Clinical relevance of orthostatic hypotension in patients with atrial fibrillation and suspected transient ischemic attack

Alex S. Mankoo[1], Jatinder S. Minhas[1,2], Briana Coles[3], Shazia T. Hussain[4], Kamlesh Khunti[3,5], Thompson G. Robinson[1,2], *Amit K. Mistri[4], *David J. Eveson[4] on behalf of the LeiSTAR Steering Committee

***Joint Senior Authors**

[1]Cerebral Haemodynamics in Ageing and Stroke Medicine (CHiASM) Research Group, Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom

[2]National Institute for Health Research Leicester Biomedical Research Centre, University of Leicester, Leicester, United Kingdom

[3]Leicester Real World Evidence Unit, Diabetes Research Centre, University of Leicester, Leicester, UK

[4]University Hospitals of Leicester NHS Trust, Leicester, United Kingdom

[5]National Institute for Health Research, Collaboration for Leadership in Applied Health Research and Care, East Midlands, United Kingdom

Correspondence to: Professor Thompson G. Robinson, Department of Cardiovascular Sciences, Sir Robert Kilpatrick Clinical Sciences Building, Leicester Royal Infirmary, Leicester, LE2 7LX, UK.

Email: tgr2@le.ac.uk

Conflict of Interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Abstract

Introduction: Orthostatic hypotension (OH) and atrial fibrillation (AF) are both regarded as independent risk factors for transient ischemic attack (TIA). However, the clinical implication of OH in the presence of AF is unclear. This study investigates, for the first time, the association between blood pressure (BP), OH and mortality in a cohort of patients with AF and TIA symptoms.

Aims: We aimed to investigate the incidence of the association between OH, AF and TIA.

Material and Methods: This retrospective observational study utilised the Leicester one-stop transient TIA clinic patient database to consider the initial systolic and diastolic BP of 688 patients with a diagnosis of AF. The primary outcome was time until death. Covariant measures included status of AF diagnosis (known or new AF), cardiovascular risk factors, and primary clinic diagnosis (cerebrovascular [CV] versus non-cerebrovascular [non-CV]). Statistical models adjusted for sex, age, previous AF diagnosis.

Results: Mortality rate was higher in the over 85 age group (191.5 deaths per 1,000 person years(py) [95%CI 154.0-238.1]) and lower in the aged 75 and younger age group (40.0 deaths per 1,000py [95%CI 27.0-59.2]) compared to intermediate groups. A 10mmHg increase in supine diastolic BP was associated with a significant reduction in the hazard of mortality for patients suspected of TIA with AF (adjusted HR 0.79 [95%CI 0.68-0.92], $p<0.001$). The mortality rate for patients with OH was 119.0 deaths per 1,000py compared with a rate of 98.0 for patients without OH (rate ratio 1.2, $p=0.275$).

Conclusion: Higher diastolic BP may be a marker for reduced mortality risk in patients with a previous AF diagnosis and non-CV diagnosis. Lower diastolic BP and the presence of AF pertain to a higher mortality risk. This study raises the importance of opportunistic screening for both OH and AF in patients presenting to TIA clinic.

Introduction

Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction [1,2]. The etiology of TIA is heterogeneous. The two most common causes in Caucasian populations are large-artery atherosclerosis (50%) and atrial fibrillation (20%) [4]. Patients suspected of suffering a TIA are promptly managed with secondary prevention therapy [3]. Current international guidelines advise a secondary prevention target of 130mmHg systolic BP for all patients irrespective of AF status, despite a paucity of data to support a specific BP target in those with AF [5]. In people with AF, increased BP variability may influence the prognostic implications of BP. Management of new AF involves initiation of rate control treatment, and screening using assessment tools such as CHA_2DS_2-VASc and HAS-BLED to assess stroke and bleeding risk, respectively, to inform a decision regarding the introduction of anticoagulation therapy for stroke prevention [5]. Patients attending TIA clinics with known AF or who receive a new diagnosis of AF receive BP management in accordance with hypertension guidelines, failing to consider OH.

The management of hypertension may be further complicated as OH is more common in individuals with AF [6,7,8]. OH is independently implicated with an increased risk of AF incidence, and is prevalent in 25% of outpatients with stroke [6]. OH is common in patients presenting to a TIA clinic, with one study citing a prevalence of 24% in patients diagnosed with TIA/stroke and even 20% in those without a TIA/stroke diagnosis [7].

In this retrospective cohort study, we examined the incidence of OH in those presenting with suspected TIA with an existing or new AF diagnosis. We examined the predictors of mortality from BP measurements, including the assessment of OH, in AF patients within in a UK-based outpatient TIA clinic setting. The aim of this study is to highlight the relationship between BP and mortality rates in patients presenting to the TIA clinic with AF.

Methods

Study design and data source

This retrospective observational study was part of the Leicester Stroke and TIA Research (LeiSTAR) study, including patients attending the Leicester one-stop TIA clinic. Ethical approval was provided by the Cambridge Central REC (19/04/2018; REC: 17/EE/0412), the University of Leicester Ethics Sub-Committee for Medicine and Biological Sciences (41-jm591-ls) and regulatory approval by the University Hospitals of Leicester NHS Trust. The data include information collected at the first clinic visit for patients with atrial fibrillation (AF, previously diagnosed or newly diagnosed at the TIA clinic). Patients without complete BP information from the first clinic visit were excluded from the analysis. Follow-up began on the date of the first clinic visit. Patients were followed up until death or date of last linkage to hospital mortality data (March 12, 2019).

Exposure

The exposure of interest was BP (supine and standing) obtained by a trained nurse to an agreed protocol with a standard device at the first rapid access clinic appointment. BP was treated as a continuous variable. Hazard ratios were calculated as a ratio of the hazard of death for a 10mmHg unit increase in BP. The change in BP from supine to standing was also calculated. Patients were determined to have systolic orthostatic hypotension (OH) if they experienced a reduction in systolic BP $\geq$ 20 mmHg within three minutes of standing and diastolic OH if they experienced a reduction in diastolic BP $\geq$ 10 mmHg within three minutes of standing.

Outcome

The outcome of interest was time until death.

Covariates

Previous AF diagnosis was determined from either “atrial fibrillation” or “AF” listed in the relevant past medical history or current treatment with Apixaban, Dabigatran, Rivaroxaban or Warfarin. All

other patients received a new diagnosis of AF within the clinic setting. Cerebrovascular diagnoses (CV) included the following principal diagnoses made at the first rapid access clinic appointment: transient ischemic attack, ischemic stroke, transient monocular blindness, retinal artery occlusion, intracerebral hemorrhage, subdural hemorrhage, subarachnoid hemorrhage.

Statistical analyses

The mortality rate was calculated as the number of deaths per unit of time at risk. In this case, the rate was deaths per 1,000 patients per year (py). Mortality rate was calculated overall, by status of AF diagnosis (new vs. previous diagnosis), by primary diagnosis during TIA clinic visit (CV/non-CV) stratified by sex, age group, and presence of OH. Kaplan-Meier curves and log-rank tests were used to compare unadjusted overall survival between patients with a new or previous AF diagnosis stratified by sex. Cox regression modelling was used to investigate the association between supine and standing BP measures, as well as systolic and diastolic OH and time until death. Crude and adjusted hazard ratios were calculated for supine and standing BP and systolic and diastolic OH, and adjusted hazard ratios were plotted. Models were adjusted for sex, age, previous AF diagnosis, and whether the primary diagnosis was CV. All analyses were performed in STATA 15 and SAS v9.4.

Results

Demographics

Clinical records of 799 patients were initially extracted from the TIA patient database (Supplemental Figure 1). The clinic has been running since 2012, with approximately 1800 attendances per year. Referrals for patients with TIA symptoms are received from primary and secondary care physicians, and following triage. A total of 688 patients with AF (58.4% male, 93.9% white Caucasian ethnicity) were included in the analysis with a mean age 78.6 years (range 43 to 105) and were well balanced by new or previous AF diagnosis (Table 1). There were 185 deaths that occurred during 1,814 total years of follow up. A total of 126 patients (18.3%) were diagnosed with systolic and/or diastolic OH (Table 1). The percentage of AF diagnoses that were new decreased from 39.4% of patients in 2013 to 20.2% in 2018, the latest year with complete data. Primary diagnoses were predominantly CV (60.7%), with the most common specific diagnosis being TIA for both patients with a new and previous diagnosis of AF (Supplemental Table 1). Overall, there were no significant differences in the mean change (delta [Δ]) in systolic or diastolic BP from supine to standing between those with a new versus previous AF diagnosis, or indeed CV versus non-CV diagnosis (Table 2)

Mortality

The mortality rate of the entire cohort independent of covariate factors was 102.0 deaths per 1,000 py (95% CI 88.3-117.8). Mortality rate increased with age (Figure 1) independent of the primary diagnosis and the status of AF diagnosis; mortality rate of patients aged 85 years and older being nearly fives times that of patients aged <75 years (Table 3). OH was associated with higher mortality in all age groups. Patients with non-CV diagnoses had a higher mortality rate, irrespective of OH status. There was no significant difference in mortality rates by sex.

Survival following a 10mmHg increase in systolic or diastolic BP

Table 4 shows crude and adjusted hazard of mortality associated with 10mmHg increases in systolic or diastolic BP when supine or standing. A 10mmHg increase in standing diastolic BP was associated with

a significant reduction in the hazard of mortality (21% reduction). No significant association was observed between OH (in total or systolic OH or diastolic OH) and the hazard of mortality (Table 5).

Previous AF diagnosis was associated with a lower survival rate for the first five years of follow-up compared with a new AF diagnosis, though the equality of survivor functions was not significantly different (log-rank test p=0.224). By the sixth year of follow-up, the survival for patients with a previous AF diagnosis was 53.8% compared with 45.1% for patients with a new diagnosis.

Supine and standing BP

In patients with a new AF diagnosis, the hazard of mortality was significantly higher for patients with supine systolic BP <100mmHg (Figure 2). To a lesser degree, the hazard of mortality was also high for supine diastolic BP <60mmHg. This trend was not the case for patients with a previous AF diagnosis. In patients with a previous AF diagnosis, the lowest mortality hazard was in patients with supine systolic BP >200mmHg, while standing diastolic BP was inversely related to the hazard of mortality. A similar but less strong trend was observed in patients with a previous AF diagnosis (Figure 3).

Discussion

This study demonstrates a relationship between BP and mortality in a population of patients with AF and suspected TIA. Firstly, we report higher diastolic BP pertains to a lower mortality rate in AF patients suspected of TIA. This finding emphasises the importance of diastolic BP when considering initiation of anti-hypertensive treatment. Our results contradict currently established associations between high blood pressure and cerebrovascular disease [13]. Current literature describes higher BP pertaining to an increased risk of cardiovascular and cerebrovascular disease [13]. This is because hypertension results in increased afterload, increased systolic and diastolic dysfunction of the heart, resulting in ischemia, myocardial infarction and heart failure [13-14]. Chronic hypertension is associated with increased damage to the vessel wall and accelerated atherosclerosis [13]. These are two key risk factors for cerebrovascular disease. Therefore, multiple studies have shown the benefit of reducing BP to the accepted 'normal' range of 120/80mmHg [13-14]. However, we report a 21% decrease in mortality for every 10mmHg increase in standing blood pressure, even beyond the accepted 'normal' range. The conflicting evidence may be due to the 'normal' range being identified in studies which excluded patients diagnosed with AF. Chronic hypertension results in an alteration in the limits of cerebral autoregulation of BP [24]. This results in higher pressures being required for sufficient autoregulatory function, increasing the chance of ischemia at lower BP levels [15]. This may account for the reduced mortality rate in patients with higher diastolic BP.

The inverse relationship between increasing standing diastolic BP and mortality rate may also be explained by the increase in diastolic BP providing a reduction in risk of MI. Both systolic and diastolic OH are independent risk factors for AF, ischemic stroke, and heart failure [9,10,11]. In particular, diastolic OH shows a strong association with coronary artery disease [10]. Dysfunctional diastole, as seen in diastolic OH, can result in hypoperfusion of the heart, increasing the risk of myocardial infarction (MI) [16]. This is supported by Fedorowski (2014) [16] who report diastolic OH to be a predictor of MI. Therefore, higher diastolic BP may limit the risk of diastolic OH which could explain the lower mortality rate at higher diastolic BP.

We hypothesise that higher standing diastolic BP lowers mortality due to an increased capability to adequately perfuse the heart to a greater extent compared to those with lower diastolic BP. In addition, the perceived protective effects of higher diastolic BP can be explained by physiological studies on OH [16,17]. Brent (2011) suggests preventing diastolic hypertension is more important than systolic hypertension in patients aged 50 and younger [13]. Despite current evidence to support specific BP target for AF patients, current guidelines are focussed on systolic BP control as a prompt to consider anti-hypertensive treatment irrespective of AF status [5]. However, our investigation outlines the importance of considering standing diastolic pressure for patients with AF.

The second key concept we raise relates to a three-factor model to hypothesise a synergistic relationship between OH, AF and cerebrovascular incidents. In this study of people with suspected TIA, OH was associated with higher mortality in newly diagnosed AF. Whilst the association of OH with increased mortality is known, this relationship has not been investigated before in people with AF. Current literature considers AF and OH independently in relation to TIA and cerebrovascular disease. AF is shown to be an independent risk factor for cerebrovascular disease [18, 19, 20]. This could be explained by the unsynchronised cardiac myocyte activity, resulting in stasis of blood, which increases the risk of thrombogenesis as per Virchow's triad [20]. Most recent studies have hypothesised the abnormal atrial substrate model. This places emphasis on aging and vascular risk factors causing structural change in atrial cells. This structural change in atrial cells results in failure of atrial cells to contract, causing stasis hence increasing the risk of thromboembolism [20]. The atrial substrate model supports our findings of the greatest mortality rate being observed in patients aged 85 years of age and older.

Similarly, when considered independent of AF, OH is associated with increased risk of cardiovascular events [10,13]. One limitation of our investigation was the failure to distinguish between symptomatic and asymptomatic OH. However, Eigenbrodt (2000) showed OH was predictive of ischemic stroke independent of the type of OH [11]. Current screening for OH is considered only when symptomatic; hence this raises the importance of a postural BP assessment to screen for OH even when asymptomatic.

Our investigation also considered how the status of AF diagnosis impacts mortality rate. Patients with AF diagnoses in the presence of OH have higher mortality rates compared to patients without OH. We propose a three-factor model to explain this. This model suggests OH increases the thrombogenic risk during AF, which in-turn will increase the risk of TIAs to a greater extent compared to when OH is not present. This is supported by Shaikh (2016) who suggests OH is associated with endothelial dysfunction which contributes to arterial stiffness, subsequently resulting in AF [21]. Wijkman (2016) found increased arterial wall stiffness and atherosclerosis in patients with OH [16]. Arterial stiffness is associated with endothelial dysfunction and increased thrombogenic risk [22, 23]; both of which are associated with OH and AF [21]. Therefore, according to our hypothesised three factor model, patients with OH and AF have enhanced arterial stiffness; hence higher thrombogenic risk compared to patients without OH. This is supported by a higher mortality rate for patients with OH compared to without OH with a primary non-CV and CV diagnosis. Also, the presence of AF is shown to induce independent structural changes to the left atrium which alter the cardiovascular prognostic outcomes [26]. We report a significantly lower mortality rate in patients aged <75 with a new diagnosis of AF. The higher mortality in older populations may be attributed to worsening autonomic and baroreceptor function, induced by vascular stiffening [22-23]. Therefore, an AF diagnosis could affect the prognosis of patients this cohort of patients. Bacchini (2019) report opportunistic screening can identify up to 3% of non-diagnosed AF [25]. This supports the importance of opportunistic AF screening.

It is important to acknowledge a number of limitations of this singe-centre, retrospective database study. Variability in measurement of BP in patients with AF is common. Current guidelines suggest repeated BP measurements to account for the beat-to-beat variability [23]. However, this investigation is an observational study conducted in a clinic with a standardised approach to BP measurement. The binary nature of mortality reported in this study has limitations as the specific cause of death remains unknown. Finally, due to the observational nature of the study causality cannot be inferred. With our interpretations based on one data set, we recognise our findings are insufficient to alter policy and corroboration with other datasets is suggested.

Patients with non-CV primary diagnoses had a higher mortality rate compared to patients with CV diagnoses. This may be due to the non-CV diagnoses group comprising of conditions with known lower survival rates compared to CV disease. Further investigation of the mortality associated with distinct non-CV diagnoses in this population is required.

Conclusion

Older (≥85 years) adults with diastolic OH, a previous AF diagnosis and a non-cerebrovascular diagnosis within the clinic have the highest mortality risk. Higher supine diastolic BP in those with AF relates to a lower mortality rate. This study provides novel insights into the benefits of higher diastolic BP on mortality rates in AF patients with and without OH.

Funding: This work was supported by a Collaborations for Leadership in Applied Health Research and Care Phase V Grant (East Midlands). JSM is an NIHR Clinical Lecturer at the Department of Cardiovascular Sciences, University of Leicester. Professor TG Robinson is a National Institute for Health Research Senior Investigator. The funders stated above did not have any involvement in the design, conduct, reporting or decision to submit for publication.

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Figure Captions

Figure 1. Mortality rate by status of AF diagnosis in TIA clinic patients with AF overall and stratified by sex, age, and OH status.

Figure 2. Kaplan Meier estimate of survival by status of AF diagnosis in TIA clinic patients with AF in total and stratified by sex.

Figure 3. Adjusted Cox proportional hazard ratios of mortality in TIA clinic patients with AF by supine BP stratified by status of AF diagnosis, systolic reference = 130mmHg, diastolic reference = 90mmHg.

Figure 4. Adjusted Cox proportional hazard ratios of mortality in TIA clinic patients with AF by standing BP stratified by status of AF diagnosis, systolic reference = 130mmHg, diastolic reference = 90mmHg.

Tables

Table 1. Cohort characteristics by status of AF diagnosis in TIA clinic patients with AF.

		AF diagnosis	
	Total	**New diagnosis**	**Previous diagnosis**
	N=688	**N=203**	**N=485**
Age	78.6 (9.2)	78.0 (9.5)	78.8 (9.1)
Sex			
Male	402 (58.4%)	127 (62.6%)	275 (56.7%)
Female	286 (41.6%)	76 (37.4%)	210 (43.3%)
Ethnicity			
Non-white	40 (6.1%)	9 (4.9%)	31 (6.5%)
White	619 (93.9%)	176 (95.1%)	443 (93.5%)
Unknown	29	18	11
Systolic BP			
Supine (mmHg)	134.3 (19.9)	136.8 (19.3)	133.2 (20.0)
Standing (mmHg)	132.0 (19.7)	134.6 (19.0)	130.9 (20.0)
OH	37 (5.4%)	10 (4.9%)	27 (5.6%)
Diastolic BP			
Supine (mmHg)	78.2 (13.3)	80.4 (13.2)	77.3 (13.3)
Standing (mmHg)	77.8 (13.0)	79.5 (12.9)	77.1 (12.9)
OH	101 (14.7%)	34 (16.7%)	67 (13.8%)
OH (sys and/or dia)	126 (18.3%)	40 (19.7%)	86 (17.7%)

Continuous variables are shown as mean and standard deviation while categorical are shown as number and percentage.

Table 2. Supine and standing blood pressure for TIA clinic patients with AF by status of AF diagnosis and final diagnosis.

			AF diagnosis				Primary diagnosis			
	Total		New diagnosis		Previous diagnosis		Non-CV		CV	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Systolic (mmHg)										
Supine	134.3 (19.9)	133.5 (26)	136.8 (19.3)	136 (24)	133.2 (20.0)	132 (24)	134.1 (20.1)	133.5 (26.5)	134.4 (19.8)	133.5 (26)
Standing	132.0 (19.7)	131 (25)	134.6 (19.0)	132 (27)	130.9 (20.0)	130 (25)	131.1 (20.0)	130 (25.5)	132.6 (19.6)	131 (25)
Δ	2.3 (10.4)	2 (13)	2.1 (10.2)	1 (12)	2.3 (10.5)	2 (13)	3.0 (11.1)	2 (14)	1.8 (9.9)	1 (11.5)
Diastolic (mmHg)										
Supine	78.2 (13.3)	76.5 (16)	80.4 (13.2)	79 (16)	77.3 (13.3)	76 (18)	78.0 (13.6)	76 (18)	78.4 (13.2)	78 (16)
Standing	77.8 (13.0)	77 (17.5)	79.5 (12.9)	78 (17)	77.1 (12.9)	76 (18)	77.4 (12.8)	77 (16.5)	78.0 (13.1)	78 (19)
Δ	0.5 (9.2)	1 (11)	1.0 (9.6)	2 (10)	0.2 (9.1)	0 (10)	0.6 (8.8)	0 (10)	0.4 (9.5)	1 (11)

Δ=supine-standing bp, cardiovascular (CV), atrial fibrillation (AF), standard deviation (SD), interquartile range (IQR).

Table 3. Mortality rate for TIA clinic patients with AF by status of AF diagnosis and final diagnosis, stratified by sex, age group, and presence of OH.

	Primary diagnosis at clinic			
	Non-CV		CV	
	Deaths	**Rate (95% CI)**	**Deaths**	**Rate (95% CI)**
Sex				
Male	42	114.1 (84.3-154.4)	59	84.5 (65.4-109.0)
Female	33	118.5 (84.2-166.6)	51	108.7 (82.6-143.0)
Age group				
<75	10	43.0 (23.1-79.8)	15	38.3 (23.1-63.5)
75-84	36	127.8 (92.2-177.2)	43	88.6 (65.7-119.5)
85+	29	219.3 (152.4-315.5)	52	178.9 (136.3-234.8)
OH				
No	57	109.0 (84.1-141.3)	87	91.9 (74.5-113.4)
Yes	18	145.5 (91.7-230.9)	23	104.1 (69.2-156.7)
Total	75	116.0 (92.5-145.4)	110	94.2 (78.1-113.5)

Rate per 1,000 person-years. Systolic OH is defined as a reduction in systolic blood pressure ≥20 mmHg within 3 min of standing. Diastolic OH is defined as a reduction in diastolic BP ≥10 mmHg within 3 min of standing. OH includes systolic OH and/or diastolic OH.

Table 4. Crude and adjusted Cox proportional hazard of mortality for supine and standing blood pressure.

	Supine				Standing			
	Crude		Adjusted		Crude		Adjusted	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Systolic bp (10 mmHg)	1.07 (0.97-1.17)	0.163	0.97 (0.87-1.07)	0.505	1.13 (1.03-1.25)	0.013	1.05 (0.95-1.16)	0.334
Diastolic bp (10 mmHg)	0.83 (0.72-0.95)	0.008	0.95 (0.82-1.09)	0.445	0.71 (0.61-0.82)	0.000	0.79 (0.68-0.92)	0.002

Each crude model included only systolic and diastolic bp for that body position. Adjusted included sex, age, previous AF diagnosis, and TIA clinic CV diagnosis. HR reflects the ratio for a 10 mmHg unit change in bp.

Table 5. Crude and adjusted Cox proportional hazard of mortality for systolic and diastolic OH.

	Crude		Adjusted	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
Systolic OH	1.15 (0.64-2.07)	0.638	0.98 (0.54-1.76)	0.938
Diastolic OH	1.36 (0.94-1.96)	0.099	1.36 (0.94-1.95)	0.100
OH	1.21 (0.85-1.71)	0.290	1.16 (0.82-1.65)	0.393

Systolic orthostatic hypotension (OH) is defined as a reduction in systolic blood pressure ≥ 20 mmHg within 3 min of standing. Diastolic OH is defined as a reduction in diastolic BP≥ 10 mmHg within 3 min of standing. OH includes systolic OH and/or diastolic OH. Each crude model included only the OH indicator of interest. Adjusted for sex, age, previous AF diagnosis, and TIA clinic CV diagnosis.