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Original Article

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

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ABSTRACT

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], $p?< 0.001$; $I2 = 69.4\%$). 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 $I2 = 0$).

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.

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-fold[2,3] and a 50–100% increased mortality rate comparing with those without OH.[3–5] The presence of OH is also linked to higher incidence of coronary heart disease and heart failure.[2] The prevalence of OH is estimated to be up to 18.2% in patients over 65 years of age.[6] 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,[10,11] altered autonomic tone in patients with obstructive sleep apnea,[12] and hypertension.[13] 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.

Abbreviations: AF, Atrial fibrillation; ANS, Autonomic nervous system; BP, Blood pressure; CHF, Congestive heart failure; CI, Confidence interval; ECG, Electrocardiogram; MI, Myocardial infarction; OH, Orthostatic hypotension; OR, Odds ratio.

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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.[14]

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).

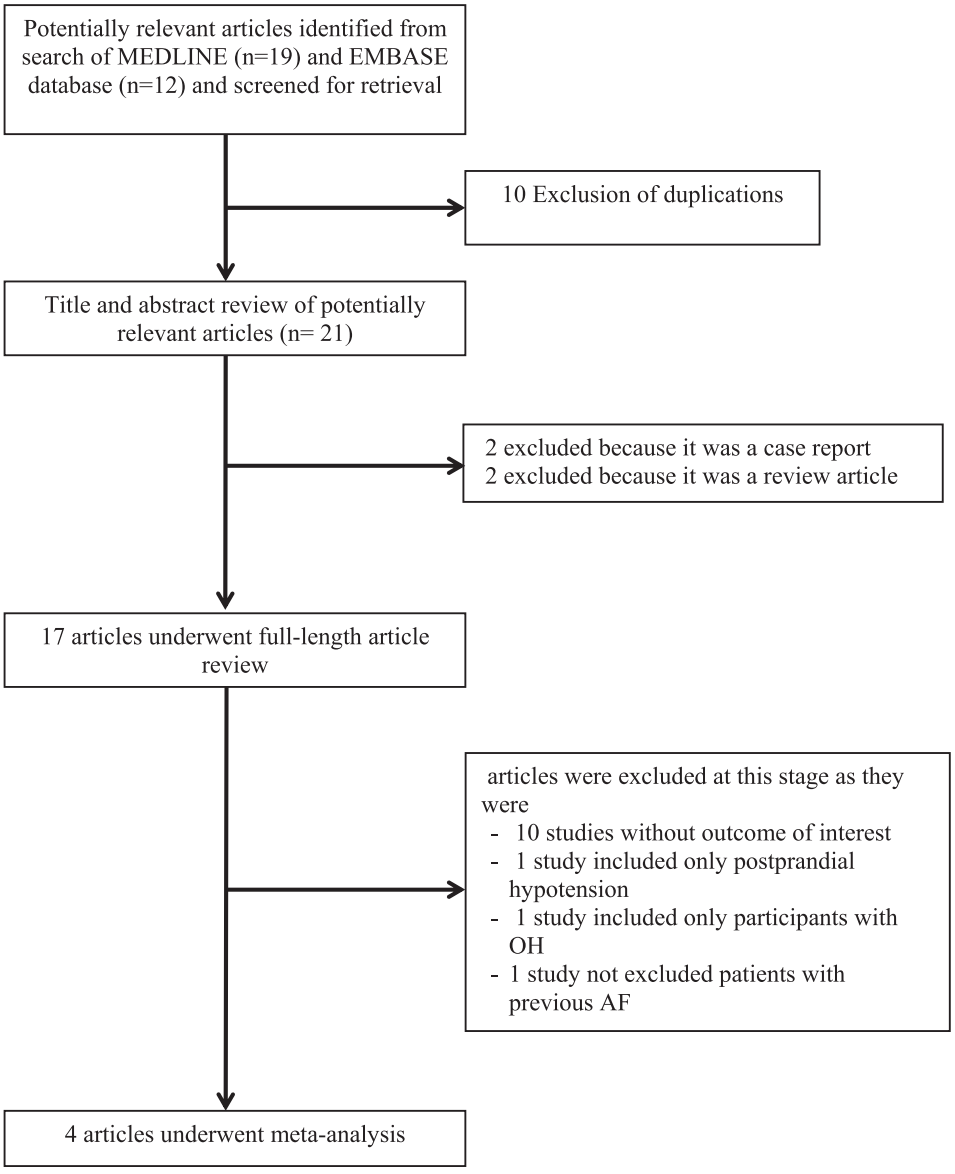

Fig. 1. Search methodology and selection process.

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.[15] The heterogeneity of effect size estimates across these studies was quantified using the I^2 statistic and Q statistic. For the Q statistic, substantial heterogeneity was defined as $p < 0.10$. The I^2 statistic ranges in value from 0 to 100% ($I^2 < 25\%$ is interpreted as low heterogeneity; $I^2 = 25\%–50\%$, moderate heterogeneity; and $I^2 > 50\%$, substantial heterogeneity).[16] A sequential exclusion strategy, as described by Patsopoulos et al,[17] 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 I^2 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.[18] All analyses were performed using Review manager version 5.3 and STATA version 14.1 (College Station, TX).

Table 1
Studies characteristics.

First author	Agarwal	Fedorowski	Ko	Yasa
Year	2013	2010	2018	2018
Country	USA	Sweden	USA	Sweden
Study type	Prospective cohort	Prospective cohort	Retrospective cohort	Prospective cohort
Participant description	Men and women aged 45–64 years from the Atherosclerosis Risk in Communities (ARIC) study	Men and women from Malmo, Sweden	Participants from the Framingham Heart Study Original cohort	Men and women born between 1923 and 1945, 1950 respectively
Exclusion criteria	- Missing or poor quality of BP data - Prevalent AF/atrial flutter from baseline - Underlying heart rhythm abnormality	- Missing BP data - Prevalent AF - History of heart failure - Prevalent MI	- Missing BP data - Preexisting AF	- Cases with current prevalent CVS disease
Participants, N				
Total	12,071	32,628	1736	30,528
OH	603	1987	256	504
Non-OH	11,468	30,641	1480	30,024
OH definition	SBP drop of ≥20 mmHg or DBP of ≥10 mmHg when changing position from supine to standing	SBP drop of ≥20 mmHg or DBP of ≥10 mmHg within 3 min of changing position from supine to standing	SBP drop of ≥20 mmHg or DBP of ≥10 mmHg within 2 min of changing position from supine to standing	SBP drop of ≥20 mmHg or DBP of ≥10 mmHg within 3 min of changing position from supine to standing
Mean age (years)	54.1 ± 5.7	45.6 ± 7.4	71.7 ± 6.5	58 ± 8
Gender (male), N (%)	5431 (45%)	21,958 (67.3%)	690 (39.8%)	12,221 (40%)
Follow-up time (years)	Mean of 18	Mean of 24	Mean of 8.3	Median of 15 ± 4
AF diagnosis	ICD-9 code 427.31, 427.32, 427.3 ICD-10 code I48	ICD-9 code 427.3	ECG from routine examination	ICD-8 code 427.92 ICD-9 code 427D ICD-10 code I48
Participants developing AF, N (%)				
Total	1438 (11.9%)	2312 (7.1%)	224	2824
OH	111 (18.4%)	196 (9.6%)	N/A	N/A
Non-OH	1327 (11.6%)	2116 (6.9%)	N/A	N/A
Odd/hazard ratio (95% CI)	Adjusted HR: 1.40 (1.15–1.71)	Adjusted HR: 1.20 (1.01–1.41)	Adjusted HR: 1.61 (1.17–2.20)	Adjusted HR: 1.89 (1.48–2.41)
Confounder adjustment	Age, gender, race, DM, BMI, heart rate, SBP, DBP, hypertension and antihypertensive medication, CHD, smoking status, alcohol consumption	Age, gender, BMI, SBP, DBP, DM, smoking, total cholesterol	Age, gender, SBP, DBP, BMI, heart rate, hypertension and antihypertensive medication, smoking status, history of heart failure and MI	Age, gender, BMI, SBP, antihypertensive medication, DM, smoking status
Conclusion by author	OH is associated with higher AF incidence	OH predicts incidence of AF	OH is associated increased risk of incident AF	Patients with OH or syncope show higher incidence of CVS disease and mortality
Newcastle–Ottawa quality assessment	8	7	7	7

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.

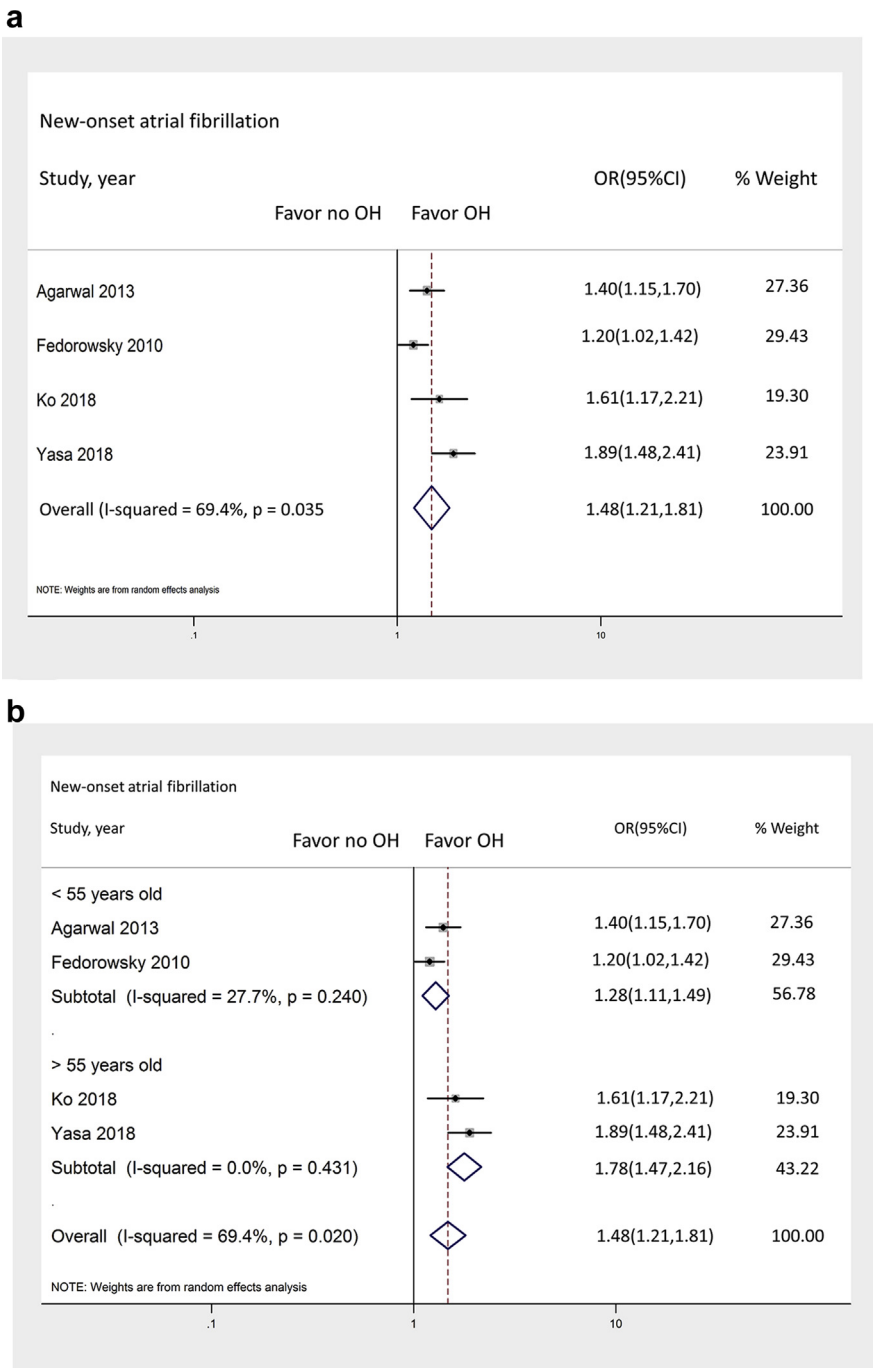

Fig. 2. a) Forest plot of studies comparing new-onset AF in patients with and without OH. Horizontal lines represent the 95% CIs with marker size reflecting the statistical weight of the study using the random effects model. A diamond data marker represents the overall adjusted OR and 95% CI for the 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.

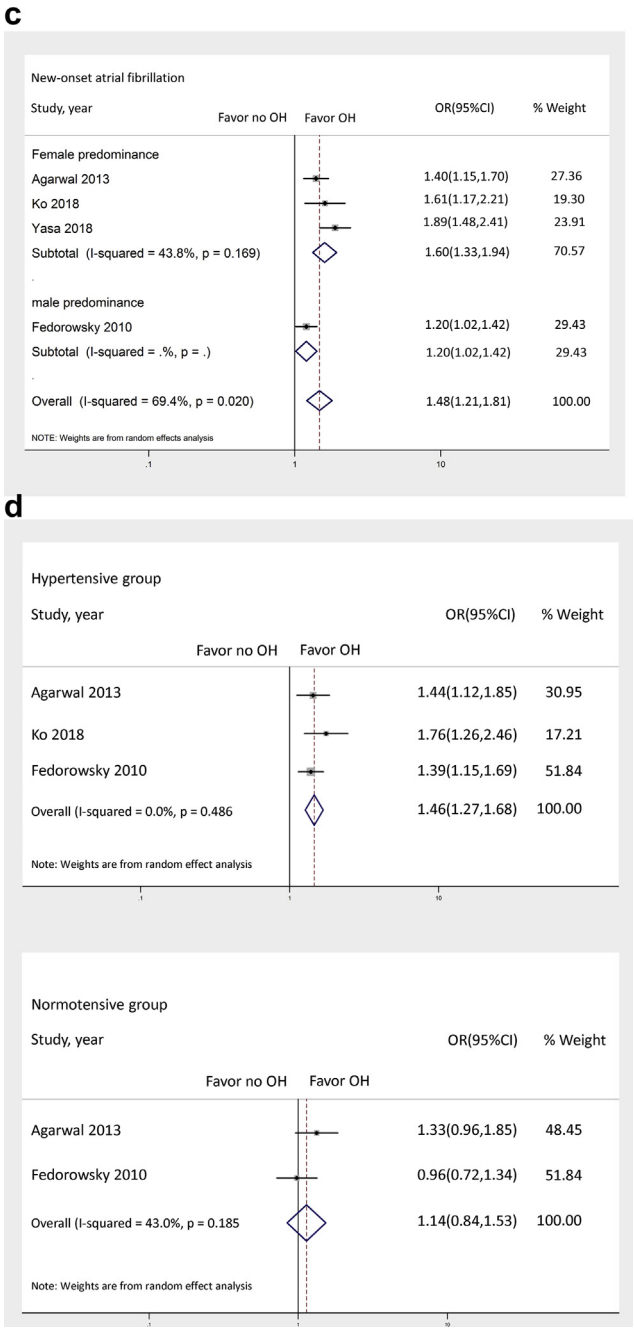

Fig. 2. (*continued*).

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).

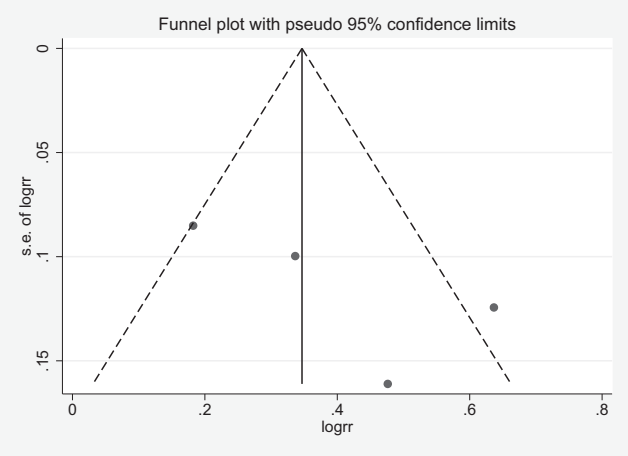

Fig. 3. Funnel plot of OH and new-onset AF. Circles represent published studies.AF, atrial fibrillation; OH, orthostatic hypotension.

3.3. Meta-analysis result

A total of four studies (3 prospective, 1 retrospective) with 76,963 participants were included in the meta-analysis. The prevalence of OH ranged from 1.6 to 12.9%. There was an association between OH and new-onset AF (OR 1.48; 95% CI [1.21, 1.81], $p < 0.001$) with substantial heterogeneity ($I^2 = 69.4\%$) (Fig. 2a). Owing to substantial heterogeneity, we performed subgroup analyses by mean age, sex predominance, normotensive group, and hypertensive group to determine their impacts. In the subcategory for mean age, we further subdivided the group into a 'greater than 55 year-old' sample[19,20] or a 'less than 55 year-old' sample.[21,22] Both age subgroups revealed a strong association between new-onset AF and OH (OR 1.28; 95% CI [1.11, 1.49], p = 0.003 with $I^2 = 27.7\%$ and OR 1.78; 95% CI [1.48, 2.16], p < 0.001 with $I^2 = 0\%$, respectively) (Fig. 2b). In relation to sex, we found that both female and male groups exhibited a statistical association between OH and the incidence of new-onset AF (OR 1.60; 95% CI [1.3, 1.94], $p < 0.001$ with $I^2 = 43.8\%$ and OR 1.20; 95% CI [1.02,1.42], $p < 0.001$). Given that there was only one study for the male group, heterogeneity could not be calculated (Fig. 2c).

Two studies provided conditional probabilities for new onset AF given OH (18.4% according to Agarwal and 9.6% according to Fedorowski). The probability of new onset AF for all comers was 11.9% in Agarwal and 7.1% in Feodowski. Through the application of Bayes' theorem, the posterior probability of OH given AF was estimated to be 7.7% and 8.2%, for Agarwal and Fedorowski, respectively. The marginal probability of OH was 5% and 6.1%, respectively.

In hypertensive patients,[20–22] 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 $I^2 = 0$). Conversely, in normotensive patients,[21,22] the correlation between OH and new-onset AF was not statistically significant (OR 1.14; 95% CI [0.84, 1.53] with $I^2 = 43\%$) (Fig. 2d). Funnel plot analysis did not suggest publication bias (Fig. 3). Egger's test was ultimately not performed due to an insufficient number of studies included in the meta-analysis. Sensitivity analysis performed to explore heterogeneity showed no significant change in the findings when each study was separately omitted.

4. Discussion

OH is notoriously associated with higher morbidity and mortality. Several observational studies have suggested that patients with OH are susceptible to adverse cardiac events.[4,5,23–27] It was also associated with a higher risk of falls, especially in elderly patients.[7,28,29] Additionally, OH is associated with new-onset AF, one of the most common cardiac arrhythmias[9] contributing to adverse outcomes.[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 figures reported in the literature.

Given substantial heterogeneity in our study, we conducted subgroup analyses to evaluate for possible confounding factors. We suspected age, sex predominance, or blood pressure status (normotensive or hypertensive) might explain such findings. Regarding age, the group with patients 55 years or older had a higher risk than the group with patients younger than 55 years (OR 1.78 versus 1.28, respectively). This finding was consistent with previous studies, which determined that the prevalence and incidence of AF increased with age.[9,33–35] Surprisingly, our subgroup analysis suggested that female sex was more associated with new-onset AF than male sex (OR 1.61 versus 1.20, respectively). This finding appears to contradict the fact that female sex was, in general, found to be protective against AF.[9] However, it may reflect a lack of sensitivity in the meta-analysis given that only one study included a male sex arm.[22] Considering the exclusion criteria and demographic data, all patients with a previous myocardial infarction (MI) and history of heart failure were not included and the mean age was 45 which was the lowest mean when compared with other studies. 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.

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, demographical data, comorbidity, and mean duration of follow-up were totally different. These factors are thought to be a substantial source of errors in our study, contributing to significant heterogeneity. Thus, one should interpret the results cautiously as diverse methods among the studies exist.

We found a statistical correlation between OH and new-onset AF in hypertensive patients but not normotensive patients. We suspect two reasons for this result. First, only two studies provided enough data to abstract for analysis, which may have resulted in insufficient power. Second, participants from Fedorowski et al[22] seemed healthier, and thus, our subgroup analysis is likely to be affected by this fact. Hence, this may justify further study to evaluate the effect of OH in the setting of normotensive status.

The link between OH and new-onset AF has remained elusive. Several mechanisms have been proposed but are yet to be verified. In general, blood pressure control following postural change is regulated by the sympathetic and parasympathetic nervous system, which are collectively referred to as the ANS.[36] To start, the pathogenesis for OH is thought to be secondary to an impaired ANS. It is believed that ANS dysregulation may play a role in the pathogenesis of AF as well, by impairing neurohormonal signal transmission and modulation in the heart thereby precipitating AF.[37,38] This mechanism implies that OH may be a harbinger for developing AF.

Many conditions are associated with OH including advancing age,[39,40] structural heart disease such as aortic stenosis,[41] chronic heart failure,[22] diabetes,[42] and hypertension,[43,44]; all of which are

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[45] as well as supine hypertension,[46] commonly found in OH patients, may instigate periodic increases in afterload leading to end-organ damage[47–49] such as left ventricular hypertrophy and renal impairment.[50] As a result, either MI[51,52] or CHF may develop and AF may follow given the high risk of these conditions.[53] In other words, OH may indirectly induce AF through other related processes.

In addition, ANS dysregulation may result in arterial stiffness[54] which may consequently lead to both OH and AF.[55,56] One study showed that restoration of sinus rhythm from AF improved baroreceptor reflex impairment, a proposed mechanism for the pathogenesis of OH.[36] 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 underestimate 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, baroceptor 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 Kewcharoen contributed in data acquisition and drafted the manuscript. Natthapon Angsubhakorn contributed in data acquisition and data interpretation. Pakawat Chongsathidkiet contributed in data acquisition. Pattara Rattanawong 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.

References

1. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res : offi J Clin Auto Res Soc*. 2011;21(2):69–72.
2. Eigenbrodt ML, Rose KM, Couper DJ, Arnett DK, Smith R, Jones D. Orthostatic hypotension as a risk factor for stroke: the atherosclerosis risk in communities (ARIC) study, 1987-1996. *Stroke*. 2000;31(10):2307–2313.
3. Ricci F, Fedorowski A, Radico F, et al. Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies. *Eur Heart J*. 2015;36(25):1609–1617.
4. Rose KM, Eigenbrodt ML, Biga RL, et al. Orthostatic hypotension predicts mortality in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2006;114(7):630–636.
5. Masaki KH, Schatz IJ, Burchfiel CM, et al. Orthostatic hypotension predicts mortality in elderly men: the Honolulu Heart Program. *Circulation*. 1998;98(21):2290–2295.
6. Rutan GH, Hermanson B, Bild DE, Kittner SJ, LaBaw F, Tell GS. Orthostatic hypotension in older adults. The cardiovascular health study. CHS collaborative research group. *Hypertension*. 1992;19(6 Pt 1):508–519. Dallas, Tex : 1979.
7. van Hateren KJ, Kleefstra N, Blanker MH, et al. Orthostatic hypotension, diabetes, and falling in older patients: a cross-sectional study. *Br J Gen Pract*. 2012;62(603):696–702.
8. Kirchhof P, Bax J, Blomstrom-Lundquist C, et al. Early and comprehensive management of atrial fibrillation: executive summary of the proceedings from the 2nd AFNET-EHRA consensus conference 'research perspectives in AF'. *Eur Heart J*. 2009;30(24):2969–2977c.
9. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285(18):2370–2375.
10. Arora R. Recent insights into the role of the autonomic nervous system in the creation of substrate for atrial fibrillation: implications for therapies targeting the atrial autonomic nervous system. *Circ Arrhyth Electrophysiol*. 2012;5(4):850–859.
11. Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S. Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy. *Circ Res*. 2014;114(9):1500–1515.
12. Gami AS, Hodge DO, Herges RM, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol*. 2007;49(5):565–571.
13. Okin PM, Wachtell K, Kjeldsen SE, et al. Incidence of atrial fibrillation in relation to changing heart rate over time in hypertensive patients: the LIFE study. *Circ Arrhyth Electrophysiol*. 2008;1(5):337–343.
14. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25(9):603–605.
15. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Contr Clin Trials*. 1986;7(3):177–188.
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560.
17. Patsopoulos NA, Evangelou E, Ioannidis JP. Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. *Int J Epidemiol*. 2008;37(5):1148–1157.
18. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol*. 2001;54(10):1046–1055.

19. Yasa E, Ricci F, Magnusson M, et al. Cardiovascular risk after hospitalisation for unexplained syncope and orthostatic hypotension. *Heart (British Cardiac Society)*. 2018;104(6):487–493.
20. Ko D, Preis SR, Lubitz SA, et al. Relation of orthostatic hypotension with new-onset atrial fibrillation (from the framingham heart study). *Am J Cardiol*. 2018;121(5):596–601.
21. Agarwal SK, Alonso A, Whelton SP, et al. Orthostatic change in blood pressure and incidence of atrial fibrillation: results from a bi-ethnic population based study. *PLoS One*. 2013;8(11), e79030.
22. Fedorowski A, Engstrom G, Hedblad B, Melander O. Orthostatic hypotension predicts incidence of heart failure: the Malmo preventive project. *Am J Hypertens*. 2010;23(11):1209–1215.
23. Luukinen H, Koski K, Laippala P, Kivela SL. Prognosis of diastolic and systolic orthostatic hypotension in older persons. *Arch Intern Med*. 1999;159(3):273–280.
24. Verwoert GC, Mattace-Raso FU, Hofman A, et al. Orthostatic hypotension and risk of cardiovascular disease in elderly people: the Rotterdam study. *J Am Geriatr Soc*. 2008;56(10):1816–1820.
25. Luukinen H, Koski K, Laippala P, Airaksinen KE. Orthostatic hypotension and the risk of myocardial infarction in the home-dwelling elderly. *J Intern Med*. 2004;255(4):486–493.
26. Fedorowski A, Stavenow L, Hedblad B, Berglund G, Nilsson PM, Melander O. Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals (The Malmo Preventive Project). *Eur Heart J*. 2010;31(1):85–91.
27. Angelousi A, Girerd N, Benetos A, et al. Association between orthostatic hypotension and cardiovascular risk, cerebrovascular risk, cognitive decline and falls as well as overall mortality: a systematic review and meta-analysis. *J Hypertens*. 2014;32(8):1562–1571. discussion 1571.
28. Gangavati A, Hajjar I, Quach L, et al. Hypertension, orthostatic hypotension, and the risk of falls in a community-dwelling elderly population: the maintenance of balance, independent living, intellect, and zest in the elderly of Boston study. *J Am Geriatr Soc*. 2011;59(3):383–389.
29. Ooi WL, Hossain M, Lipsitz LA. The association between orthostatic hypotension and recurrent falls in nursing home residents. *Am J Med*. 2000;108(2):106–111.
30. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *BMJ*. 2016;354:i4482.
31. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015;386(9989):154–162.
32. Chen LY, Benditt DG, Alonso A. Atrial fibrillation and its association with sudden cardiac death. *Circ J : off J Japan Circ Soc*. 2014;78(11):2588–2593.
33. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med*. 1995;155(5):469–473.
34. Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ. Epidemiology and natural history of atrial fibrillation: clinical implications. *J Am Coll Cardiol*. 2001;37(2):371–378.
35. Heeringa J, van der Kuip DA, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J*. 2006;27(8):949–953.
36. Ricci F, De Caterina R, Fedorowski A. Orthostatic hypotension: epidemiology, prognosis, and treatment. *J Am Coll Cardiol*. 2015;66(7):848–860.
37. Bettoni M, Zimmermann M. Autonomic tone variations before the onset of paroxysmal atrial fibrillation. *Circulation*. 2002;105(23):2753–2759.
38. Krummen DE, Narayan SM. Mechanisms for the initiation of human atrial fibrillation. *Heart Rhythm*. 2009;6(8 Suppl):S12–S16.
39. Tonkin AL, Wing LM. Effects of age and isolated systolic hypertension on cardiovascular reflexes. *J Hypertens*. 1994;12(9):1083–1088.
40. Huang CC, Sandroni P, Sletten DM, Weigand SD, Low PA. Effect of age on adrenergic and vagal baroreflex sensitivity in normal subjects. *Muscle Nerve*. 2007;36(5):637–642.
41. Taneja I, Marney A, Robertson D. Aortic stenosis and autonomic dysfunction: co-conspirators in syncope. *Am J Med Sci*. 2004;327(5):281–283.
42. Krolewski AS, Warram JH, Cupples A, Gorman CK, Szabo AJ, Christlieb AR. Hypertension, orthostatic hypotension and the microvascular complications of diabetes. *J Chronic Dis*. 1985;38(4):319–326.
43. Strogatz DS, Keenan NL, Barnett EM, Wagner EH. Correlates of postural hypotension in a community sample of elderly blacks and whites. *J Am Geriatr Soc*. 1991;39(6):562–566.
44. Shin C, Abbott RD, Lee H, Kim J, Kimm K. Prevalence and correlates of orthostatic hypotension in middle-aged men and women in Korea: the Korean Health and Genome Study. *J Hum Hypertens*. 2004;18(10):717–723.
45. Voichanski S, Grossman C, Leibowitz A, et al. Orthostatic hypotension is associated with nocturnal change in systolic blood pressure. *Am J Hypertens*. 2012;25(2):159–164.
46. Ejaz AA, Haley WE, Wasiluk A, Meschia JF, Fitzpatrick PM. Characteristics of 100 consecutive patients presenting with orthostatic hypotension. *Mayo Clin Proc*. 2004;79(7):890–894.
47. Mancia G, Parati G. The role of blood pressure variability in end-organ damage. *J Hypertens Suppl : Off J Int Soc Hypertens*. 2003;21(6):S17–S23.
48. Shibao C, Biaggioni I. Orthostatic hypotension and cardiovascular risk. *Hypertension*. 2010;56(6):1042–1044.
49. Vagaonescu TD, Saadia D, Tuhrim S, Phillips RA, Kaufmann H. Hypertensive cardiovascular damage in patients with primary autonomic failure. *Lancet*. 2000;355(9205):725–726.
50. Luft FC, Mervaala E, Muller DN, et al. Hypertension-induced end-organ damage : a new transgenic approach to an old problem. *Hypertension*. 1999;33(1 Pt 2):212–218.
51. Wong CK, White HD, Wilcox RG, et al. New atrial fibrillation after acute myocardial infarction independently predicts death: the GUSTO-III experience. *Am Heart J*. 2000;140(6):878–885.
52. Liberthson RR, Salisbury KW, Hutter Jr AM, DeSanctis RW. Atrial tachyarrhythmias in acute myocardial infarction. *Am J Med*. 1976;60(7):956–960.
53. Santhanakrishnan R, Wang N, Larson MG, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation*. 2016;133(5):484–492.
54. Milazzo V, Maule S, Di Stefano C, et al. Cardiac organ damage and arterial stiffness in autonomic failure: comparison with essential hypertension. *Hypertension*. 2015;66(6):1168–1175.
55. Shen MJ, Choi EK, Tan AY, et al. Neural mechanisms of atrial arrhythmias. *Nat Rev Cardiol*. 2011;9(1):30–39.
56. Tan AY, Zhou S, Ogawa M, et al. Neural mechanisms of paroxysmal atrial fibrillation and paroxysmal atrial tachycardia in ambulatory canines. *Circulation*. 2008;118(9):916–925.