Ottawa scale for study quality for all three included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome/exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allan et al.[23]</td>
<td>★ ★ ★</td>
<td>★ ★</td>
<td>★ ★ ★ ★</td>
</tr>
<tr>
<td>Gangavati et al. [10]</td>
<td>★ ★ ★</td>
<td>★ ★</td>
<td>★ ★ ★ ★</td>
</tr>
<tr>
<td>Heitterachi et al. [11]</td>
<td>★ ★ ★</td>
<td>★ ★</td>
<td>★ ★ ★ ★</td>
</tr>
</tbody>
</table>

NOS: Newcastle-Ottawa Scale: on a 9-point scale, the NOS evaluates the quality of observational studies on three broad categories: selection of the study groups (maximum of 4 stars); comparability of the groups (maximum of 2 stars); and ascertainment of the outcome of interest (maximum of 3 stars).

Appendix Table 2. Subgroup analyses. Adjusted odds ratios and Hazard ratios for the effect of orthostatic hypotension on the risk of falling with individual patient data in a ‘one-stage’ model. The odds ratios can be interpreted as a measure of the association of OH to falling (the dependent variables).

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Odds ratio (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH (model 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic patients</td>
<td>0.87 (0.44-1.73)</td>
<td>1.15 (0.72-1.86)</td>
</tr>
<tr>
<td>OH (model 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic patients</td>
<td>0.85 (0.42-1.69)</td>
<td>1.17 (0.72-1.90)</td>
</tr>
<tr>
<td>OH (model 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic patients</td>
<td>0.97 (0.44-2.15)</td>
<td>1.38 (0.80-2.38)</td>
</tr>
<tr>
<td>OH (model 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-diabetic patients</td>
<td>0.89 (0.65-1.21)</td>
<td>1.29 (1.05-1.59)</td>
</tr>
<tr>
<td>OH (model 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-diabetic patients</td>
<td>0.90 (0.66-1.24)</td>
<td>1.29 (1.05-1.58)</td>
</tr>
<tr>
<td>OH (model 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-diabetic patients</td>
<td>1.26 (0.88-1.81)</td>
<td>1.53 (1.21-1.93)</td>
</tr>
<tr>
<td>OH (model 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.02 (0.57-1.85)</td>
<td>1.06 (0.68-1.64)</td>
</tr>
<tr>
<td>OH (model 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.94 (0.51-1.71)</td>
<td>0.99 (0.64-1.55)</td>
</tr>
<tr>
<td>OH (model 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.01 (0.53-1.93)</td>
<td>1.05 (0.65-1.71)</td>
</tr>
<tr>
<td>OH (model 1)</td>
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<td></td>
</tr>
<tr>
<td>No Hypertension</td>
<td>0.98 (0.51-1.86)</td>
<td>0.92 (0.60-1.41)</td>
</tr>
<tr>
<td>OH (model 2)</td>
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<tr>
<td>No Hypertension</td>
<td>0.99 (0.52-1.91)</td>
<td>0.93 (0.60-1.43)</td>
</tr>
<tr>
<td>OH (model 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Hypertension</td>
<td>1.07 (0.54-2.16)</td>
<td>0.99 (0.63-1.58)</td>
</tr>
</tbody>
</table>

OH = orthostatic hypotension. DM = Diabetes Mellitus.