

Etiology of Syncope and Unexplained Falls in Elderly Adults with Dementia: Syncope and Dementia (SYD) Study

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OBJECTIVES: To investigate the etiology of transient loss of consciousness (T-LOC) suspected to be syncope and unexplained falls in elderly adults with dementia.

DESIGN: Prospective, observational, multicenter study.

SETTING: Acute care wards, syncope units or centers for the diagnosis of dementia.

PARTICIPANTS: Individuals aged 65 and older with a diagnosis of dementia and one or more episodes of T-LOC of a suspected syncopal nature or unexplained falls during the previous 3 months were enrolled.

MEASUREMENTS: The causes of T-LOC suspected to be syncope and unexplained falls were evaluated using a simplified protocol based on European Society of Cardiology guidelines.

RESULTS: Of 357 individuals enrolled, 181 (50.7%) had been referred for T-LOC suspected to be syncope, 166 (46.5%) for unexplained falls, and 10 (2.8%) for both. An initially suspected diagnosis of syncope was confirmed in 158 (87.3%), and syncope was identified as the cause of the event in 75 (45.2%) of those referred for unexplained falls. Orthostatic hypotension was the cause of the event in 117 of 242 (48.3%) participants with a final diagnosis of syncope.

CONCLUSION: The simplified syncope diagnostic protocol can be used in elderly people with dementia referred for suspected syncope or unexplained falls. Unexplained falls may mask a diagnosis of syncope or pseudosyncope in almost 50% of cases. Given the high prevalence of orthostatic syncope in participants (~50%), a systematic reappraisal of drugs potentially responsible for orthostatic hypotension is warranted. *J Am Geriatr Soc* 2016.

Key words: dementia; syncope; falls; transient loss of consciousness

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Falling is a major cause of morbidity and mortality in the elderly general population¹ and the primary cause of hospitalization in those with dementia.² The risk of falling is eight times as high in elderly adults with dementia as in their cognitively intact counterparts and is frequently related to syncope.³ Although neuroautonomic evaluation is a reliable diagnostic tool in cognitively impaired elderly adults with unexplained falls,⁴ individuals with dementia are a particular clinical subset in which suspected syncope is less likely to be fully investigated. This may be because of several factors, ranging from difficulty collecting information on falls in individuals with dementia to an ageist attitude that tends to underestimate the relevance of falls and syncope in older persons, particularly those that are cognitively impaired.⁵ However, identification of the causes of falls and of individuals with syncope-related falls may have important clinical and therapeutic implications that, in turn, may reduce the burden of falls-related morbidity and mortality in this subset of frequent fallers.

A prospective, observational, multicenter study was conducted to define the etiology of syncope and unexplained falls in elderly adults with dementia using a simplified protocol based on European Society of Cardiology (ESC) guidelines.⁶

METHODS

This prospective, observational, multicenter study was conducted in nine geriatric departments of academic and nonacademic Italian hospitals. Individuals aged 65 and older consecutively referred to various settings (syncope units, units for Alzheimer's diagnosis, day hospitals, nursing homes, acute care units) between February 2012 and April 2015 were enrolled. Inclusion criteria were diagnosis of dementia defined according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV)*,⁷ and one or more episodes of transient loss of consciousness (T-LOC) of a suspected syncopal nature or of an unexplained fall during the previous 3 months. The Gruppo Italiano per lo studio della Sincope (GIS, Italian Group for the Study of Syncope) designed the study, whose methods are reported in the SYNCOPE and Dementia Study,⁸ with the endorsement of the Italian Society of Gerontology and Geriatrics.

Dementia

According to the DSM IV,⁷ dementia was diagnosed based on the following criteria:

- The development of multiple cognitive deficits, manifested by memory impairment (impaired ability to learn new information or to recall previously learned information) and one or more of the following cognitive disturbances: aphasia (language disturbance), apraxia (impaired ability to perform motor activities despite intact motor function), agnosia (failure to recognize or identify objects despite intact sensory function), disturbance in executive functioning (planning, organizing, sequencing, abstracting).
- Each of the cognitive defects listed above results in significant impairment in social or occupational functioning and represents a significant decline from a previous level of functioning.
- The course is characterized by gradual onset and continuing cognitive decline.
- The cognitive deficits in criterion A are not due to other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor), systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, human immunodeficiency virus infection), or substance-induced conditions.
- The deficits do not occur exclusively during the course of delirium.

Syncope

Syncope was defined as a T-LOC attributed to transient global cerebral hypoperfusion because of its rapid onset, short duration, and spontaneous, complete recovery.⁶

Unexplained Falls

An unexplained fall was defined as a fall not related to extrinsic factors such as poor lighting, unsafe stairways,

and irregular floor surfaces or to a precise medical or drug-induced cause.⁹

Exclusion Criteria

Exclusion criteria were previous evaluation for syncope and unwillingness or inability of the individual or a legal caregiver to provide informed consent.

Diagnostic Protocol

Clinical and functional characteristics were evaluated using standardized assessment tools, including detailed information about pharmacological treatment before the T-LOC or fall. In particular, functional status, expressed as the number of lost activities 1 month before the T-LOC or fall, was assessed in a participant and proxy interview about activities of daily living (ADLs)¹⁰ and instrumental ADLs.¹¹ Cognitive function were investigated using the Mini Mental State Examination (MMSE)¹² and depressive symptoms using the Geriatric Depression Scale, which was used only in participants with a MMSE score greater than 16.¹³ Comorbidity was assessed using the Cumulative Illness Rating Scale.¹⁴

Simplified Protocol Based on ESC Guidelines for the Diagnosis and Management of Syncope

All participants were evaluated as the ESC guidelines recommend.⁶ In particular, a detailed history was collected for each participant with the assistance of proxy information, a physical examination was performed, and clinostatic blood pressure was measured. Electrocardiography (ECG) was also performed, as well as carotid sinus massage with the participant in a supine position under ECG and blood pressure monitoring. Orthostatic blood pressure was measured in 77.3% of participants 1 and 3 minutes after they resumed an upright position. Contraindications to carotid sinus massage were stroke in the previous 6 months and carotid stenosis of greater than 75%. Orthostatic hypotension was considered a cause of syncope only when symptoms of spontaneous episodes were reproduced. When a reliable diagnosis could not be made after an initial evaluation, selected participants with suspected cardiac, neuroreflex, or unexplained syncope were referred to the Syncope Unit for a second-level evaluation.

Table S1 lists details of all tests performed during the diagnostic examination of participants with and without a final diagnosis of syncope.

Orthostatic Hypotension Etiology

Based on the history, physical examination, and adjunctive laboratory data from dysautonomia units, orthostatic syncope was related to primary autonomic failure (Parkinson's disease; multiple system atrophy; pure autonomic failure; Lewy body dementia; autoimmune autonomic gangliopathy; and rare hereditary disorders such as familial dysautonomia, dopamine beta-hydroxylase deficiency, and idiopathic syncope (etiology unknown)), secondary autonomic failure (diabetes mellitus; cardiovascular disease such as heart failure and aortic stenosis; pulmonary

hypertension; essential hypertension; renal failure; autoimmune disease; venous pooling; alcoholic polyneuropathy; endocrine disorder such as adrenal insufficiency, thyroid disease, and diabetes insipidus; amyloidosis; multiple myeloma; paraneoplastic syndromes; cerebrovascular disease; multiple sclerosis; and spinal cord diseases), drugs, or volume depletion.¹⁵

Syncope Unit

In the case of suspected cardiac syncope, participants underwent a cardiology evaluation consisting of echocardiography, 24-hour ECG, and blood pressure monitoring. If arrhythmic syncope was suspected, a loop recorder was implanted. The second-level neuroautonomic evaluation consisted of carotid sinus massage with the subject in an upright position and head-up tilt testing. The latter was performed according to the Italian protocol potentiated by sublingual nitroglycerin during continuous ECG and blood pressure monitoring and was considered positive in the case of syncope associated with rapid-onset hypotension or bradycardia.¹⁶ Positive responses were classified according to the Vasovagal Syncope International Study as cardioinhibitory, vasodepressive, or mixed.¹⁷ A slow progressive fall in blood pressure was considered an autonomic response dysfunction. Carotid sinus massage was performed according to the “method of symptoms” in the supine and upright positions for 10 seconds; the test is defined as positive if, during the massage, the spontaneous symptoms are reproduced in association with cardioinhibition or vasodepression.¹⁸ This procedure in the upright position is contraindicated in individuals with carotid stenosis of greater than 50%. Participants with cardiac contraindications (severe aortic stenosis or recent myocardial infarction) did not undergo carotid sinus massage. In the case of suspected neurological causes of episodes, namely, epilepsy or stroke (pseudosyncope), participants underwent a specific neurological evaluation consisting of electroencephalography, computed tomography, or magnetic resonance imaging of the brain.

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 this study.

Statistical Analysis

Assuming a 30% prevalence (95% confidence interval = 25–35%) of T-LOC, a sample size of 323 participants was required. Continuous variables are reported as means and standard deviations and categorical variables as percentages.

RESULTS

From February 2012 to April 2015, 380 individuals met the inclusion criteria and were screened for enrollment. Informed consent could not be obtained in 23 cases; so 357 individuals were enrolled in the study. All enrolled

participants had been referred consecutively to acute care wards ($n = 261$), syncope units ($n = 63$), or centers for the diagnosis of dementia ($n = 33$) in geriatric centers in Monza ($n = 69$), Modena ($n = 65$), Brescia ($n = 60$), Florence ($n = 51$), Turin ($n = 44$), Cagliari ($n = 36$), Rome ($n = 12$), Trento ($n = 10$), and Naples ($n = 10$).

Of the 357 enrolled individuals, 181 (50.7%) had been referred for T-LOC suspected to be syncope, 166 (46.5%) for unexplained falls, and 10 (2.8%) for both. Participant clinical characteristics are reported in Table 1. Participants had a mean age of 83.5 ± 6.5 (range 65–100), most were female (60.8%), and vascular dementia was the most frequent cause of cognitive impairment (MMSE 17.4 ± 5.5 , ADLs lost 3 ± 2 , instrumental ADLs lost 6 ± 2). The mean number of T-LOC episodes and falls in the previous year was 1.3 ± 1.2 , and one individual had had as many as 30 episodes (T-LOC or falls) in the previous 3 years. Almost all (92.7%) had at least one

Table 1. Participant Demographic and Clinical Characteristics (N = 357)

Characteristics	Value
Age, mean \pm SD (range)	83.5 ± 6.5 (65–100)
Female, n (%)	217 (60.8)
Cumulative Illness Rating Scale score, mean \pm SD	3.4 ± 2.0
Number of activities of daily living lost, mean \pm SD	3 ± 2
Number of instrumental activities of daily living lost, mean \pm SD	6 ± 2
Mini-Mental State Examination score, mean \pm SD	17.4 ± 5.5
Geriatric Depression Scale, mean \pm SD (N = 196)	5.6 ± 3.4
Abnormal electrocardiogram, n (%) ^a	106 (29.7)
Number of episodes of transient loss of consciousness and falls in last 3 years, mean \pm SD (range)	3.9 ± 3.6 (1–30)
Type of dementia, n (%)	
Alzheimer's disease	111 (31.1)
Vascular	153 (42.9)
Mixed (Alzheimer's disease and vascular)	57 (16.0)
Parkinson's disease	20 (5.6)
Lewy body dementia	7 (2.0)
Frontotemporal	3 (0.8)
Normal-pressure hydrocephalus	4 (1.1)
Alcoholic	2 (0.6)
Comorbidities, n (%)	
Hypertension	277 (77.6)
Structural heart disease	126 (35.3)
Atrial fibrillation	53 (14.8)
Stroke, transient ischemic attack	77 (21.6)
Carotid plaques	90 (25.2)
Epilepsy	12 (3.4)
Psychiatric disorders	117 (32.8)
Type II diabetes mellitus	81 (22.7)
Thyroid dysfunction	39 (10.9)
Pacemaker (n, %)	14 (3.9)

^aLeft bundle branch block, bifascicular block, atrial fibrillation, advanced atrioventricular block, previous myocardial infarction, coronary heart disease, heart failure, valvular disease, pulmonary embolism. SD = standard deviation.

cardiovascular condition. Fourteen (3.9%) had a pacemaker.

Pharmacological treatment, consisting of a mean of six drugs in each participant, is detailed in Table 2, grouped according to Anatomical Therapeutic Chemical Classification System codes. Antiplatelet agents, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and diuretics were the most frequently prescribed agents.

The main features of each event (T-LOC or fall) are reported in Table 3. Not surprisingly, more than 90% of events occurred when the participant was in the upright position or was changing position. More than two-thirds of participants did not have prodromal symptoms. After the event, confusion was the most frequent (33.3%) symptom. Almost 50% of participants had event-related injuries.

An initially suspected diagnosis of syncope was confirmed in 158 participants (87.3%), and syncope was diagnosed in 75 (45.2%) of the participants initially referred for an otherwise unexplained fall (Table 4). Approximately 10% of participants enrolled for syncope or falls received a different diagnosis at the end of the diagnostic examination, namely, stroke, epilepsy, metabolic disorders, or a drop or psychogenic attack. In particular, blood pressure measurement ($P = .003$) and head-up tilt testing ($P < .001$) were highly diagnostic of syncope (Table S1).

The presumed causes of syncope in individuals with different types of dementia are shown in Table 5. Of the 242 participants with final diagnosis of syncope, 107 (44.2%) had vascular dementia, and 75 (29.7%) had

Alzheimer's disease. The origin of syncope was unexplained in 31 or 242 (12.8%) participants with a final diagnosis of syncope, and a pathogenic diagnosis was made in 87.2% of cases, with orthostatic syncope being the most prevalent cause (48.3%). Antihypertensive drugs associated with orthostatic syncope in participants are listed in Table S2.

Based on the pathogenic diagnosis of syncope, a pacemaker was implanted in 16 participants (4.5%), counseling on avoidance of triggers was provided for 104 (29.1%) participants or their caregivers, pharmacological treatment was modified in 178 (49.9%), and an antiepileptic drug was started in four (1.1%).

DISCUSSION

To the knowledge of the authors, this is the first study to report the use of a simplified standardized diagnostic protocol for syncope and unexplained falls in elderly adults with dementia. The main finding of this study is that a standardized diagnostic protocol can be easily and safely used in this complex clinical scenario. The cause of syncope remained unknown only in 12.8% of cases. Moreover, it was demonstrated that an orthostatic syncopal mechanism underlies almost 50% of cases of initially unexplained falls.

Participants were individuals with dementia referred for suspected syncope and those referred for unexplained falls. This reflects the difficulty commonly encountered in daily clinical practice of differentiating, at the first evaluation, between the two types of events, particularly in cognitively impaired individuals. Retrograde amnesia and the frequent absence of witnesses complicate history collection in elderly adults who fall.¹⁹ In addition, the present study

Table 2. Drugs Used at the Time of the Event in Entire Population (N = 357)

Drug	Value
Overall number of drugs, mean \pm standard deviation (range)	6.0 \pm 2.9 (0–14)
Cardiovascular, n (%) (ATC classification codes B01; C01–C10)	
Antiplatelet	205 (57.4)
Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker	188 (52.7)
Diuretic	141 (39.5)
Beta-blocker	92 (25.8)
Statin	91 (25.5)
Calcium-channel blocker	62 (17.4)
Antiarrhythmic	55 (15.4)
Anticoagulant	48 (13.4)
Nitrate	45 (12.6)
Alpha-blocker	42 (11.8)
Antidiabetic medication, n (%) (ATC classification code A10)	67 (18.8)
Miscellaneous ATC codes, n (%)	
Antidepressant	125 (35.0)
Antipsychotic	77 (21.6)
Benzodiazepine	77 (21.6)
Cholinesterase inhibitor	45 (12.6)
Antiparkinsonian	28 (7.8)
Memantine	27 (7.6)
Anticonvulsant	23 (6.4)
Levothyroxine	21 (5.9)

ATC = Anatomical Therapeutic Chemical.

Table 3. Main Features of Event (Transient Loss of Consciousness or Fall) in the Entire Population (N = 357) and in Participants with Orthostatic Syncope (n = 117)

Main Features of Events	All	Orthostatic Syncope
	n (%)	
Circumstances just before event		
Standing	221 (61.9)	69 (59.0)
Changing position	106 (29.7)	26 (22.2)
Sitting	100 (28.0)	36 (30.8)
Walking	99 (27.7)	31 (26.5)
Situational	75 (21.0)	19 (16.2)
Lying	19 (5.3)	7 (6.0)
Warning or prodromal symptoms		
Absent	241 (67.5)	67 (57.3)
Neurovegetative	81 (22.7)	40 (34.2)
Cardiac	9 (2.5)	4 (3.4)
Symptoms after event		
Confusion	119 (33.3)	34 (29.1)
Neurological signs	62 (17.4)	11 (9.4)
Fatigue	55 (15.4)	19 (16.2)
Incontinence	30 (8.4)	11 (9.4)
Event-related injuries	173 (48.6)	46 (39.3)
Major injuries	52 (14.6)	18 (15.4)

Table 4. Initial and Final Diagnoses in Total Population (N = 357)

Initial Diagnosis	Final Diagnosis	Percentage of Initial
Suspected syncope (n = 181)	Syncope (n = 158)	87.3
	Falls (n = 10)	5.5
	Stroke (n = 6)	3.3
	Epilepsy (n = 4)	2.2
	Metabolic disorder (n = 2)	1.1
	Drop attack (n = 1)	0.6
Unexplained falls (n = 166)	Syncope (n = 75)	45.2
	Falls (n = 71)	42.8
	Stroke (n = 13)	7.8
	Epilepsy (n = 2)	1.2
	Metabolic disorder (n = 4)	2.4
	Psychogenic attack (n = 1)	0.6
Syncope and falls (n = 10)	Syncope (n = 9)	90.0
	Falls (n = 1)	10.0

demonstrated that the typical clinical presentation of syncope (presence of prodromes; rapid, complete recovery) is less frequent than usually reported. An atypical pattern of symptoms, characterized by the absence of prodromes, and a high prevalence of postevent confusion were found.²⁰

The ESC diagnostic protocol confirmed the initial diagnosis in most individuals referred for suspected syncope. Most importantly, approximately 50% of individuals referred for an initially unexplained fall had a final diagnosis of syncope, which is similar to the percentage obtained in fallers without dementia.^{4,5,21} Individuals with syncope and repeated falls frequently report severe injuries that are a major cause of hospitalization, high healthcare costs,

further functional loss, and poor quality of life. Therefore, these results strengthen on clinical grounds the ethical value of not considering cognitive impairment a criterion for contraindicating a structured diagnostic protocol.

In contrast with epidemiological findings,²² dementia was of vascular origin in most of the participants. Specifically, participants had a previous diagnosis of vascular dementia based on two major requirements: clinical diagnosis of dementia and determination of its vascular origin. Consequently, as previously recommended,²³ brain computed tomography and magnetic resonance imaging was performed in participants with a clinical diagnosis of vascular dementia. The high prevalence of vascular dementia probably reflects the inclusion criteria of the study, in which most participants had a final diagnosis of syncope, and syncope is often associated with cardiovascular disease.²⁴ In keeping with this result, the prevalence of a cardiovascular condition irrespective of type was as high as 93%.

The prevalence of an orthostatic mechanism was 10% in 48- to 81-year-old participants in the Evaluation of Guidelines in Syncope Study 2 (after admission to an emergency department for suspected syncope).²⁵ This is much lower than the prevalence of orthostatic syncope (~30%) in the oldest group of GIS participants,²⁶ whose mean age (82) was similar to that of the present study (83). Autonomic disturbance and orthostatic hypotension may often be involved in syncope or falls, particularly in individuals with Parkinson's disease,²⁷ but it was not possible to verify this because of the low prevalence of such participants (6%) in the current study. Almost three-quarters of the participants were receiving antihypertensive drugs (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, antiadrenergic agents, calcium-channel blockers). This may explain why the prevalence of orthostatic syncope was much higher (~50%) than reported in above-cited studies conducted in a general population²⁵ or in older adults without dementia.²⁶ This reinforces the clinical recommendation to

Table 5. Final Diagnosis of Syncope in General Population and According to Most Common Types of Dementia

Cause	All, n = 242	AD, n = 75	VD, n = 107	Mixed, n = 37 ^a	Lewy Body Dementia and Parkinson's Disease, n = 18
					n (%)
Cardiac	33 (13.6)	8 (10.7)	19 (17.8)	6 (18.2)	0 (0.0)
Arrhythmic	25 (10.3)	6 (8.0)	16 (15.0)	3 (8.1)	0 (0.0)
Structural	8 (3.3)	2 (2.7)	3 (2.8)	3 (8.1)	0 (0.0)
Reflex	61 (25.2)	18 (24.0)	25 (23.4)	13 (35.1)	5 (27.8)
Vasovagal	21 (8.7)	8 (10.7)	7 (6.5)	5 (13.5)	1 (5.6)
Situational	26 (10.7)	8 (10.7)	11 (10.3)	6 (16.2)	1 (5.6)
Carotid sinus syndrome	13 (5.4)	2 (2.7)	7 (6.5)	2 (5.4)	2 (11.1)
Atypical	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)
Orthostatic	117 (48.3)	38 (50.7)	53 (49.5)	12 (32.4)	11 (61.1)
Primary autonomic failure	7 (2.9)	2 (2.7)	3 (2.8)	0 (0.0)	2 (11.1)
Secondary autonomic failure	34 (14.0)	7 (9.3)	14 (13.1)	4 (10.8)	9 (50.0)
Drug induced	55 (22.7)	19 (25.3)	27 (25.2)	7 (18.9)	0 (0.0)
Volume depletion	21 (8.7)	10 (13.3)	9 (8.4)	1 (2.7)	0 (0.0)
Unexplained	31 (12.8)	11 (14.7)	10 (9.3)	6 (16.2)	2 (11.1)

^aAlzheimer's disease (AD) and vascular dementia (VD) combined.

routinely assess for orthostatic hypotension in elderly adults with dementia and to reappraise the individual's antihypertensive therapy. At the end of the diagnostic examination, hypotensive drugs were reduced or withdrawn in approximately 50% of cases. Withdrawal of drugs that increase the risk of falling, including hypotensive compounds, was effective in preventing falls in elderly outpatients without dementia.²⁸ Low systolic blood pressure in individuals with hypertension treated with hypotensive drugs was recently found to accelerate cognitive decline in individuals with mild cognitive impairment or mild to moderate dementia²⁹ and to increase mortality in nursing home residents.³⁰ In such individuals, the age-related impairment of brain circulatory autoregulation may dramatically increase the risk of syncope and falls.^{31,32}

Limitations of the Study

Medical history plays a critical role in the diagnosis and risk stratification of individuals with syncope.³³ Thus, the main limitation of the current study is the difficulty in collecting reliable clinical information about the syncope or unexplained falls in individuals with varying degrees of cognitive impairment; 40.4% of participants remembered the event, and witnesses were present in 59.3% of cases, but only 50.3% of witnesses provided information that helped to formulate a diagnosis of syncope.

CONCLUSION

A simplified syncope diagnostic protocol based on ESC guidelines can be used in elderly adults with dementia referred for suspected syncope and unexplained falls. The most important clinical implication of this study is that unexplained falls may mask a diagnosis of syncope or pseudosyncope in almost 50% of cases and that a precise pathogenic mechanism of syncope can be identified in almost 90% of individuals with syncope and dementia. Similarly, the high prevalence of orthostatic syncope in these individuals is clinically relevant and indicates that people should undergo a systematic reappraisal of drugs potentially responsible for orthostatic hypotension.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Tests Performed.

Table S2. Hypotensive Drugs Used in All Participants with a Final Diagnosis of Syncope, Orthostatic Syncope, or Nonorthostatic Syncope.

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