Orthostatic hypotension is associated with new-onset atrial fibrillation: Systemic review and meta-analysis

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Introduction: Orthostatic hypotension (OH) is common among elderly patients. Its presence may herald severe underlying comorbidities and be associated with a higher risk of mortality. Interestingly, recent studies suggest that OH is associated with new-onset atrial fibrillation (AF). However, a systematic review and meta-analysis of the literature has not been performed. We assessed the association between AF and OH through a systematic review of the literature and a meta-analysis.

Methods: We comprehensively searched the databases of MEDLINE and EMBASE from inception to November 2018. Published prospective or retrospective cohort studies that compared new-onset AF between male patients with and without OH were included. Data from each study were combined using the random-effects, generic inverse-variance method of DerSimonian and Laird to calculate risk ratios and 95% confidence intervals.

Results: Four studies from October 2010 to March 2018 were included in the meta-analysis involving 76,963 subjects (of which 3318 were diagnosed with OH). The presence of OH was associated with new-onset AF (pooled risk ratio 1.48; 95% confidence interval [1.21, 1.81], \( p < 0.001 \); \( I^2 = 69.4\% \)). In hypertensive patients, analysis revealed an association between OH and the occurrence of new-onset AF (OR 1.46; 95% CI [1.27, 1.68], \( p < 0.001 \) with \( I^2 = 0\) ).

Conclusions: OH was associated with new-onset AF up to 1.5-fold compared with those subjects without OH. The interplay between OH and AF is likely bidirectional.

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1. Introduction

Orthostatic hypotension (OH) is a condition reflecting the impaired capability of the autonomic nervous system (ANS) to maintain blood pressure in an upright position. It is defined as a supine-to-standing drop in systolic blood pressure (SBP) by more than 20 mmHg or in diastolic blood pressure (DBP) by more than 10 mmHg.1 Patients with OH have a significantly increased stroke risk of over two-fold2,3 and a 50–100% increased mortality rate comparing with those without OH.4−5 The presence of OH is also linked to higher incidence of coronary heart disease and heart failure.6 The prevalence of OH is estimated to be up to 18.2% in patients over 65 years of age.7 There is a higher prevalence among patients with diabetes.7

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with significantly increased morbidity and mortality.8 The prevalence of AF is estimated to be 6.1% in patients over 65 years of age.9 Several mechanisms play a role in the pathogenesis, including ANS dysregulation,10 altered autonomic tone in patients with obstructive sleep apnea,11 and hypertension.12 Hypertension, in particular, was found to be related to the occurrence of AF, suggesting a relationship between the ANS and AF. We hypothesized that individuals who have OH may be at an increased risk of AF. We performed a meta-analysis of observational studies reporting on the association between OH and AF.
2. Methods

2.1. Search strategy

Two investigators (J.K. and N.A.) independently searched for published studies indexed in MEDLINE and EMBASE databases from inception to November 2018 using a search strategy (Fig. 1) that included the terms ‘atrial fibrillation’, ‘orthostatic hypotension’, ‘postural hypotension’, and ‘orthostatic intolerance.’ Only English language publications were included. A manual search for additional pertinent studies and review articles using references from retrieved articles was also completed.

2.2. Study eligibility criteria

Two main criteria were assessed for the inclusion of studies. The first criterion was a reported incidence of AF in patients with or without OH. The second was a reported relative risk, hazard ratio, odds ratio (OR), incidence ratio, and/or standardized incidence ratio with 95% confidence intervals (CIs) (or sufficient data for the calculation to be performed by a third party). Patients without OH were used as controls. Study eligibility was independently determined by two investigators (J.K. and N.A.). Differences were resolved by mutual consensus. The Newcastle–Ottawa quality assessment scale was used to evaluate each study in three domains: (1) recruitment and selection of the participants, (2) similarity and comparability between the groups, and (3) ascertainment of the outcome of interest among cohort studies.

2.3. Definitions

OH was defined slightly differently between studies regarding the timing between repeat blood pressure measurements (Table 1), but all were in agreement regarding change in SBP or DBP. AF was also defined slightly differently among studies but all involved an ICD code or Electrocardiogram (ECG) interpretation (Table 1).

Fig. 1. Search methodology and selection process.
2.4. Data extraction

A standardized data abstraction form was used to obtain information from each study, these included the title, name of the first author, year of study, year of publication, country of origin, number of participants, demographic data of participants, method used to identify cases and controls, method used to diagnose the outcomes of interest (AF), average duration of follow-up, adjusted and unadjusted risk ratios and their corresponding 95% CI, and list of confounders that were adjusted for in the multivariate analysis. To ensure accuracy, all investigators independently performed this data abstraction process. Any discrepancies were resolved by referring back to the original articles.

2.5. Statistical analysis

Meta-analysis of the combined data was performed using a random-effects, generic inverse-variance method of DerSimonian and Laird. The heterogeneity of effect size estimates across these studies was quantified using the I² statistic and Q statistic. For the Q statistic, substantial heterogeneity was defined as p < 0.10. The I² statistic ranges in value from 0 to 100% (I² < 25% is interpreted as low heterogeneity; I² = 25%–50%, moderate heterogeneity; and I² > 50%, substantial heterogeneity). A sequential exclusion strategy, as described by Patsopoulos et al., was used to examine whether overall estimates were influenced by the substantial heterogeneity observed. We sequentially and cumulatively excluded studies that accounted for the largest share of heterogeneity until I² was less than 50%. We then examined whether relative risk estimates were consistent. In accordance with Cochrane, publication bias was assessed using funnel plot analysis. Funnel plot asymmetry was to be further confirmed with Egger's test if there were more than 10 available studies. All analyses were performed using Review manager version 5.3 and STATA version 14.1 (College Station, TX).

| First author | Year | Country | Study type | Participant description | Exclusion criteria | Participants, N | Mean age (years) | Gender (male), N (%) | Follow-up time (years) | AF diagnosis | Participants developing AF, N (%) | Conclusion by author |
|--------------|------|---------|------------|------------------------|-------------------|-----------------|-----------------|-------------------|---------------------|-------------|---------------------------------|-------------------|
| Agarwal      | 2013 | USA     | Prospective cohort | Men and women aged 45–64 years from the Atherosclerosis Risk in Communities (ARIC) study | - Missing or poor quality of BP data | 12,071          | 54.1 ± 5.7     | 5431 (45%)        | Mean of 18          | ICD-9 code 427.31, 427.32, 427.3 | OH predicts incidence of AF |
| Ko           | 2018 | USA     | Prospective cohort | Men and women from Malmo, Sweden | - Prevalent AF | 32,628          | 45.6 ± 7.4      | 21,958 (67.3%)     | Mean of 24          | ICD-9 code 427.3 | OH is associated with higher AF incidence |
| Yasa         | 2018 | Sweden  | Retrospective cohort | Participants from the Framingham Heart Study Original cohort | - History of heart failure | 1736            | 71.7 ± 6.5      | 690 (39.8%)        | Mean of 48          | ECG from routine examination | Patients with OH or syncope show higher incidence of CVS disease and mortality |
|              |      |         | Prospective cohort | Men and women born between 1923 and 1945, 1950 respectively | - Prevalent MI | 30,528          | 58 ± 8          | 12,221 (40%)       | Median of 15 ± 4    | ICD-8 code 427.92, ICD-9 code 427D, ICD-10 code 148 |                       |

AF, atrial fibrillation; BP, blood pressure; BMI, body mass index; CHD, coronary heart disease; CVS, cardiovascular; DBP, diastolic blood pressure; DM, diabetes mellitus; HR, hazard ratio; MI, myocardial infarction; OH, orthostatic hypotension; SBP, systolic blood pressure; CI, confidence interval; OR, odds ratio.
Fig. 2. a) Forest plot of studies comparing new-onset AF in patients with and without OH. Horizontal lines represent the 95% CIs with marker size reflecting the statistical weight of the study using the random effects model. A diamond data marker represents the overall adjusted OR and 95% CI for the outcome of interest. (b) Forest plot of subgroup studies categorized by age (more than or less than 55 years old), comparing the occurrence of new-onset AF in patients with and without OH. Horizontal lines represent the 95% CIs with marker size reflecting the statistical weight of the study using the random effects model. A diamond data marker represents the overall adjusted OR and 95% CI for the outcome of interest. (c) Forest plot of subgroup studies categorized by sex, comparing the occurrence of new-onset AF in patients with and without OH. Horizontal lines represent the 95% CIs with marker size reflecting the statistical weight of the study using the random effects model. A diamond data marker represents the overall adjusted OR and 95% CI for the outcome of interest. (d) Forest plot of subgroup studies categorized as hypertensive or normotensive, comparing the occurrence of new-onset AF in patients with and without OH. Horizontal lines represent the 95% CIs with marker size reflecting the statistical weight of the study using the random-effects model. A diamond data marker represents the overall adjusted OR and 95% CI for the outcome of interest. AF, atrial fibrillation; OH, orthostatic hypotension; CI, confidence interval; OR, odds ratio.
3. Results

3.1. Description of included studies

Our search strategy yielded 31 potentially relevant articles (19 articles from EMBASE and 12 articles from MEDLINE). After the exclusion of 10 duplicate articles, 21 articles underwent title and abstract review. Four studies were excluded at this stage because they were review articles (two) or case reports (two), leaving 17 articles for full-length article review. Ten studies were excluded as there was no outcome of interest. One study was excluded because analysis was performed only in a ‘postprandial hypotension’ group. One study examined the incidence of AF in the presence of OH only without a control group and was, therefore, eliminated. Finally, one study did not exclude patients with previously diagnosed AF from the cohort. In summary, three prospective cohort studies and one retrospective cohort study with and without OH patients were included in this meta-analysis. The clinical characteristics are described in Table 1.

3.2. Quality assessment of included studies

The Newcastle–Ottawa scale (0–9) was used to evaluate included studies in 3 domains: (1) selection, (2) comparability, and (3) outcomes. Higher scores represent higher study quality. All studies received a score of 7–8, which reflect the inclusion of high quality studies. Detailed evaluation of each study is presented in a supplementary table (Table S1).
with OH are susceptible to adverse cardiac events.\textsuperscript{4,5,23–27} It was also associated with a higher risk of falls, especially in elderly patients.\textsuperscript{7,28,29} Additionally, OH is associated with new-onset AF, one of the most common cardiac arrhythmias\textsuperscript{3} contributing to adverse outcomes.\textsuperscript{30–32}

Our meta-analysis demonstrated that the presence of OH was associated with new-onset AF up to 1.5-fold. In addition, our subgroup analyses all consistently correlated OH with AF. The prevalence of OH in our study ranged from 1.6 to 12.9%, due to lower mean subject age. However, the incidence of AF approached those older than 65 years of age.

Considering methodological aspects, despite similar OH definitions among studies, the interval between blood pressure recordings after position changes was divergent, likely confounding overall results in this analysis. In addition, the inclusion and exclusion criteria, demographic data, comorbidity, and mean duration of follow-up were totally different. These factors might explain the higher rate of new-onset AF in the female sex subgroup and the lower prevalence of OH than that previously reported in those older than 65 years of age.

### 4. Discussion

OH is notoriously associated with higher morbidity and mortality. Several observational studies have suggested that patients...
known AF risk factors. Thus, the presence of OH may serve to raise the suspicion for these underlying comorbidities which are often related to AF. Of note, abnormal diurnal BP variation as well as supine hypertension, commonly found in OH patients, may instigate periodic increases in afterload leading to end-organ damage such as left ventricular hypertrophy and renal impairment. As a result, either MI or CHF may develop and AF may follow given the high risk of these conditions. In other words, OH may indirectly induce AF through other related processes.

In addition, ANS dysregulation may result in arterial stiffness which may consequently lead to both OH and AF. One study showed that restoration of sinus rhythm from AF improved baroreceptor reflex impairment, a proposed mechanism for the pathogenesis of OH. This finding further supports the association between AF and OH and suggests that the interplay between AF and OH may be bidirectional.

4.1. Limitations

There are a number of limitations with our meta-analysis. First, there is substantial heterogeneity in our study which is a major limitation. This is likely due to the included studies which were all observational in nature, with different methodologies, demographic data, and heterogeneous comorbidities. Hence, the influence of residual confounders could not be completely excluded. Second, it is possible that AF was underdetected given the methods used to detect the incidence of AF in each study. For instance, paroxysmal AF could be easily missed. Third, we did not perform subgroup analyses of OH subcategories including initial OH and delayed OH because of insufficient data. In addition, the subtype of OH such as neurogenic OH was not separately investigated. Each OH subtype may produce different conditional probabilities and posterior probabilities for AF. Fourth, OH documentation in all studies was determined at the first visit leading to a possible underestimation of the prevalence. Finally, only four studies were included in our analysis. Despite a seemingly symmetrical funnel plot, the possibility of false negative test could not be excluded as a small number of studies were included, resulting in reduced sensitivity of such an analysis. Nevertheless, we believe the number of recruited participants were substantial enough to yield meaningful results.

5. Conclusion

In summary, the presence of OH is associated with new-onset AF. Our meta-analysis revealed a clear association between OH and AF as evidenced by ORs of up to 1.5. The association appears to be bidirectional, given multiple proposed mechanisms and supporting evidence from other studies involving dysregulation of the ANS, baroreceptor impairment in AF, and comorbidities such as CHF and MI which may themselves be a result of OH. However, our results favor OH as a predisposing risk factor for the development of AF. Thus, addressing autonomic instability may serve to reduce the prevalence and incidence of OH as well as the incidence of AF. Certainly, further studies are warranted in the future clarifying the relationship between OH and AF and determining causation.

Author contribution

Narut Prasitlumkum contributed in design conception and data interpretation, drafted the manuscript, and is the corresponding author. Jakrin Kewchaoren contributed in data acquisition and drafted the manuscript. Nathapon Angusbhakorn contributed in data acquisition and data interpretation. Pakawat Chongsathidkiet contributed in data acquisition. Pattara Ratanawong contributed in data interpretation and statistical analysis.

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Conflict of interest

All authors have none to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2019.07.009.

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