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## Editorial

## Increasing Prevalence of Orthostatic Hypotension as a Cause of Syncope With Advancing Age and Multimorbidity

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During recent years, syncope studies have included an increasing number of older subjects with multimorbidity.<sup>1–4</sup> Moreover, increasing awareness of pathophysiology today allows a more accurate differential diagnosis of this condition.<sup>5</sup> Yet how syncope etiology changes with advancing age and increasing multimorbidity is still unclear. The present paper thus aimed at comparing and discussing the results of 3 multicentre studies, and analysing how syncope etiology changes with age and the presence of chronic conditions, with a specific focus on dementia.

In 2006, the EGSYS-2 study (Evaluation of Guidelines in Syncope Study 2) enrolled 745 subjects aged 48–81 years (mean age 67 years) admitted to the emergency department of 19 hospitals for suspected syncope. Patients were managed according to the recommendations of the European Society of Cardiology guidelines on syncope, and a diagnosis of syncope was confirmed in 671 cases. Of these, 466 ( $\approx 70\%$ ) had reflex syncope, 74 ( $\approx 10\%$ ) had orthostatic syncope, and 96 ( $\approx 15\%$ ) had cardiac syncope; in 35 patients ( $\approx 5\%$ ), syncope was unexplained.<sup>1</sup>

In 2006, the GIS study [Gruppo Italiano Sincope (Italian Group for the Study of Syncope Study)] was carried out, enrolling 231 patients aged 65 years or older (mean age 79 years) consecutively referred to geriatric acute care units and outpatient clinics. The study compared the diagnosis of syncope in patients younger than 75 years to those older than 75 years. A previous diagnosis of dementia was not considered among the inclusion criteria and the study participants reported a mean score of 27 on the Mini-Mental State Examination. In this study, neurally mediated syncope (including reflex, orthostatic, and drug-induced syncope) was most prevalent ( $\approx 70\%$ ), whereas cardiac and unexplained syncope accounted for  $\approx 15\%$  and  $\approx 10\%$  of the episodes, respectively. In  $\approx 5\%$  of the patients, syncope had a multifactorial etiology, but no details were provided concerning the overlapping diagnoses. Reflex syncope (including vasovagal syncope,

situational syncope, and carotid sinus syndrome) was more common in younger patients ( $\approx 60\%$  vs  $\approx 35\%$ ), whereas orthostatic syncope, including drug-induced forms, was more frequent in older ones ( $\approx 35\%$  vs  $\approx 10\%$ ).<sup>2</sup>

The “Syncope and Dementia (SYD) registry” was published in 2016 and was the first study investigating syncope etiology in older patients with dementia. The SYD population included patients from geriatric acute care units and outpatient clinics, with a mean age of 84 years. Participants mainly had vascular dementia and Alzheimer’s disease, while Parkinson’s, dementia with Lewy body, and other forms of dementia were less common. A diagnosis of syncope was confirmed in 242/357 patients:  $\approx 50\%$  orthostatic syncope,  $\approx 25\%$  reflex syncope, and  $\approx 15\%$  cardiac syncope. In  $\approx 10\%$  of the patients, syncope was unexplained. Patients with orthostatic syncope were taking a higher number of drugs and had a higher comorbidity burden as compared to patients with a different syncope mechanism.<sup>3</sup>

The present article analyzes the etiological diagnoses of syncope reported in these 3 large studies. Particularly, we provide a comparison of syncope diagnoses between a representative sample of the general population from the EGSYS-2 study, the older group of patients from the GIS study, and older patients with dementia from the SYD study.<sup>1–3</sup> In all the above studies, syncope was diagnosed in accordance with the European Society of Cardiology guidelines on syncope.<sup>5</sup>

As illustrated in Figure 1, orthostatic syncope was poorly represented in the general population,<sup>1</sup> whereas it was more common in older subjects<sup>2</sup> and was the leading cause of syncope in older patients with dementia.<sup>3</sup>

Syncope and orthostatic hypotension are well-recognized potential complications of intensive blood pressure control in older patients.<sup>6</sup> Interestingly, in the SYD population, drug-induced orthostatic hypotension played a major role in the etiology of syncope, representing the most prevalent cause of orthostatic syncope and  $\approx 25\%$  of all the diagnoses of syncope.<sup>3</sup> The prevalence of drug-induced orthostatic hypotension was lower in the GIS population, causing a fifth of orthostatic syncope episodes and  $\approx 5\%$  of all the diagnoses.<sup>2</sup> The SYD population had a higher burden of comorbidities

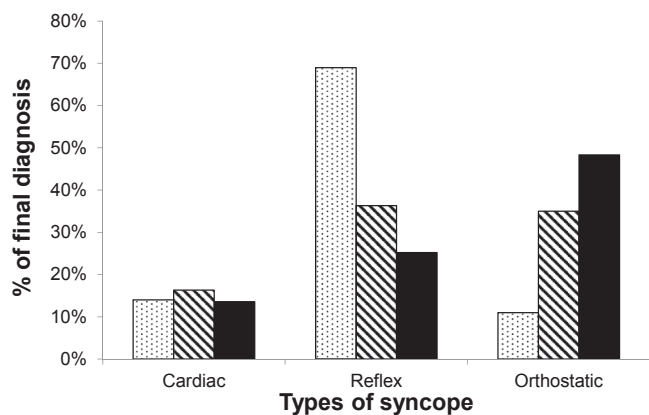
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**Fig. 1.** Prevalence of cardiac, reflex, and orthostatic syncope in Evaluation of Guidelines in Syncope Study 2 (EGSYS-2) study, Italian Group for the Study of Syncope (GIS) study, and Syncope and Dementia (SYD) registry.

□ = Evaluation of Guidelines in Syncope Study 2 (EGSYS-2) study  
 ▨ = Italian Group for the Study of Syncope (GIS) study  
 ■ = Syncope and Dementia (SYD) registry.

and polypharmacy as compared to the GIS study, justifying a higher prevalence of drug-induced orthostatic hypotension. Particularly, the mean number of drugs per patient was higher ( $6 \pm 2$  vs  $4 \pm 2$  drugs per patient in SYD and GIS, respectively) and mainly included antihypertensives ( $\approx 75\%$ ).<sup>2,3</sup>

The relationship between orthostatic syncope and hypotensive drugs has been widely investigated in the SYD population, identifying an association between orthostatic syncope and treatment with nitrates or the combination of angiotensin-converting enzyme inhibitors with diuretics or nitrates.<sup>7</sup> These data highlight the importance of re-evaluating hypotensive therapies in patients with orthostatic syncope, particularly in the presence of dementia. In this regard, it should be considered that a higher blood pressure target is advisable in patients with dementia, given the greater susceptibility to hypotension-related adverse effects.<sup>8</sup>

In addition to polypharmacy, the presence of neurodegenerative diseases (ie, Parkinson's disease), peripheral neuropathies (ie, diabetes), dehydration, malnutrition, and deconditioning should be investigated in patients with orthostatic syncope. In the SYD population, the second most frequent cause of orthostatic syncope was secondary dysautonomia ( $\approx 15\%$ ), followed by volume depletion ( $\approx 10\%$ ) and primary autonomic failure ( $\approx 3\%$ ).<sup>3</sup> Different causes of orthostatic syncope were not illustrated in the GIS and EGSYS-2 studies.

Dementia and orthostatic hypotension frequently coexist, suggesting an association between these clinical entities; however, their causal relationship remains controversial. Orthostatic hypotension is a recognized risk factor for cognitive impairment. Among 3121 patients aged 80 years and older from the Hypertension in the Very Old Trial (HYVET), a baseline orthostatic fall of at least 15 mmHg systolic blood pressure and/or a fall of 7 mmHg diastolic blood pressure was associated with a 36% increased risk of cognitive decline,<sup>9</sup> suggesting a cautious approach to hypertension treatment in these older patients.<sup>10</sup> Moreover, patients with autonomic failure showed a worse performance on cognitive tests.<sup>11</sup> Indeed, hypotension may result in transient or sustained cerebral hypoperfusion, which could be involved in the pathogenesis of cognitive decline<sup>12</sup> because neurodegeneration may develop from cerebral hypoperfusion.<sup>13</sup> Simultaneously, neuronal degeneration occurring in dementia may contribute to neurocardiovascular instability and blood pressure dysregulation, leading to hypotension.<sup>13–15</sup>

Reflex syncope includes a heterogeneous group of conditions characterized by an abnormal and inappropriate activation of cardiovascular reflexes normally involved in blood pressure and heart rate regulation.<sup>16</sup> Reflex syncope usually occurs in association with typical triggering situations, that is, intense emotions or orthostatic stress ("vasovagal syncope"), micturition, gastrointestinal stimulation, or after exercise ("situational syncope"). Carotid sinus syncope is triggered by the mechanical manipulation of the carotid sinuses, and it is diagnosed with the carotid sinus massage. In patients in whom a diagnosis of reflex syncope is suspected but not confirmed by the initial evaluation (medical history, physical examination, orthostatic blood pressure measurements, and electrocardiogram), tilt testing is recommended to reproduce the reflex mechanism.<sup>5</sup>

Conversely to what is expected by the typical bimodal distribution of reflex syncope, it was more common in adults<sup>1</sup> than in older patients—especially those with dementia<sup>3</sup>—showing an apparent reversal trend. The current knowledge concerning the pathophysiology of reflex syncope is mainly derived from adolescents and adults and cannot therefore be directly extrapolated to older people with the same condition. It could be hypothesized that reflex syncope in older patients is a more complex disorder, favored by age-related pathophysiological changes, comorbidities, and polypharmacy.<sup>17</sup>

Moreover, the aging process per se is characterized by typical changes in neural control of vascular function, including increased sympathetic/parasympathetic balance and decreased baroreflex sensitivity. On one hand, this can explain orthostatic hypotension on brisk standing, as homeostatic cardio-acceleration in response to stand-up and other stressors can be impaired by a reduced vagal withdrawal on standing,<sup>18</sup> and on the other might be associated with a reduced vasodepressive or cardioinhibitory response on tilt testing.<sup>19</sup>

The sum of mechanisms cited above could justify the low prevalence of reflex and higher risk of hypotensive syncope in older dementia patients included in SYD. In fact, in the SYD population, tilt-induced reflex syncope was mainly characterized by a hypotensive response,<sup>3</sup> indicating a susceptibility to orthostatic stress, which may contribute to syncope irrespective of its main etiology.<sup>20</sup>

Finally, we cannot exclude that the prevalence of reflex syncope may have been underestimated in the SYD study. Indeed, history collection is usually difficult in patients with dementia, who are unable to provide a detailed description of spontaneous episodes; in addition, tilt testing and carotid sinus massage have been performed in a reduced number of patients in this particular population.<sup>3</sup>

Cardiac syncope had a similar prevalence in the 3 samples (13%–15%), as well as structural heart disease and abnormal electrocardiogram findings, which could be associated with arrhythmic syncope.<sup>1–3</sup> The prevalence of cardiac syncope did not show any increase with age, probably because of the survival bias associated with high morbidity and mortality of cardiac syncope.<sup>20</sup>

In conclusion, data from these large studies indicate that advanced age and cognitive impairment should not prevent clinicians from providing the patient with appropriate diagnostic assessment and treatment for syncope. Indeed, in older patients with syncope, a thorough diagnostic assessment is able to identify specific causes in the vast majority of cases, thus potentially allowing for events recurrence. Particularly, the prevalence of orthostatic syncope increases with advancing age and dementia, and the causes, first of all polypharmacy, are often reversible and thus potentially amenable to treatment.

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