Clinical clustering of eight orthostatic haemodynamic patterns in The Irish Longitudinal Study on Ageing (TILDA)

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Abstract

Background

Identifying orthostatic hypotension (OH) has become complex due to implementation of non-invasive continuous beat-to-beat haemodynamic monitoring during active stand (AS) testing; this has resulted in large volumes of data outside the scope of the traditional OH definition. We explored clinical associations of different AS patterns in participants from Wave 1 of The Irish Longitudinal Study on Ageing (TILDA).

Methods

AS patterns were generated based on three sequential binary systolic blood pressure features: drop ≥40mmHg within 10 seconds post-stand ("immediate deficit"), failure to return to within 20mmHg of supine level at 40 seconds after standing ("stabilisation deficit"), and drop ≥20mmHg at any time between >40 and 120 seconds post-stand ("late deficit"). Eight AS groups resulted from combining the presence/absence of the three sequential features. The groups were cross-sectionally characterised, and their ability to independently predict orthostatic intolerance (OI) during AS, and falls or syncope in the past year, was evaluated using multivariate logistic regression models.

Results

4899 participants were included (mean age 61), of which 3312 (68%) had no deficits. There were significant differences in age, sex, co-morbidities and medication usage across groups. Regression models identified independent associations between OI and three immediate-deficit groups; those associations seemed stronger as more deficits were present. There was a significant association between falls history and the three-deficit group (OR 1.54, 95% CI: 1.15-2.07, p=0.004).

Conclusions

More deficits seemed associated with higher risk of OI and history of falls. Understanding the underlying pathophysiology of these groups may help clinicians identify risk and personalise therapies.

Keywords

Physiologic monitoring; Active stand; Orthostatic hypotension; Orthostatic intolerance; Falls

Key points

- The orthostatic hypotension definition does not apply to continuous active stand (AS) data.
- Clinicians can identify ‘deficits’ in the immediate, stabilisation and recovery phases of the AS.
- We characterised eight AS groups resulting from simultaneous consideration of those deficits.
- More deficits seemed associated to higher risk of orthostatic intolerance and history of falls.
- Understanding the pathophysiology of these groups may help personalise therapies.

Introduction

Orthostatic hypotension (OH) increases in prevalence as people age [1] and is associated with falls [2], cognitive decline [3] and mortality [4]. OH is traditionally defined by consensus statement as a reduction of systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) of at least 10 mmHg within 3 minutes of standing [5]. This definition is based on information available from intermittent blood pressure measurements via sphygmomanometer during a 3-minute orthostatic blood pressure assessment.

The clinical assessment of OH has become more complex due to the implementation of non-invasive continuous beat-to-beat hemodynamic monitoring during active stand (AS) testing [6]. This methodology provides a more detailed picture of a person's early orthostatic blood pressure behaviour and, as a result, generates a much larger volume of data. This data is outside the scope of the traditional OH definition [7] and require overall clinical interpretation by the clinician.

Numerous research efforts have taken place in the last decade aimed at identifying single features of the continuous AS pattern that may be associated with increased clinical risk. Thus, there has been interest in the immediate blood pressure drop (which takes place within the first 10-15 seconds post-stand and is not captured by the traditional sphygmomanometer assessment) [8, 9], and the early (i.e. within 30-40 seconds) blood pressure recovery phase [10, 11], which is often missed by the traditional method. By 2-3 minutes post-stand, the ability of the sphygmomanometer method to detect a given blood pressure drop is comparable to that of the AS method [12].

There is recognition that hemodynamic patterns following AS are morphologically heterogeneous [13] and differ across orthostatic blood pressure recovery patterns [14]. AS features appear sequentially in time and hence are not independent from each other. Yet, there is no evidence to support that such

sequential recognition approach can result in clinically meaningful AS patterns to help guide risk assessment and treatment.

Accumulation of health deficits is associated with higher cardiovascular morbidity and mortality [15]. By applying this principle to adverse blood pressure features during the AS, we hypothesised that their sequential accumulation may be associated with more adverse clinical features such as higher risk of orthostatic intolerance, history of falls or syncope. To test that hypothesis, we manually modelled AS patterns according to the presence/absence of immediate, early and late blood pressure deficits, and explored their clinical associations in participants from Wave 1 of The Irish Longitudinal Study on Ageing (TILDA).

Methods

Sample

An analysis was conducted on data from Wave 1 (June 2009–June 2011) of TILDA, a nationally representative cohort of community-dwelling adults aged ≥50 years. The study data was collected in three processes: (1) a computer-aided personal interview performed by trained interviewers in participants' homes; (2) a self-completion questionnaire; and (3) a health assessment performed by research nurses in one of two health centres. Full details of the study design, sampling and methodology have been described elsewhere [16, 17]. Participants who were unwilling/unable to provide informed consent, did not attend the health assessment, or had inadequate AS data were not included.

Active stand protocol

Participants who attended the health assessment centre underwent an AS test, which measures beat-to-beat haemodynamic responses to orthostasis using non-invasive continuous monitoring based on digital artery photoplethysmography (Finometer MIDI device, Finapres Medical Systems BV, Amsterdam, The Netherlands), recorded at 200 Hz. The AS test was performed by trained research nurses. Participants underwent the AS following approximately 10 minutes of supine rest. Baseline blood pressure was calculated as the mean value between 60 and 30 seconds before stand, during the supine rest period. Data was downsampled to 1 Hz. Two smoothing filters were applied, a 10-point moving average filter and an 11-point median filter. Onset of the stand was detected via an algorithm using data from the Finometer height correction unit [18]. Here we utilised blood pressure response data up to 120 seconds post-stand, at 10-second intervals.

Active stand features and groupings

The decision to focus on systolic blood pressure (SBP) features was based on a study by Fedorowski *et al.*, which found that approximately 95% of patients with classical OH can be identified by SBP

changes alone [19]. Eight mutually exclusive AS patterns were manually extracted based on three sequential binary SBP deficits previously utilised by our research group: SBP drop ≥40mmHg within 10 seconds post-stand ("immediate drop": yes or no [20]), failure to return to within 20mmHg of supine level at 40 seconds after standing ("stabilisation failure": yes or no [11]), and drop ≥20mmHg at any time between >40 and 120 seconds post-stand ("late deficit": yes or no [21]) (Figure 1). We reported 2-minute post-stand data (not the traditional 3 minutes) due to our interest in early SBP changes.

Clinical characterisation variables

The following variables were used to characterise the eight AS patterns: age (years), sex, a binary Fried's frailty phenotype category (non-frail vs. pre-frail/frail) [22], time taken to stand during the AS [18], cognition as per Mini-Mental State Examination (MMSE) score, multimorbidity (history of two or more self-reported diseases among the following: myocardial infarction, heart failure, angina, atrial fibrillation, hypertension, hypercholesterolemia, stroke, diabetes mellitus, chronic obstructive pulmonary disease, asthma, arthritis, osteoporosis, cancer, Parkinson's disease, and hip fracture). We also characterised the groups according to usage of antihypertensive and psychoactive medications. Polypharmacy was defined as concomitant use of 5 or more regular medications.

Although there are many clinical variants of orthostatic intolerance (OI) [23], our study defined it as present if participants self-reported dizziness, light-headedness or unsteadiness during the AS. Participants were also asked about history of falls in the past 12 months (yes or no), and blackouts in the past 12 months (i.e. recent syncope: yes or no).

Statistical analyses

Statistical analyses were performed in Stata version 14.1 (Stata Corp., College Station, TX, USA). The graphical visualisation of the eight AS patterns was performed with IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA), using mean SBP +/- 1 standard error (SE) for each group.

Descriptive statistics were given as mean with standard deviation (SD), median with interquartile range (IQR), or number (n) with percentage (%). Overall differences between the eight AS groups (as nominal variable) were assessed using analysis of variance (ANOVA) in the case of normally distributed continuous variables, or the Kruskal-Wallis test in the case of interval, non-normal variables; for categorical (e.g. dichotomous) variables, the Chi-squared test was used. Given the projected number of comparisons (around 30), and considering an Alpha level of 0.05, a Bonferroni's adjustment calculation recommended to lower $p<0.05$ to $p<0.001$ to detect statistical significance during the characterisation of the sample.

For the cross-sectional associations between the AS groups and OI, falls and syncope, three logistic regression models were fitted for each outcome:

- model A, a univariate model with AS groups as independent variable using the "no deficits" group as reference;
- model B, a multivariate model controlling for the fixed effects of age and sex;
- and model C, a multivariate model controlling for the fixed effects of age, sex, baseline SBP, time to stand, Fried's frailty status, MMSE, multimorbidity, polypharmacy, and use of antihypertensive, antidepressant, benzodiazepine [24], and Z-drug medications.

In these models, the threshold for statistical significance was set at $p<0.05$.

Ethics

The study was approved by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin, and all participants provided written informed consent. All experimental procedures adhered to the Declaration of Helsinki.

Results

In total, 8174 participants over the age of 50 were recruited to wave 1 of the TILDA study, of whom 5034 attended the health assessment centre. There were 4905 participants with adequate active stand data for analysis, of whom 4899 had complete data for the generation of the eight AS groups using the decision tool in Figure 1. Overall, the mean age was 61, and 55% were female.

As Figure 1 shows, the largest group was the one with no deficits (68%), followed by immediate deficit only (13%), all three deficits (6%), and late deficit only (5%). The other groups contained fewer than 5% of participants each. The graphical visualisation of the groups (mean SBP) is presented in Figure 2. An interactive version with SEs is available in the Supplementary Data, available in Age and Ageing online.

The clinical characteristics of the total sample and the eight AS groups are summarised in Table 1. Overall, OI was reported by 38% of participants; 20% had history of falls, and 5% reported recent syncope.

Participants in the largest group with no deficits had the lowest baseline SBP and were among the youngest, least frail, least comorbid and least medicated. They were also among the groups with lowest proportion of OI (Table 1).

The group with all three deficits was not among the oldest but seemed to have the highest use of beta-blockers, benzodiazepines, antidepressants, highest baseline SBP, highest proportion of falls and one of the highest proportions of OI (Table 1). Groups 2, 5 and 6 (sharing the impaired stabilisation feature) had proportions of diabetes mellitus over 10%.

The results of the three logistic regression models for the prediction of OI, falls and syncope (Models C) are shown in Table 2; full information for Models A, B and C is available in the Supplementary Data, available in Age and Ageing online.

In models C (Table 2), there were statistically significant associations between OI and three groups with immediate deficit, with a seemingly incremental Odds Ratio (OR) according to the number of deficits: OR 1.42 (95% CI: 1.19-1.70, $p<0.001$) for immediate only; OR 1.60 (95% CI: 1.20-2.13, $p=0.001$) for immediate and late; and OR 1.83 (95% CI: 1.41-2.38, $p<0.001$) for immediate, stabilisation and late. There was also a statistically significant association between the group with all three deficits and falls (OR 1.54, 95% CI: 1.15-2.07, $p=0.004$).

Discussion

In this large population-based study of Irish participants aged 50+ undergoing continuous orthostatic blood pressure measurements, we showed eight different orthostatic blood pressure patterns based on three sequential systolic blood pressure deficits. We showed that the most common patterns were characterised by no deficits or an immediate deficit only. Groups with an immediate deficit had higher risk of OI, with a seemingly incremental OI risk as more deficits were present. The group with all three deficits was associated with recent falls. Our findings confirm and expand previous observations that hemodynamic AS patterns are heterogeneous [14], highlighting the need to take a nuanced approach to the interpretation of the AS that considers potentially different pathophysiological mechanisms and clinical associations. To our knowledge, ours is the largest study to date and may serve as a population-wide reference to help clinicians identify normal and abnormal AS responses, inform their bedside interpretation and potentially lead to more personalised medical care.

Our results are consistent with the definition of initial OH in that the immediate SBP drop is associated with OI [8]; however, our results underscore the merit of considering the immediate blood pressure drop and OI separately. Indeed, the fact that the strength of the association with OI seemed stronger as more deficits were seen in the AS pattern acknowledges the importance of not just the immediate blood pressure change but also the recovery phase [7]. In addition, this finding is consistent with the theory of accumulation of health deficits [15, 25], which postulates that deficit accumulation may be a useful measure of biological ageing and thus of increased clinical risk [26]. Interestingly, the three-deficit pattern was not seen in the oldest group. While this association cannot be determined to be causative it is in keeping with the principle that accumulation of health deficits is very heterogeneous across the life course, resulting in poor correlation with chronological age [25].

In terms of the pathophysiology behind the accumulation of deficits effect in association with OI, some studies have suggested that the presence of an isolated immediate blood pressure deficit (without OI

symptoms) may not be pathological and is often seen in young healthy people [27]. However, in older people who may be affected by comorbidities, initial orthostatic hypotension may be a risk factor for unexplained syncope [28]. Our study suggests that an isolated immediate blood pressure deficit is common in a healthier group of older people, but it is seen with other deficits in less healthy groups. One possible explanation for the variable relationship between immediate SBP drops and health status is that the healthier the person is, the faster they are generally able to stand up [18]. This increased speed in changing from supine to standing gives the body less time to compensate for the stress of orthostasis and, as a result, there may be a greater immediate SBP drop. Therefore, the clinical significance of an immediate blood pressure deficit needs to be assessed in the context of the subsequent SBP recovery. Cooke *et al*. came to a similar conclusion in their study that attempted to classify OH into 3 different subtypes based on how the SBP responded to the initial SBP drop. They similarly found a wide range of SBP response patterns and felt that the recovery patterns may guide predicting future adverse outcomes in OH [29].

Our study has limitations. Firstly, it is of cross-sectional nature and further research is necessary to establish the longitudinal stability of the AS patterns and their association with future health outcomes. Future research will consider more objective health outcomes such as incident diagnosed disease, objective disability, or mortality.

As regards clinical outcomes, our definitions of falls and syncope are limited by recall bias. In addition, our binary OI variable is limited in that postural dizziness is very common in older people and is often multifactorial [23]. Despite not being the oldest, the group with all three deficits had one of the highest OI proportions and the highest use of beta-blockers, benzodiazepines and antidepressants; the latter medications may independently contribute to OI [13, 24] and in this regard clinicians should retain a high level of clinical alertness.

Finally, the method of classifying individuals is open to bias as this was done manually and unblinded. However, our classification method is not intended to represent a gold standard as we acknowledge that some of the resulting groups were small and there may have been some clinical overlap between them. In practice, some individuals may fit into more than one category, or there may be a spectrum of risk rather than discrete categories. Our data invite hypotheses, but they cannot answer them.

Further research will apply artificial intelligence techniques, which we hope will more efficiently divide the sample into a smaller number of more different groups. Automatic clustering approaches could be compared with manual approaches in their ability to predict outcomes.

Conclusion

The interpretation of AS patterns requires consideration of immediate, stabilisation and late deficits simultaneously. An immediate blood pressure deficit should be assessed in the context of deficits in the subsequent recovery. This approach can be implemented at the bedside to help clinicians identify risk. Further research is required to assess the longitudinal stability of these patterns and their ability to predict objective future outcomes.

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Table 1. Characterisation of the overall sample and the eight active stand groups. SD: standard deviation; * Kruskal-Wallis test; # Chi-square test.

	Overall	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	p
Number (%)	4899 (100.0)	272 (5.6)	43 (0.9)	209 (4.3)	632 (12.9)	145 (3.0)	38 (0.8)	248 (5.1)	3312 (67.6)	
Mean age in years (SD)	61.0 (8.8)	64.5 (9.3)	68.1 (10.5)	60.3 (7.7)	61.6 (8.6)	66.9 (9.2)	68.8 (9.5)	61.3 (9.2)	60.2 (8.5)	<0.001*
Female gender, n (%)	2703 (55.2)	172 (63.2)	23 (53.5)	142 (67.9)	364 (57.6)	101 (69.7)	18 (47.4)	153 (61.7)	1730 (52.2)	<0.001#
Non-frail, n (%)	3471 (72.6)	174 (65.4)	31 (75.6)	155 (74.9)	448 (72.4)	80 (57.6)	24 (64.9)	156 (65.3)	2403 (74.3)	<0.001#
Pre-frail or frail, n (%)	1313 (27.5)	92 (34.6)	10 (24.4)	52 (25.1)	171 (27.6)	59 (42.5)	13 (35.1)	83 (34.7)	833 (25.7)	<0.001#
Mean time to stand in seconds (SD)	7.6 (3.0)	7.9 (2.7)	8.3 (3.5)	7.3 (2.3)	7.5 (2.8)	9.7 (4.5)	9 (3.8)	8.1 (3.2)	7.5 (2.9)	<0.001*
Median MMSE (IQR)	29 (2)	29 (2)	28 (3)	29 (2)	29 (2)	29 (2)	29 (3)	29 (2)	29 (2)	<0.001*
Multimorbidity, n (%)	2236 (45.6)	132 (48.5)	22 (51.2)	85 (40.7)	303 (47.9)	92 (63.5)	27 (71.1)	113 (45.6)	1462 (44.1)	<0.001#
Atrial Fibrillation, n (%)	109 (2.3)	7 (2.6)	2 (4.7)	2 (1.0)	16 (2.6)	3 (2.1)	4 (10.5)	3 (1.2)	72 (2.2)	0.024#
Parkinson's disease, n (%)	15 (0.3)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.1)	0 (0.0)	3 (1.2)	7 (0.2)	<0.001#
Diabetes Mellitus, n (%)	300 (6.1)	17 (6.3)	5 (11.6)	7 (3.4)	35 (5.5)	15 (10.3)	5 (13.2)	14 (5.7)	202 (6.1)	0.065#
Hypertension, n (%)	1934 (39.7)	119 (44.1)	24 (57.1)	98 (47.1)	294 (46.9)	63 (43.8)	16 (42.1)	108 (43.9)	1212 (36.7)	0.001#
Polypharmacy, n (%)	830 (17.0)	68 (25.1)	13 (30.2)	25 (12.0)	98 (15.6)	46 (32.4)	9 (24.3)	55 (22.4)	516 (15.6)	<0.001#
Anti-hypertensive medications, n (%)										
Overall	1553 (31.7)	99 (36.4)	16 (37.2)	60 (28.7)	211 (33.4)	67 (46.2)	19 (50.0)	77 (31.1)	1004 (30.3)	<0.001#
Beta blockers	563 (11.5)	55 (20.3)	7 (16.3)	28 (13.5)	81 (12.9)	27 (19.0)	3 (8.1)	26 (10.6)	336 (10.2)	<0.001#
Diuretics	289 (5.9)	17 (6.3)	5 (11.6)	7 (3.4)	35 (5.0)	13 (9.2)	4 (10.8)	16 (6.5)	192 (5.8)	0.211#
ACE inhibitors/Angiotensin receptor blockers	1047 (21.5)	53 (19.6)	13 (30.2)	33 (15.9)	150 (23.9)	44 (31.0)	10 (27.0)	54 (22.0)	690 (20.9)	0.014#
Calcium channel blockers	402 (8.2)	23 (8.5)	6 (14.0)	11 (5.3)	38 (6.0)	19 (13.4)	11 (29.7)	22 (8.9)	272 (8.2)	<0.001#
Alpha blockers	71 (1.5)	8 (3.0)	1 (2.3)	0 (0)	9 (1.4)	6 (4.2)	0 (0)	6 (2.4)	41 (1.2)	0.010#
Psychoactive medications, n (%)										
Overall	444 (9.1)	46 (16.9)	6 (14.0)	16 (7.7)	67 (10.6)	21 (14.5)	3 (7.9)	28 (11.3)	257 (7.8)	<0.001#
Z-drugs	109 (2.2)	12 (4.4)	2 (4.7)	3 (1.4)	14 (2.2)	11 (7.8)	1 (2.7)	5 (2.0)	61 (1.9)	<0.001#
Benzodiazepines	140 (2.9)	17 (6.3)	0 (0.0)	9 (4.3)	15 (2.4)	5 (3.5)	2 (5.4)	10 (4.1)	82 (2.5)	0.009#
Antidepressants	281 (5.7)	35 (12.9)	4 (9.3)	9 (4.3)	47 (7.4)	12 (8.3)	1 (2.6)	15 (6.1)	158 (4.8)	<0.001#
Orthostatic Intolerance during active stand, n (%)	1880 (38.4)	130 (47.8)	21 (48.8)	93 (44.5)	271 (42.9)	57 (39.3)	13 (34.2)	103 (41.7)	1192 (36.0)	<0.001#
At least 1 fall in the past 12 months, n (%)	960 (19.6)	77 (28.3)	6 (14.0)	36 (17.3)	125 (19.8)	32 (22.1)	7 (18.4)	47 (19.0)	630 (19.0)	0.025#
At least 1 syncope in the past 12 months, n (%)	226 (4.62)	13 (4.8)	1 (2.3)	11 (5.3)	23 (3.7)	11 (7.8)	2 (5.3)	9 (3.6)	156 (4.7)	0.585#
Mean baseline SBP, mmHg (SD)	135.8 (22.3)	147.7 (24.9)	142.1 (27.9)	142.9 (25.0)	140.3 (23.0)	143.5 (23.0)	141.8 (19.1)	143.8 (24.3)	132.4 (20.6)	<0.001*
Mean baseline HR, beats per minute (SD)	65.0 (9.9)	61.9 (9.9)	63.5 (9.8)	61.2 (9.2)	63.1 (9.5)	67.1 (11.7)	69.9 (10.9)	65.0 (9.9)	65.7 (9.7)	<0.001*

Table 2. Results of the fully adjusted logistic regression models (Models C). Statistically significant results are highlighted in bold. OI: orthostatic intolerance; OR: odds ratio; CI: confidence interval.

	Group 1		Group 2		Group 3		Group 4		Group 5		Group 6		Group 7		Group 8
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	
OI	**1.83 (1.41, 2.38)**	**<0.001**	1.85 (0.98, 3.47)	0.056	**1.60 (1.20, 2.13)**	**0.001**	**1.42 (1.19, 1.70)**	**<0.001**	1.20 (0.84, 1.73)	0.314	0.99 (0.49, 20.3)	0.981	**1.32 (1.00, 1.74)**	**0.048**	(Base)
Falls	**1.54 (1.15, 2.07)**	**0.004**	0.64 (0.27, 1.56)	0.326	0.86 (0.58, 1.26)	0.440	1.00 (0.80, 1.26)	0.957	0.90 (0.58, 1.40)	0.641	0.91 (0.39, 2.12)	0.824	0.94 (0.67, 1.33)	0.732	(Base)
Recent syncope	0.91 (0.49, 1.66)	0.750	0.56 (0.05, 4,21)	0.658	1.27 (0.67, 2.41)	0.464	0.72 (0.45, 1.16)	0.180	1.29 (0.64, 2.58)	0.478	0.60 (0.80, 4.47)	0.616	0.74 (0.37, 1.50)	0.409	(Base)

Figure 1. Hypothesised eight mutually exclusive groups based on three sequential systolic blood pressure features during the active stand. The column on the right shows the classification result (in brackets: number of participants in the group, percentage of the total sample).

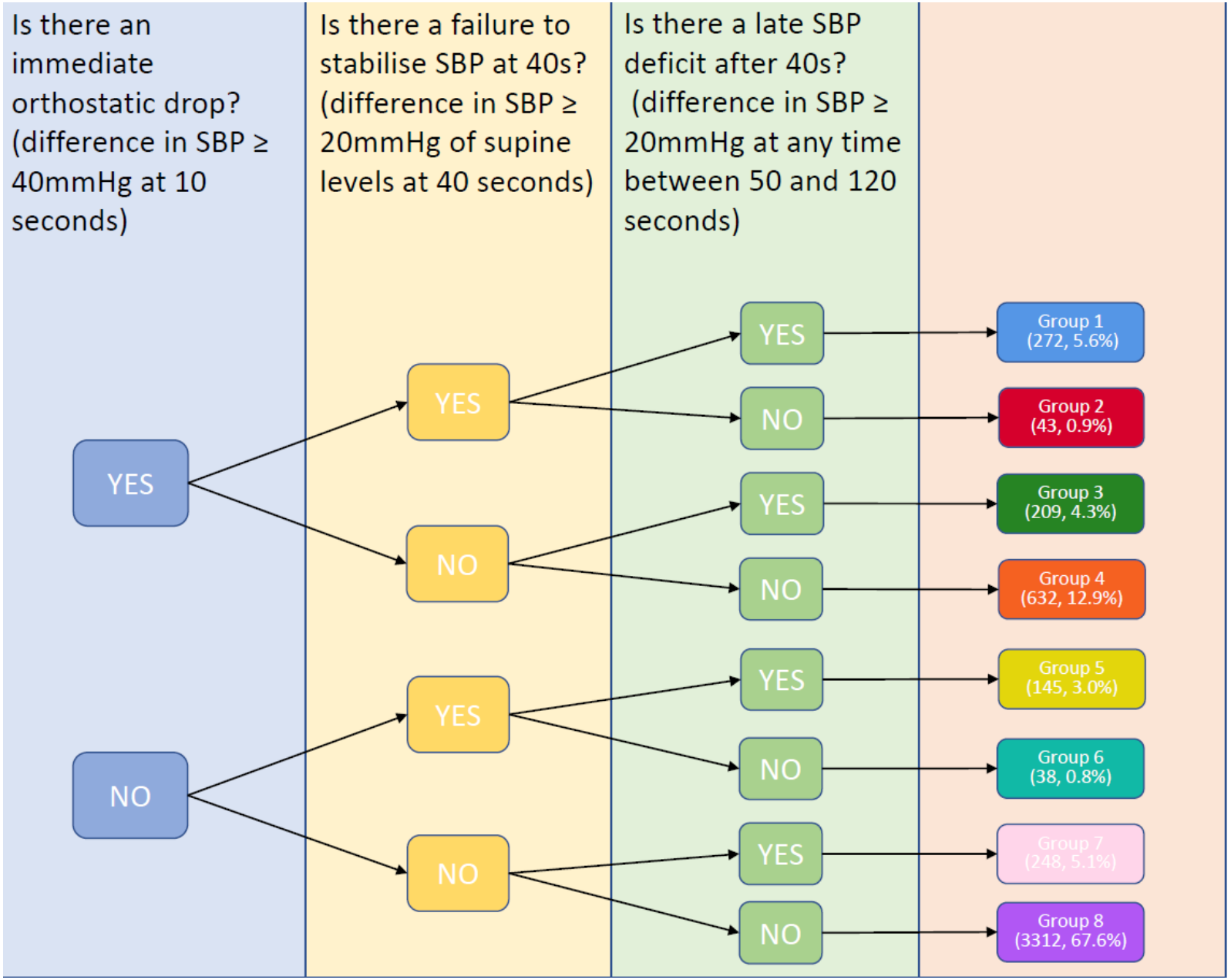
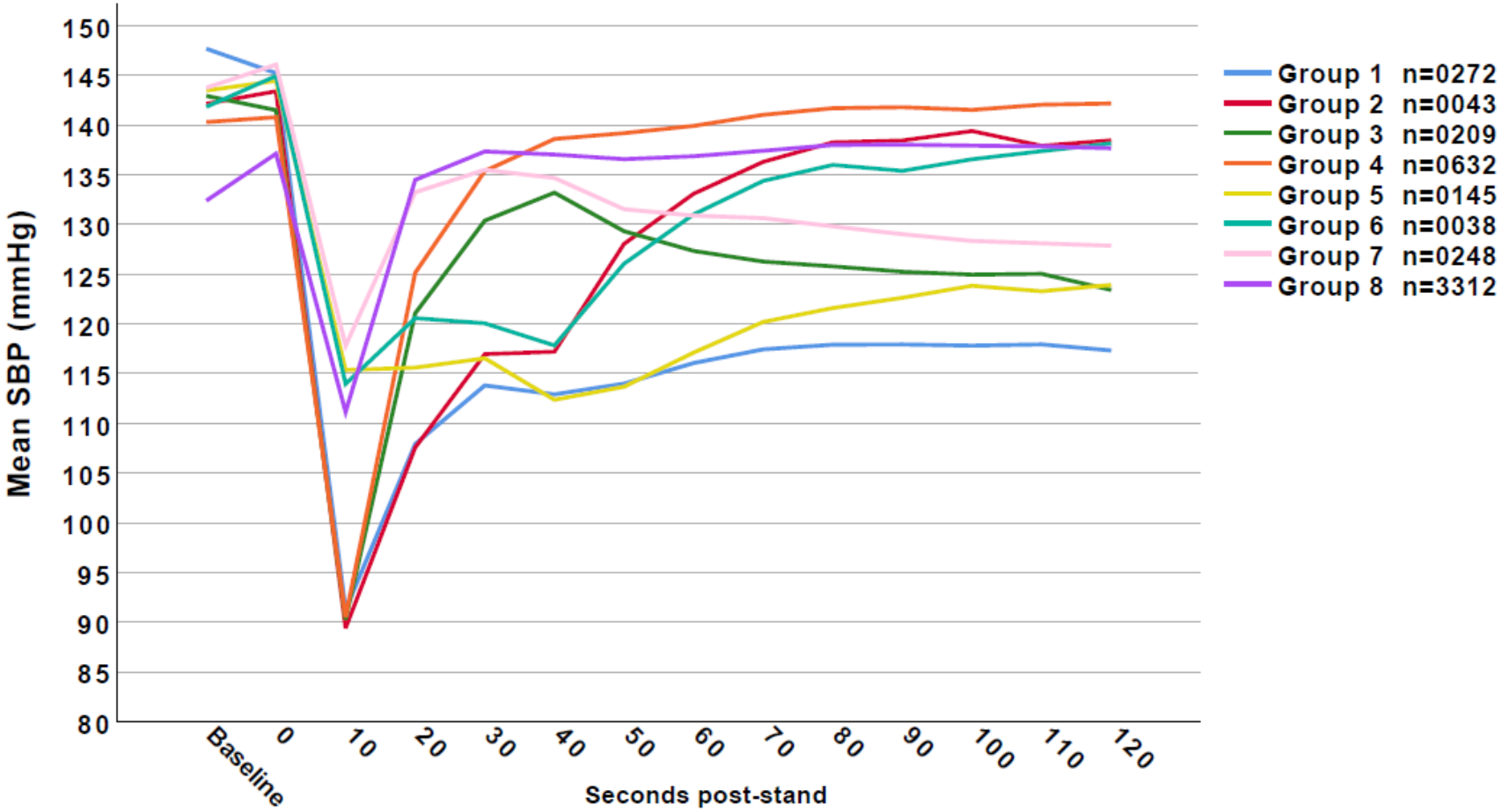
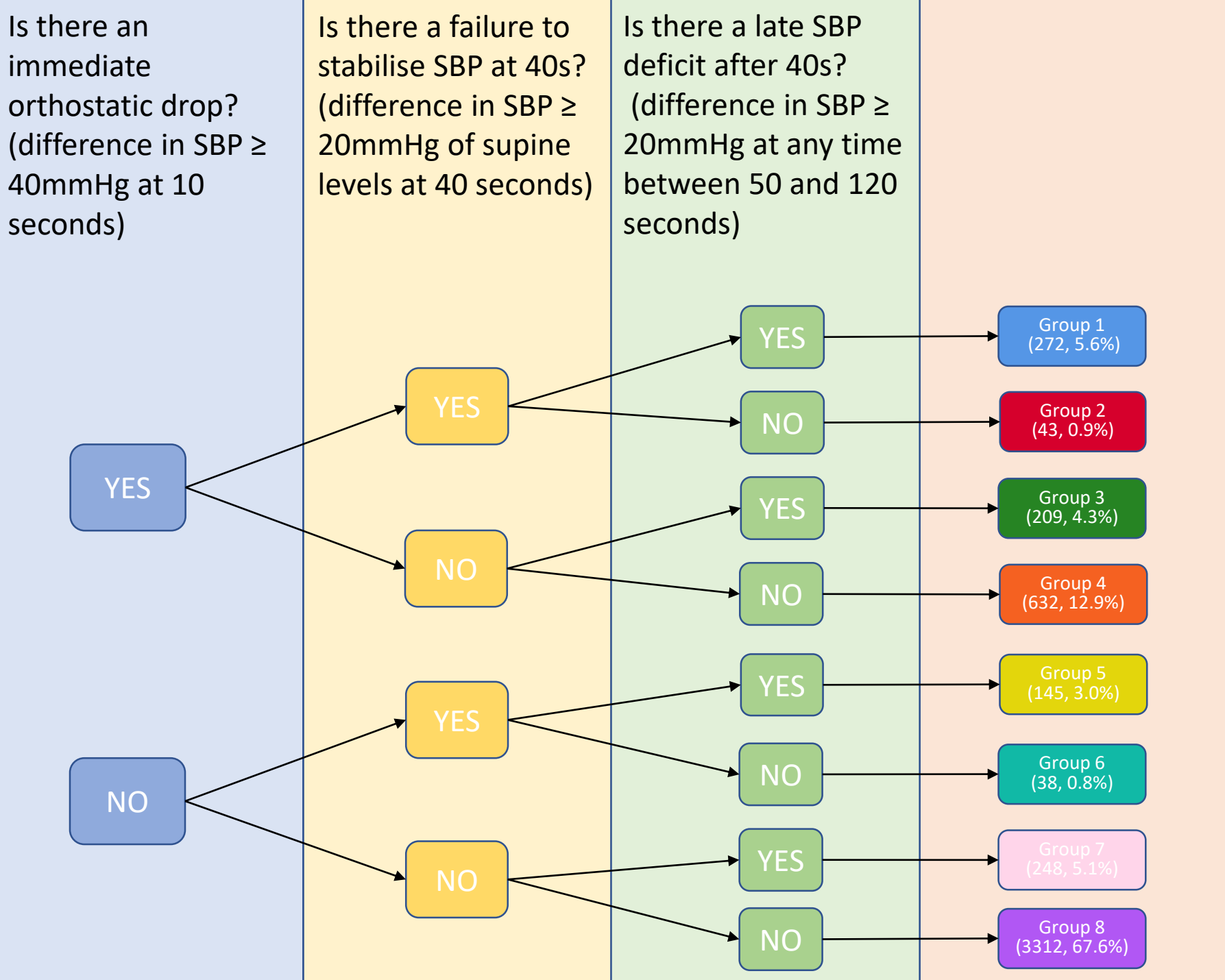
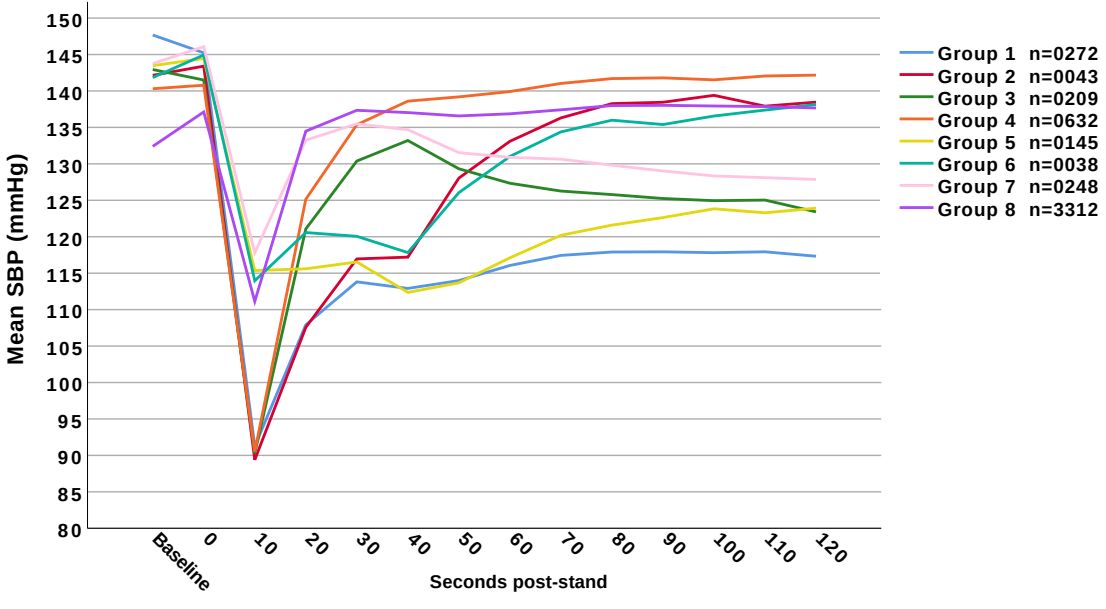


Figure 2. Graphical visualisation of the eight active stand groups. SBP: Systolic Blood Pressure.




Is there an immediate orthostatic drop? (difference in SBP ≥ 40mmHg at 10 seconds)
Is there a failure to stabilise SBP at 40s? (difference in SBP ≥ 20mmHg of supine levels at 40 seconds)
Is there a late SBP deficit after 40s? (difference in SBP ≥ 20mmHg at any time between 50 and 120 seconds)
YES
NO
YES
NO
YES
NO
YES
NO
YES
NO
YES
NO
YES
NO
Group 1 (272, 5.6%)
Group 2 (43, 0.9%)
Group 3 (209, 4.3%)
Group 4 (632, 12.9%)
Group 5 (145, 3.0%)
Group 6 (38, 0.8%)
Group 7 (248, 5.1%)
Group 8 (3312, 67.6%)


Mean SBP (mmHg)
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
Baseline
0
10
20
30
40
50
60
70
80
90
100
110
120
Seconds post-stand
Group 1 n=0272
Group 2 n=0043
Group 3 n=0209
Group 4 n=0632
Group 5 n=0145
Group 6 n=0038
Group 7 n=0248
Group 8 n=3312

Supplementary Table 1. Results of the logistic regression models (Models A, B and C).

		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6		Group 7		Group 8
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	
	Orthostatic intolerance															
Model A		1.63 (1.27, 2.08)	<0.001	1.7 (0.93, 3.10)	0.086	1.42 (1.07, 1.89)	0.140	1.33 (1.12, 1.58)	0.001	1.15 (0.82, 1.62)	0.420	0.92 (0.47, 1.81)	0.817	1.27 (0.98, 1.65)	0.074	(Base)
Model B		1.73 (1.35, 2.23)	<0.001	1.85 (1.01, 3.39)	0.046	1.46 (1.10, 1.94)	0.009	1.37 (1.15, 1.62)	<0.001	1.27 (0.90, 1.79)	0.175	1.00 (0.51, 1.97)	0.988	1.3 (1.00, 1.70)	0.490	(Base)
Model C		1.83 (1.41, 2.38)	<0.001	1.85 (0.98, 3.47)	0.056	1.60 (1.20, 2.13)	0.001	1.42 (1.19, 1.70)	<0.001	1.20 (0.84, 1.73)	0.314	0.99 (0.49, 20.3)	0.981	1.32 (1.00, 1.74)	0.048	(Base)
	Falls in the past year															
Model A		1.34 (1.12, 2.12)	0.003	0.50 (0.21, 1.56)	0.345	0.87 (0.41, 1.24)	0.643	1.01 (0.32, 1.45)	0.864	1.01 (0.34, 1.87)	0.965	0.78 (0.23, 1.98)	0.754	0.87 (0.45, 1.67)	0.875	(Base)
Model B		1.53 (1.15, 2.03)	0.003	0.58 (0.24, 1.40)	0.226	0.88 (0.61, 1.28)	0.503	1.02 (0.82, 1.26)	0.875	1.04 (0.69, 1.56)	0.857	0.81 (0.35, 1.85)	0.611	0.96 (0.69, 1.34)	0.831	(Base)
Model C		1.54 (1.15, 2.07)	0.004	0.64 (0.27, 1.56)	0.326	0.86 (0.58, 1.26)	0.440	1.00 (0.80, 1.26)	0.957	0.90 (0.58, 1.40)	0.641	0.91 (0.39, 2.12)	0.824	0.94 (0.67, 1.33)	0.732	(Base)
	Syncope in the past year															
Model A		1.02 (0.57, 1.82)	0.949	0.48 (0.07, 3.52)	0.472	1.12 (0.60, 2.11)	0.716	0.77 (0.49, 1.20)	0.240	1.66 (0.88, 3.13)	0.118	1.12 (0.27, 4.71)	0.873	0.76 (0.39, 1.52)	0.443	(Base)
Model B		0.98 (0.55, 1.76)	0.943	0.45 (0.06, 3.29)	0.430	1.12 (0.60, 2.10)	0.722	0.75 (0.48, 1.18)	0.217	1.56 (0.82, 2.98)	0.177	1.04 (0.25, 4.39)	0.957	0.76 (0.38, 1.50)	0.423	(Base)
Model C		0.91 (0.49, 1.66)	0.750	0.56 (0.05, 4,21)	0.658	1.27 (0.67, 2.41)	0.464	0.72 (0.45, 1.16)	0.180	1.29 (0.64, 2.58)	0.478	0.60 (0.80, 4.47)	0.616	0.74 (0.37, 1.50)	0.409	(Base)