CLINICAL INVESTIGATION

Hypotensive Drugs and Syncope Due to Orthostatic Hypotension in Older Adults with Dementia (Syncope and Dementia Study)

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OBJECTIVES: To determine whether hypotensive drugs may play a pivotal role in inducing orthostatic hypotension (OH)-related syncope.
DESIGN: Prospective, observational, multicenter study.
SETTING: Acute care wards, syncope units, and centers for the diagnosis of dementia.
PARTICIPANTS: Individuals aged 65 and older with a diagnosis of dementia and 1 or more episodes of transient loss of consciousness of a suspected syncopal nature or unexplained falls during the previous 3 months
MEASUREMENTS: Blood pressure was measured in the supine position and in the orthostatic position after 1 and 3 minutes. OH was defined as a decrease in systolic blood pressure of 20 mmHg or more and in diastolic blood pressure of 10 mmHg or more within 3 minutes of standing. Univariate and multivariate analyses were used to evaluate associations between hypotensive drugs and their combinations with OH-related syncope.
RESULTS: The mean age of the study population (n=522; women, n=324) was 83.5±6.1, and the most frequent comorbidity was arterial hypertension (74.5%); 324 (67.8%) participants had had a syncopal fall and 168 (32.2%) a nonsyncopal fall. The mean number of hypotensive drugs administered (2.9±3.1) did not differ between the two groups. Syncopal falls was OH-related in 170 participants (48.0%). OH-related syncopal falls were more frequent in participants receiving nitrates (15.3% vs 9.8%, p=.06), alpha-blockers (16.5% vs 9.8%, p=.04), or combinations of angiotensin-converting enzyme inhibitors (ACE-Is) and diuretics (20.6% vs 13.0%, p=.04), alpha-blockers and diuretics (8.2% vs 3.3%, p=0.036), and ACE-Is and nitrates (8.2% vs 3.3%, p=.10). Multivariate analysis confirmed a greater risk of OH-related syncopal fall for nitrates (relative risk (RR)=1.77), combinations of ACE-Is and diuretics (RR=1.66), and combinations of ACE-Is and nitrates (RR=2.32).
CONCLUSION: In older adults with dementia, OH-related syncopal falls are significantly related to treatment with nitrates, combinations of ACE-Is and diuretics, and combinations of ACE-Is and nitrates. **J Am Geriatr Soc 2018.**

Key words: hypotensive drugs; orthostatic hypotension; syncope; fall; dementia

Syncope is defined as a transient loss of consciousness (T-LOC) due to global cerebral hypoperfusion and is characterized by rapid onset, short duration, and spontaneous and complete recovery.[1] After the age of 70, the incidence of syncope increases progressively to approximately 80 cases per 1,000 individuals per year, with a prevalence of 10% overall in individuals aged 70 and older and 23% in institutionalized older adults, who have a 2-year recurrence rate of 30%.[2] The type of syncope differs substantially between younger and older adults, the neuromediated form being the most frequent syncope type

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in younger adults and the orthostatic form in older adults.[3]

Syncope due to orthostatic hypotension (OH) is one of the most frequent causes of hospitalization in older people. It is difficult to establish the cause of syncope in these individuals, probably because of their characteristics, which include a high prevalence of cognitive deficiency.[4] In a recent study conducted in a population of older adults with dementia and recurrent syncope (the Syncope and Dementia (SYD) Study), syncope due to OH was the most common type of syncope (≈50%), and in almost half of participants, dementia was vascular in origin.[5]

Arterial hypertension is one of the most common clinical conditions in older adults and is often associated with the onset of cognitive impairment.[6] Appropriate blood pressure control is a clinical challenge in such individuals because of the need to counteract the hypotensive effect of antihypertensive drugs that may result in altered brain perfusion.[6] In this context, a somewhat paradoxical feature in older adults with hypertension with cognitive impairment is the progressive reduction of blood pressure observed in advanced disease states, probably due to a form of vascular autonomic dysfunction associated with chronic impairment of brain circulation.[6] Consequently, in older adults, a greater risk of syncope and falls may follow initially effective treatment of arterial hypertension because of the onset of OH, which is often underestimated.[7] We investigated whether hypotensive drugs could be related to the prevalence of OH syncope in older adults with dementia and recurring syncope enrolled in the SYD study.[5]

METHODS

The SYD study, which the Gruppo Italiano per lo Studio della Sincope (Italian Group for the Study of Syncope) designed with the endorsement of the Italian Society of Gerontology and Geriatrics, was conducted in 9 geriatric departments of academic and nonacademic Italian hospitals.[8] Briefly, the SYD study enrolled individuals aged 65 and older with a diagnosis of dementia (according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*), and one or more episodes of T-LOC of a suspected syncopal nature or an unexplained fall during the previous 3 months.

Participants were nursing home or acute care unit residents and outpatients attending syncope units, units for Alzheimer diagnosis, and day hospitals. The only exclusion criterion was unwillingness or inability of the individual or his or her legal caregiver to provide informed consent.

Clinical characteristics were evaluated using standardized assessment tools. Information on pharmacological treatment before the T-LOC or fall was also collected. Functional status, expressed as the number of lost activities of daily living (ADLs) or instrumental activities of daily living (IADLs) 1 month before the T-LOC or fall, was assessed through individual and proxy interviews. Cognitive function was investigated using the Mini-Mental State Examination (MMSE) and depressive symptoms using the Geriatric Depression Scale. The latter was used only in individuals with a MMSE score greater than 16. Comorbidity was assessed using the Cumulative Illness Rating Scale (CIRS). Syncope was defined as a T-LOC attributed to transient global cerebral hypoperfusion if it was of rapid onset and short duration and was characterized by spontaneous, complete recovery.[1] An unexplained fall was defined as a clearly nonaccidental fall not related to a precise medical or drug-induced cause and without any apparent cause.[9]

Diagnostic Protocol

All participants were evaluated according to the European Society of Cardiology syncope guidelines[1]. All underwent the initial evaluation, which consists of detailed, specific history-taking (collected with the assistance of proxy information) and physical examination.[1] Blood pressure was measured with the participant in the supine position and then in the orthostatic position after 1 and 3 minutes. Accordingly, OH was measured during the diagnostic protocol within a maximum 72 hours after the last episode and defined as a decrease of 20 mmHg or more in systolic blood pressure and 10 mmHg or more in diastolic blood pressure within 3 minutes of standing. All participants underwent electrocardiography and carotid sinus massage in the supine position with electrocardiographic monitoring (when not contraindicated).[1] A second-level neuroautonomic, neurological, or cardiological (when needed according to European Society of Cardiology guidelines) evaluation was undertaken in participants in whom a reliable diagnosis could not be established from the initial evaluation.[8] At the end of the diagnostic protocol, participants were divided into 2 groups: syncopal falls and nonsyncopal falls. Nonsyncopal falls included unexplained falls, falls without loss of consciousness (e.g., drop attacks, psychiatric disorders), and falls with nonsyncopal loss of consciousness (e.g., epilepsy, stroke, other metabolic disturbances).

A syncopal fall was attributed to OH after other possible causes of syncope were excluded or in case of a positive OH test, a positive head-up tilt test, predisposing factors, precipitating factors, or a history of OH.

Ethics

The Research Ethics Committee of the University of Naples Federico II School of Medicine, and the institutional review boards of all participating centers approved the study.

Statistical Analysis

The baseline characteristics of the sample are expressed as means±standard deviations. Participants were stratified based on hypotensive drugs taken and presence or absence of syncope due to OH. Univariate and multivariate analyses were performed using binary logistic regression; hypotensive drugs (alone or in combination) that significantly affected the presence of OH-related syncope were considered dependent variables, and age, sex, prodromes, number of hypotensive drugs, comorbidity (CIRS severity), presence of a pacemaker, and lost ADLs (disability) were

Table 1. Baseline Participant Characteristics

Characteristic	Total, N = 522	Syncopal Fall, n = 354 (67.8%)	Nonsyncopal Fall, n = 168 (32.2%)	P-Value
Age, mean ± SD	83.5 ± 6.1	83.3 ± 6.4	83.9 ± 5.7	.24
Female, n (%)	324 (62.1)	218 (61.6)	106 (63.1)	.41
Systolic blood pressure, mmHg, mean ± SD	130.0 ± 18.8	130.6 ± 20.0	129.8 ± 18.4	.71
Diastolic blood pressure, mmHg, mean ± SD	80.4 ± 12.8	81.2 ± 11.4	78.2 ± 10.5	.13
Prodromes, n (%)	180 (34.5)	143 (40.4)	37 (22.0)	<.001
Cumulative Illness Rating Scale score, mean ± SD	1.6 ± 0.4	1.6 ± 0.3	1.7 ± 0.4	.02
Lost activities of daily living, mean ± SD	3 ± 2	3 ± 2	3 ± 2	.17
Lost instrumental activities of daily living, mean ± SD	6 ± 2	6 ± 2	6 ± 2	.90
Mini-Mental State Examination score, mean ± SD	16.7 ± 5.5	16.9 ± 5.4	16.2 ± 5.7	.16
Geriatric Depression Scale score, mean ± SD	5.6 ± 3.4	5.5 ± 3.4	5.6 ± 3.4	.95
Number of hypotensive drugs, mean ± SD	2.7 ± 3.0	2.9 ± 3.1	2.5 ± 2.7	.18
Taking <2 hypotensive drugs n (%)	255 (48.9)	177 (50.0)	78 (56.4)	.45
Type of dementia, n (%)				
Alzheimer's	172 (33.0)	113 (31.9)	59 (35.1)	.26
Vascular	217 (41.6)	152 (42.9)	65 (38.7)	.20
Mixed	81 (15.5)	55 (15.5)	26 (15.5)	.55
Parkinson's	31 (5.9)	20 (5.6)	11 (6.5)	.41
Lewy bodies	10 (2.0)	7 (2.0)	3 (1.8)	.59
Frontotemporal	5 (1.0)	3 (0.8)	2 (1.2)	.52
Normal pressure hydrocephalus	5 (1.0)	3 (0.8)	2 (1.2)	.52
Alcoholic	1 (0.2)	1 (0.3)	0 (0.0)	.88
Comorbidities, n (%)				
Arterial hypertension	389 (74.5)	263 (74.3)	126 (75.0)	.48
Coronary artery disease	100 (19.2)	69 (19.5)	31 (18.5)	.44
Chronic heart failure	47 (9.0)	30 (8.5)	17 (10.1)	.32
Atrial fibrillation	129 (24.7)	89 (25.1)	40 (23.8)	.41
Stroke	74 (14.2)	41 (11.6)	33 (19.6)	.01
Transient ischemic attack	39 (7.5)	27 (7.6)	12 (7.1)	.50
Carotid atherosclerosis	131 (25.1)	97 (27.4)	34 (20.2)	.08
Epilepsy	20 (3.8)	12 (3.4)	8 (4.8)	.30
Psychiatric disease	168 (32.2)	119 (33.6)	49 (29.2)	.18
Type 2 diabetes mellitus	115 (22.0)	74 (20.9)	41 (24.4)	.21
Dysthyroidism	57 (10.9)	34 (10.9)	23 (10.9)	.16
Pacemaker	20 (3.8)	20 (3.8)	0 (0.0)	<.001

SD = standard deviation.

considered confounding variables. All statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL). P<.05 was considered statistically significant.

RESULTS

The clinical features of the 522 participants are reported in Table 1. The mean age of our study population was 83.5±6.1, and 60% were female. Participants had a mean 3±2 ADLs and 6±2 IADLs lost, and the average MMSE score was 16.7±5.5. Subjects were stratified according to syncopal (n=354, 67.8%) and nonsyncopal (n=168, 32.2%) falls. CIRS severity score was significantly higher in participants with nonsyncopal falls (1.6±0.3) than in those with syncopal falls (1.7±0.4) (p=.02). Vascular dementia was the most frequent form of dementia (41.6%) followed by Alzheimer's disease (33%) and mixed dementia (15.5%), with no significant difference between participants with syncopal and nonsyncopal falls. The most frequent comorbidity was arterial hypertension (74.5%), followed by psychiatric disease (32.2%), carotid atherosclerosis (25.1%), atrial fibrillation (24.7%), and type II diabetes mellitus (22.0%). Participants with nonsyncopal falls were more likely to have a history of stroke (11.6%) than those with syncopal falls (19.6%) (p=.01), whereas the prevalence of transient ischemic attacks did not differ significantly between the two groups. The presence of prodromes differed significantly between participants with syncopal and non-syncopal falls (Table 1).

Syncope with fall due to OH was the most frequent type of syncope (n=170, 48.0%) followed by neuromediated syncope (n=102, 28.8%), cardiac syncope (n=45, 12.7%), and syncope of unknown origin (n=37, 10.5%). Syncopal falls were attributed to OH in the case of a positive OH test (n=112/170, 65.9%), a positive head-up tilt test (n=9/170, 5.3%), predisposing factors (n=20/170, 11.8%), precipitating factors (n= 19/170, 11.2%), or a history of OH (n=10/170, 5.9%).

Clinical features of participants with syncopal falls stratified according to presence of syncope due to OH did not differ significantly between the 2 groups, although the incidence of stroke was higher in participants without than in those with syncope due to OH (Table 2). All participants with an implanted pacemaker enrolled in the study were in the group without syncope due to OH (20 vs 0, p<.001). The presence of prodromes differed

Table 2. Baseline Participant Characteristics Stratified According to Presence of Syncope Due to Orthostatic Hypotension (OH)

Characteristic	Syncopal Fall Due to OH		P-Value
	Yes, n = 170 (48.0%)	No, n = 184 (52.0%)	
Age, mean ± SD	83.5 ± 6.1	83.3 ± 6.1	.24
Female, n (%)	96 (56.5)	228 (64.8)	.04
Systolic blood pressure, mmHg, mean ± SD	129.2 ± 19.1	130.5 ± 18.7	.49
Diastolic blood pressure, mmHg, mean ± SD	76.2 ± 11.4	81.6 ± 10.5	.26
Number of syncope episodes, mean ± SD	3.6 ± 3.3	3.3 ± 2.8	.37
Prodromes, n (%)	70 (41.2)	110 (31.3)	.02
Cumulative Illness Rating Scale score, mean ± SD	1.6 ± 0.4	1.6 ± 0.4	.79
Lost activities of daily living, mean ± SD	2 ± 2	3 ± 2	.10
Lost instrumental activities of daily living, mean ± SD	6 ± 2	6 ± 2	.63
Mini-Mental State Examination score, mean ± SD	17.7 ± 4.9	16.2 ± 5.7	.005
Geriatric Depression Scale score, mean ± SD	5.7 ± 3.5	5.4 ± 3.3	.42
Number of hypotensive drugs, mean ± SD	3.1 ± 3.2	2.7 ± 3.0	.18
Taking <2 hypotensive drugs n (%)	93 (52.5)	84 (47.5)	.11
Type of dementia, n (%)			
Alzheimer's	56 (32.9)	116 (33.0)	.54
Vascular	74 (43.5)	143 (40.6)	.29
Mixed	19 (11.2)	62 (17.6)	.04
Parkinson's	14 (8.2)	17 (4.8)	.09
Lewy bodies	4 (2.4)	6 (1.7)	.42
Frontotemporal	1 (0.6)	4 (1.8)	.48
Normal pressure hydrocephalus	1 (0.6)	4 (1.1)	.48
Alcoholic	1 (0.6)	0 (0.0)	.33
Comorbidities, n (%)			
Arterial hypertension	131 (77.1)	258 (73.3)	.21
Coronary artery disease	36 (21.2)	64 (18.2)	.24
Chronic heart failure	18 (10.6)	29 (8.2)	.23
Atrial fibrillation	40 (23.5)	89 (25.3)	.41
Stroke	18 (10.6)	56 (15.9)	.06
Transient ischemic attack	10 (5.9)	29 (8.2)	.22
Carotid atherosclerosis	44 (25.9)	97 (24.7)	.43
Epilepsy	7 (4.1)	13 (3.7)	.49
Psychiatric disease	62 (36.5)	106 (30.1)	.09
Type 2 diabetes mellitus	39 (22.9)	76 (21.6)	.40
Dysthyroidism	16 (9.4)	41 (22.2)	.24
Pacemaker	0 (0.0)	20 (5.7)	<.001

SD = standard deviation.

significantly between participants with and without OH-related syncope (p=.02) (Table 2).

In the whole sample and in participants with syncopal and nonsyncopal falls, diuretics were the most frequently prescribed hypotensive drugs (37.9%), followed by angiotensin-converting enzyme inhibitors (ACE-Is) (33.7%), beta-blockers (26.8%), angiotensin II type 1 receptor blockers (17.8%), calcium antagonists (18.4%),

Table 3. Univariate and Multivariate Analysis of Effect of Hypotensive Drugs Alone or in Combination on Risk of Syncope Due to Orthostatic Hypotension in Older Adults with Dementia

Drug or Combinations	Univariate	Multivariate					
		Age and Sex	+ Prodromes	+ Number of Drugs	+ Comorbidity	+ Pacemaker	+ Disability
	Relative Risk (95% Confidence Interval)						
Alpha-blocker	1.67 (1.00–2.85)	1.48 (0.84–2.60)	1.56 (0.88–2.76)	1.36 (0.74–2.51)	1.31 (0.70–2.42)	1.30 (0.69–2.43)	1.26 (0.67–2.37)
Nitrate	1.74 (1.00–3.20)	1.85 (1.05–3.25)	1.77 (1.01–3.12)	1.55 (1.00–3.24)	1.62 (0.84–3.12)	1.79 (0.91–3.53)	1.85 (0.93–3.67)
Alpha-blocker + diuretic	2.01 (1.00–4.28)	1.83 (0.85–3.96)	1.89 (0.87–4.11)	1.58 (0.68–3.63)	1.54 (0.67–3.55)	1.60 (0.67–3.79)	1.52 (0.64–3.61)
ACE-I + diuretic	1.70 (1.04–2.78)	1.69 (1.03–2.76)	1.66 (1.01–2.72)	1.48 (0.83–2.63)	1.43 (0.79–2.58)	1.37 (0.76–2.47)	1.40 (0.80–2.53)
ACE-I + nitrate	2.34 (1.07–5.09)	2.43 (1.11–5.34)	2.32 (1.05–5.12)	1.98 (0.83–4.68)	1.96 (0.82–4.64)	1.96 (0.81–4.72)	2.01 (0.82–4.87)

ACE-I = angiotensin-converting enzyme inhibitor.

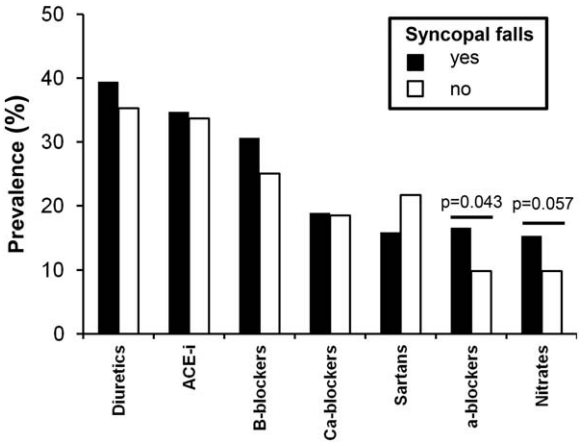

Figure 1. Prevalence of hypotensive drugs administered to participants with and without syncopal falls.

nitrates (11.3%), and alpha-blockers (12.5%). There were no significant differences in the prevalence of hypotensive drugs between participants with and without syncopal falls.

When participants with dementia and syncopal falls were stratified according to OH-related syncope and non-OH-related syncope, the prevalence of nitrates (15.3% vs 9.8%) and alpha-blockers (16.5% vs 9.8%) (Figure 1) and the combinations of ACE-Is and diuretics (20.6% vs 13.0%), alpha-blockers and diuretics (8.2% vs 3.3%), and of ACE-Is and nitrates (8.2% vs 3.3%) (Figure 2) were significantly more prevalent in participants with OH-related syncope.

Upon multivariate analysis, only the effect of nitrates on syncope due to OH was partially confirmed, maintaining its significance after adjustment for age, sex, prodromes, and number of hypotensive drugs. The relative risk of syncope due to OH was significant in participants treated with alpha-blockers and diuretics, ACE-Is and diuretics, and ACE-Is and nitrates. Multivariate analysis confirmed that the presence of a pacemaker and disability increased the relative risk in participants receiving ACE-Is and diuretics or ACE-Is and nitrates only when corrected for age, sex, and prodromes (see Table 3).

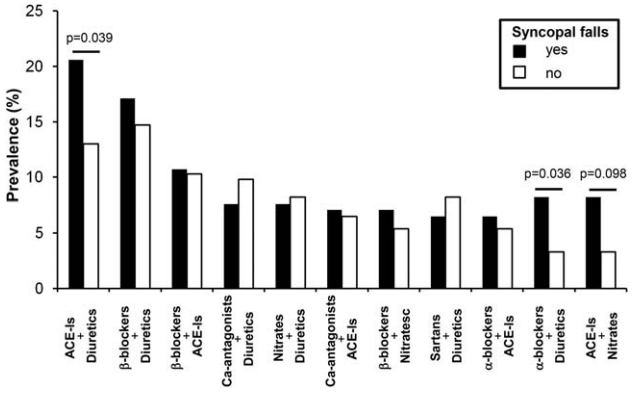

Figure 2. Prevalence of combinations of hypotensive drugs administered to participants with and without syncopal falls. ACE-Is = angiotensin-converting enzyme inhibitors.

DISCUSSION

In older adults with dementia, nitrates and alpha-blockers alone and the combinations of ACE-Is and diuretics, alpha-blockers and diuretics, and ACE-Is and nitrates are more frequent in patients with than in those without syncope due to OH. Multivariate analyses, adjusted for age and sex, prodromes, number of hypotensive drugs, comorbidity, the presence of a pacemaker, and disability, revealed a significant risk of syncope due to OH in participants treated with nitrates alone and in those treated with the combination of ACE-I's and diuretics or ACE-inhibitors and nitrates.

Syncope Due to OH in Older Adults with Dementia

Syncope is one of the most important clinical problems in individuals aged 70 and older.[2,3,8] In our sample, syncope due to OH was by far the most prevalent (≈50%) form of syncope, followed by neuromediated (≈30%), cardiac (≈10%), and unexplained (≈10%) syncope. Syncope due to OH is one of the more severe clinical manifestations of OH, and the prevalence of OH increases progressively with age,[7,10–12] but data on the prevalence of syncope due to OH are unclear. Comorbidities, hypertension, and diabetes have been implicated in these discordant observations,[6,13–15] and although the prevalence of OH is high in older people without dementia, it is not always reported as one of the main causes of syncope. In the SYD study, conducted exclusively in older adults with dementia, syncope due to OH was more frequent than the other types of syncope, but the reason is unknown.[4,5,16] Baroreceptor dysfunction at the onset of OH is closely related to aging and to the effects of hypertension and, consequently, to arterial stiffness.[13–15,17,18]

Hypotensive Drugs and OH in Older Adults with Dementia

Arterial hypertension and its consequences (coronary artery disease, atrial fibrillation, chronic heart failure) are among the most common clinical conditions in older adults and are frequently treated with hypotensive drugs.[6,17] Most individuals with syncope and dementia in our sample had one or more of these conditions, so hypotensive agents were the most frequently used drugs. In particular, the higher prevalence of syncope due to OH was associated with nitrates and alpha-blockers alone and with combinations of ACE-Is and diuretics and of ACE-Is and nitrates. The relationship between treatment with hypotensive drugs and syncope due to OH has been widely studied.[19] Aggressive blood pressure treatment has been related to OH, although the role of specific drugs and combinations is unclear.[19] In a recent study conducted in 172 older adults with dementia and mild cognitive impairment treated with antihypertensive drugs, participants with systolic pressure of 128 mmHg or less had a greater reduction of the MMSE scores (–2.8) than those with systolic pressure between 129 and 144 mmHg and 145 mmHg and higher (–0.7), which indicates that low blood pressure is associated with greater cognitive decline.[20] Thus, aggressive hypotensive therapy seems to exacerbate negative relationship among low blood pressure, dementia, and syncope due to OH.[19]

Hypotensive Drugs, OH, and Cognitive Decline: A Dangerous Relationship

The relationship between OH and cognitive decline has been attributed to a common pathological process that affects areas involved in cognition and autonomic cardiovascular control.[21,22] The cerebral areas involved in the neurodegenerative process may include areas that govern the autonomic control of the cardiovascular system, so neurodegeneration may be responsible for cognitive deficiency and OH.[20] Alternatively, OH may cause a state of cerebral hypoperfusion. In this context, frontal lobe hypoperfusion has been described in individuals with OH and reported to lead to altered executive functions.[21–23]

Antihypertensive therapy was found to be significantly associated with OH in the Rotterdam Study[24] and in the Malmoe Preventive Project.[25] In the British Women's Heart and Health Study of 4,286 women aged 60 to 80, number of hypotensive drugs was significantly associated with prevalence of OH.[26] A retrospective study of 75-year-old individuals found that the number of causative drugs (alpha blockers, antihypertensive agents, diuretics) was positively correlated with the prevalence of OH, with an increase ranging from 35% to 65% as the number of hypotensive drugs taken increased.[27]

CONCLUSIONS

The number of drugs administered, and in particular specific hypotensive drugs used alone or in combination, strongly influence syncope due to OH. Such drugs, namely, nitrates alone and combinations of ACE-Is and diuretics and of ACE-Is and nitrates significantly increase the risk of syncope due to OH and should be used with extreme caution in older adults with dementia.

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REFERENCES

1. The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC). Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J 2009;30:2631–2671.
2. Ruwald MH, Hansen ML, Lamberts M, et al. The relation between age, sex, comorbidity, and pharmacotherapy and the risk of syncope: A Danish nationwide study. Europace 2012;14:1506–1514.
3. Ungar A, Mussi C, Del Rosso A et al. for the Italian Group for the Study of Syncope in the Elderly. Diagnosis and characteristics of syncope in older patients referred to geriatric departments. J Am Geriatr Soc 2006;54:1531–1536.
4. Rudolph JL, Zanin NM, Jones RN et al. Hospitalization in community-dwelling persons with Alzheimer's disease: Frequency and causes. J Am Geriatr Soc 2010;58:1542–1548.
5. Ungar A, Mussi C, Ceccofiglio A et al. Etiology of syncope and unexplained falls in elderly adults with dementia: Syncope and Dementia (SYD) Study. J Am Geriatr Soc. 2016;64:1567–1573.
6. Abete P, Della-Morte D, Gargiulo G et al. Cognitive impairment and cardiovascular diseases in the elderly. A heart-brain continuum hypothesis. Ageing Res Rev 2014;18:41–52.
7. Benvenuto LJ, Krakoff LR. Morbidity and mortality of orthostatic hypotension: Implications for management of cardiovascular disease. Am J Hypertens 2011;24:135–144.
8. Ungar A, Mussi C, Nicosia F et al. The "syncope and dementia" study: A prospective, observational, multicenter study of elderly patients with dementia and episodes of "suspected" transient loss of consciousness. Aging Clin Exp Res 2015;27:877–882.
9. Masud T, Morris RO. Epidemiology of falls. Age Ageing 2001;Suppl 4:3–7.
10. Graafmans WC, Ooms ME, Hofstee HM, Bezemer PD, Bouter LM, Lips P. Falls in the elderly: A prospective study of risk factors and risk profiles. Am J Epidemiol 1996;143:1129–1136.
11. Ooi WL, Hossain M, Lipsitz LA. The association between orthostatic hypotension and recurrent falls in nursing home residents. Am J Med 2000;108:106–111.
12. Yap PL, Niti M, Yap KB, Ng TP. Orthostatic hypotension, hypotension and cognitive status: Early comorbid markers of primary dementia? Dement Geriatr Cogn Disord 2008;26:239–246.
13. 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;36:637–642.
14. Mattace-Raso FU, van den Meiracker AH, Bos WJ, et al. Arterial stiffness, cardiovagal baroreflex sensitivity and postural blood pressure changes in older adults: The Rotterdam Study. J Hypertens 2007;25:1421–1426.
15. Uppuluri SC, Storozynsky E, Bisognano JD. Baroreflex device therapy in the treatment of hypertension. Curr Hypertens Rep 2009;11:69–75.
16. Kim DH, Brown RT, Ding EL et al (2001) Dementia medications and risk of falls, syncope, and related adverse events: Meta-analysis of randomized controlled trials. J Am Geriatr Soc 59:1019–1031
17. Cacciatore F, Abete P, de Santis D, Longobardi G, Ferrara N, Rengo F. Mortality and blood pressure in elderly people with and without cognitive impairment. Gerontology 2005;51:53–61.
18. Chesterton LJ, Sigrist MK, Bennett T, Taal MW, McIntyre CW. Reduced baroreflex sensitivity is associated with increased vascular calcification and arterial stiffness. Nephrol Dial Transplant 2005;20:1140–1147.
19. 2013 ESH/ESC Guidelines for the management of arterial hypertension. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Euro Heart J 2013;34:2159–2219.
20. Mossello E, Pieraccioli M, Nesti N et al. Effects of low blood pressure in cognitively impaired elderly patients treated with antihypertensive drugs. JAMA Intern Med 2015;175:578–585.
21. Sambati L, Calandra-Buonaura G, Poda R, Guaraldi P, Cortelli P. Orthostatic hypotension and cognitive impairment: A dangerous association? Neurol Sci. 2014;35:951–957.
22. Idiaquez J, Roman GC. Autonomic dysfunction in neurodegenerative dementias. J Neurol Sci. 2011: 305:22–27.
23. Fukuoka S, Hayashida K, Nishiooeda Y et al. Cerebral hypoperfusion in orthostatic hypotension with globally denervated myocardium. J Nucl Med 1996; 37:1824–1826.
24. Viramo P, Luukinen H, Koski K, Laippala P, Sulkava R, Kivelä SL. Orthostatic hypotension and cognitive decline in older people. J Am Geriatr Soc 1999;47:600–604.
25. 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;31:85–91.
26. Kamaruzzaman S, Watt H, Carson C, Ebrahim S. The association between orthostatic hypotension and medication use in the British Women's Heart and Health Study. Age Ageing 2010;39:51–56
27. Poon IO, Braun U. High prevalence of orthostatic hypotension and its correlation with potentially causative medications among elderly veterans. J Clin Pharm Ther 2005;30:173–178.