Clinical Investigations

Unexplained Syncope: Implications of Age and Gender on Patient Characteristics and Evaluation, the Diagnostic Yield of an Implantable Loop Recorder, and the Subsequent Treatment

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ABSTRACT

Background: Syncope is a common clinical problem with a variety of underlying mechanisms, some of which occur more frequently in 1 of the sexes or at a certain age.

Hypothesis: There may be clinically significant age- and gender-related differences in patients with unexplained syncope.

Methods: Five hundred seventy patients (54% women) with unexplained syncope received an implantable loop recorder (ILR) and were followed until diagnosis or for at least 1 year.

Results: Women were older and more prone to severe trauma during syncope (40.8% vs 29.9%, $P = 0.007$), and hospitalization was more common at ≥65 years ($P = 0.003$) without gender difference. Muscle spasms or grand mal seizures were more common in men and at <65 years old. Carotid sinus pressure, exercise testing, coronary angiography and magnetic resonance imaging/computed tomography scans were more commonly performed in men, whereas no test was more common in women. Tilt testing, exercise test, electroencephalography, and neurological or psychiatric evaluation were more common at ≥65 years. There were no age- or gender-related differences in the diagnostic yield of the ILR, whereas patients ≥65 years old more often received specific treatment based on ILR data.

Conclusions: Gender and/or age had relevance for the clinical evaluation, rate of recurrence, and subsequent specific treatment but not for the diagnostic yield of the ILR.

Introduction

Syncope is a common clinical problem with a variety of underlying mechanisms,[1–6] some of which occur more frequently in 1 of the sexes or at a certain age in life.[3,7–12] A careful medical history, often in combination with electrocardiography (ECG) at rest, a Holter recording, carotid sinus pressure, and/or orthostatic blood pressure measurement, suggested as an initial diagnostic workup,[5] is likely to explain the cause of syncope.[13] However, despite even extensive evaluation, about one-third of patients do not receive a diagnosis, and their syncope is then called unexplained.[1,11,13,14]

The Place of Reveal In the Care pathway and Treatment of patients with Unexplained Recurrent syncopE (PICTURE)[15] is an observational international multicenter registry. It recruited patients who recently received or were about to receive an implantable loop recorder (ILR) because of unexplained syncope. This analysis of the PICTURE data describes the role of age and gender in patient characteristics, the diagnostic yield of an ILR, and the subsequent specific treatment.

Methods

Patients had unexplained syncope as judged by the investigators. Altogether, 650 patients were enrolled, and 570 of them received a Reveal Plus, DX, or XT device (Medtronic Inc., Minneapolis, MN) and were followed until

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diagnosis or for at least 1 year. The enrolment data included the syncope history in the previous 2 years, the total number of syncope events during the lifetime of the patient, the clinical characteristics of syncope, the number of syncope episodes with severe trauma (defined as fracture or injury with bleeding), other medical history, the type and number of different specialists seen in relation to syncope, the specialty of the physician who referred for ILR implant, and the type and number of diagnostic tests. Follow-up was per clinical practice and clinical characteristics of recurrent syncope, severe trauma, and admissions to the emergency room and/or hospitalizations, and tests performed were recorded. A cutoff point at 65 years was used with the hypothesis that cardiac etiology would be more frequent above 65 years and noncardiac etiology more common below 65 years of age. Informed consent was obtained from each patient and the study protocol conforms to the ethical standards of the 1975 Declaration of Helsinki and was approved by the relevant human research committees.

Statistical Methods

For patients to be included in the analysis, the implant/discharge visit together with a recurrence visit or a 1-year follow-up visit was required. If patients had no event, the last visit that took place during the prespecified follow-up period was included. Descriptive statistics were used, and for quantitative variables such as age, the mean and standard deviation or mean and interquartile range (IQR) were calculated as appropriate. For qualitative variables, counts and percentages were calculated. Time-to-event outcomes were described using Kaplan-Meier curves, with the day of implant as time 0. When the ILR played a major role in determining the mechanism and/or cause of syncope, the diagnosis was defined as "ILR-guided."

Results

Five hundred seventy patients were enrolled, 306 (54%) were women and 264 (46%) were men, with a mean age of 62 ± 18 and 60 ± 17 years, respectively. Women more often had syncope associated with severe trauma than men (41% vs 30%, $P = 0.007$) without any relation to age. Hospitalization because of syncope was of similar frequency in men and women (71% vs 69%, not significant) but was more common in patients ≥65 years than in younger patients ($P = 0.03$). The actual age at first syncope was 41 ± 17 vs 69 ± 13 years ($P < 0.0001$) in the <65 and ≥65 year groups, respectively. The average follow-up time was 10 ± 6 months. There were 3 age peaks in men, at about 20, 60, and 80 years, the latter being the highest. The curve for women was similar, except that the latter 2 peaks seem to have merged into 1 somewhat delayed peak at 60 to 80 years (Figure 1).

The number of syncope episodes per year before ILR implant was lower in the ≥65 years group, and the interval between the first and latest episode was longer. Syncope without prodrome was more common in older patients. Comorbidities were more common in patients ≥65 years, with only diabetes being more common in men than in women. Patient demographics are shown in Table 1.

Men and women differed as to how many and what kind of physicians they saw (Table 1) and the tests they

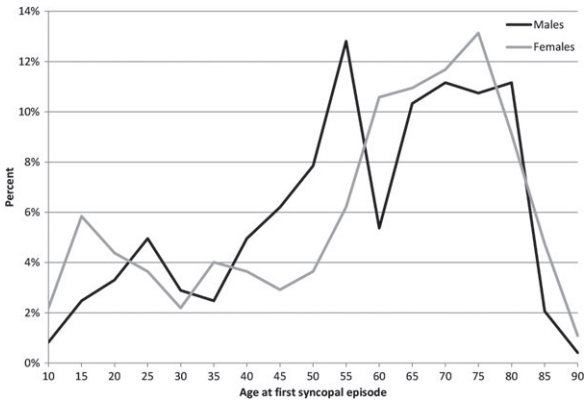

Figure 1. Distribution of age at first syncope. Note the difference between the sexes in the age span of 40 to 55 years.

underwent. There was no indication that women were less investigated once they met a physician. Men and women underwent a median of 13 (IQR, 9–20) and 12 (IQR, 9–20) tests, respectively. The median number of tests was similar in men and women <65 or ≥65 years (Table 2).

12-Lead Baseline ECG

Because symptoms vs ECG correlation was required for a confirmation of the syncope mechanism, patients with asymptomatic arrhythmias in their baseline ECG were eligible for inclusion. The baseline ECG may reflect later symptoms and findings.[16–23] There was no difference in bradycardias <40 bpm, but second-degree atrioventricular block was more common in patients <65 years old, especially in men. Atrial and supraventricular tachycardia, including atrial fibrillation, were more common in patients ≥65 years old and in women. The proportion of patients with other ECG abnormalities was higher in patients ≥65 years old, and the proportion of patients without any ECG abnormality was higher in those <65 years old, with no difference between men and women.

Body Position and Activity at the Time of Syncope

The body position at the beginning of a syncope episode was different in women and men ($P = 0.013$). Syncope when standing was more common in the younger women, syncope while sitting or in the supine position more common in men, irrespective of age. There were differences in the level of activity at the beginning of an episode ($P = 0.049$). Women had events more often during exercise than men (29% vs 21%), whereas men had events more often at rest (57% vs 47%) or after effort (6% vs 4%). There was no association between age and body position or activity at the beginning of an episode.

Neurological Symptoms During Syncope

The protocol asked the investigators to record event-related "muscle spasms, 1 sided," "muscle spasms, 2 sided," and "grand mal," and all of these were or tended to be more common in men (2.7% vs 0.3%, $P = 0.028$; 4.9% vs 2.0%, $P = 0.061$; and 3.0% vs 0.7%, $P = 0.05$, respectively). "Other

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Table 1. Patient Characteristics by Age and Gender

	Male <65 Years (N = 136)	Female <65 Years (N = 141)	Male ≥65 Years (N = 128)	Female ≥65 Years (N = 165)	Total Subjects (N = 570)
Clinical features of syncope					
Hospitalized because of syncope	86 (63.2%)	91 (64.5%)	96 (75.0%)	126 (76.4%)	399 (70.0%)
Any severe trauma (eg, fractures, hemorrhage)	39 (28.7%)	53 (37.6%)	40 (31.3%)	72 (43.6%)	204 (35.8%)
Clinical features of last episode					
Position at the beginning of the episode					
Supine	10 (7.4%)	13 (9.2%)	17 (13.3%)	12 (7.3%)	52 (9.1%)
Sitting	47 (34.6%)	24 (17.0%)	40 (31.3%)	43 (26.1%)	154 (27.0%)
Standing	54 (39.7%)	83 (58.9%)	57 (44.5%)	80 (48.5%)	274 (48.1%)
Unknown	24 (17.6%)	17 (12.1%)	14 (10.9%)	28 (17.0%)	83 (14.6%)
Activity at the beginning of the episode					
Rest	69 (50.7%)	62 (44.0%)	81 (63.3%)	82 (49.7%)	294 (51.6%)
During effort	31 (22.8%)	42 (29.8%)	25 (19.5%)	46 (27.9%)	144 (25.3%)
After effort	7 (5.1%)	9 (6.4%)	8 (6.3%)	4 (2.4%)	28 (4.9%)
Unknown	26 (19.1%)	25 (17.7%)	13 (10.2%)	33 (20.0%)	97 (17.0%)
Symptoms during the episode					
Muscle spasms (one sided)	6 (4.4%)	1 (0.7%)	1 (0.8%)	0 (0.0%)	8 (1.4%)
Muscle spasms (two sided)	7 (5.1%)	4 (2.8%)	6 (4.7%)	2 (1.2%)	19 (3.3%)
Grand mal	6 (4.4%)	2 (1.4%)	2 (1.6%)	0 (0.0%)	10 (1.8%)
Other muscle spasms	4 (2.9%)	6 (4.3%)	2 (1.6%)	2 (1.2%)	14 (2.5%)
Transpiration	23 (16.9%)	22 (15.6%)	14 (10.9%)	14 (8.5%)	73 (12.8%)
Cyanosis	5 (3.7%)	8 (5.7%)	2 (1.6%)	4 (2.4%)	19 (3.3%)
Angina pectoris	6 (4.4%)	5 (3.5%)	3 (2.3%)	9 (5.5%)	23 (4.0%)
Palpitations	18 (13.2%)	33 (23.4%)	7 (5.5%)	18 (10.9%)	76 (13.3%)
Dizziness	48 (35.3%)	45 (31.9%)	30 (23.4%)	40 (24.2%)	163 (28.6%)
Dyspnea	4 (2.9%)	16 (11.3%)	3 (2.3%)	10 (6.1%)	33 (5.8%)
Fatigue	25 (18.4%)	25 (17.7%)	18 (14.1%)	27 (16.4%)	95 (16.7%)
Comorbidity					
Hypertension	50 (36.8%)	45 (31.9%)	73 (57.0%)	109 (66.1%)	277 (48.6%)
Diabetes	13 (9.5%)	7 (5.0%)	34 (26.6%)	30 (18.1%)	84 (14.7%)
Parkinson's disease	0 (0.0%)	0 (0.0%)	2 (1.6%)	0 (0.0%)	2 (0.4%)
Transient ischemic attack	4 (2.9%)	3 (2.1%)	8 (6.3%)	5 (3.0%)	20 (3.5%)
Stroke	8 (5.9%)	5 (3.5%)	11 (8.6%)	13 (7.9%)	37 (6.5%)
Other	11 (8.1%)	13 (9.2%)	3 (2.3%)	9 (5.5%)	36 (6.3%)
Structural heart disease					
Cardiomyopathy	3 (2.2%)	4 (2.8%)	7 (5.5%)	4 (2.4%)	18 (3.2%)
Valvular heart disease	3 (2.2%)	6 (4.3%)	9 (7.0%)	12 (7.3%)	30 (5.3%)
Coronary artery disease	11 (8.1%)	8 (5.7%)	35 (27.3%)	30 (18.2%)	84 (14.7%)

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Table 1. Continued

	Male <65 Years (N = 136)	Female <65 Years (N = 141)	Male ≥65 Years (N = 128)	Female ≥65 Years (N = 165)	Total Subjects (N = 570)
Other	9 (6.6%)	5 (3.5%)	5 (3.9%)	10 (6.1%)	29 (5.1%)
Baseline ECG findings					
Asystole ≥3 seconds	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Atrial tachycardia	1 (0.7%)	4 (2.8%)	8 (6.3%)	12 (7.3%)	25 (4.4%)
Ventricular tachycardia	4 (2.9%)	5 (3.5%)	6 (4.7%)	3 (1.8%)	18 (3.2%)
Supraventricular tachycardia	3 (2.2%)	7 (5.0%)	7 (5.5%)	13 (7.9%)	30 (5.3%)
Bradycardia (<40 bpm)	3 (2.2%)	4 (2.8%)	3 (2.3%)	5 (3.0%)	15 (2.6%)
AV block II	6 (4.4%)	3 (2.1%)	0 (0.0%)	3 (1.8%)	12 (2.1%)
AV block III	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Other	15 (11.0%)	19 (13.5%)	42 (32.8%)	36 (21.8%)	112 (19.6%)
Care pathway					
Profession of first consulted specialist at the hospital					
Cardiologist	59 (43.4%)	59 (41.8%)	51 (39.8%)	63 (38.2%)	232 (40.7%)
Electrophysiologist	3 (2.2%)	4 (2.8%)	2 (1.6%)	3 (1.8%)	12 (2.1%)
Cardiothoracic surgeon	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Specialist for internal diseases	25 (18.4%)	17 (12.1%)	24 (18.8%)	34 (20.6%)	100 (17.5%)
Emergency medicine	28 (20.6%)	24 (17.0%)	33 (25.8%)	48 (29.1%)	133 (23.3%)
Imaging and Radiologist	1 (0.7%)	1 (0.7%)	0 (0.0%)	1 (0.6%)	3 (0.5%)
Neurologist	14 (10.3%)	27 (19.1%)	14 (10.9%)	8 (4.8%)	63 (11.1%)
All specialists seen in relation to syncope					
General practitioner	89 (65.4%)	90 (63.8%)	72 (56.3%)	106 (64.2%)	357 (62.6%)
Cardiologist	126 (92.6%)	132 (93.6%)	117 (91.4%)	146 (88.5%)	521 (91.4%)
Electrophysiologist	36 (26.5%)	38 (27.0%)	41 (32.0%)	51 (30.9%)	166 (29.1%)
Cardiothoracic surgeon	0 (0.0%)	1 (0.7%)	2 (1.6%)	0 (0.0%)	3 (0.5%)
Specialist for internal diseases	46 (33.8%)	47 (33.3%)	50 (39.1%)	71 (43.0%)	214 (37.5%)
Emergency medicine	45 (33.1%)	44 (31.2%)	51 (39.8%)	67 (40.6%)	207 (36.3%)
Imaging and Radiologist	21 (15.4%)	29 (20.6%)	26 (20.3%)	28 (17.0%)	104 (18.2%)
Neurologist	73 (53.7%)	70 (49.6%)	66 (51.6%)	61 (37.0%)	270 (47.4%)
Last referral					
General practitioner	13 (9.6%)	11 (7.8%)	9 (7.0%)	14 (8.5%)	47 (8.2%)
Cardiologist	72 (52.9%)	90 (63.8%)	78 (60.9%)	106 (64.2%)	346 (60.7%)
Electrophysiologist	19 (14.0%)	20 (14.2%)	11 (8.6%)	14 (8.5%)	64 (11.2%)
Cardiothoracic surgeon	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.2%)
Specialist for internal diseases	15 (11.0%)	7 (5.0%)	8 (6.3%)	20 (12.1%)	50 (8.8%)
Emergency medicine	7 (5.1%)	4 (2.8%)	11 (8.6%)	5 (3.0%)	27 (4.7%)
Imaging and Radiologist	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.6%)	2 (0.4%)
Neurologist	8 (5.9%)	5 (3.5%)	8 (6.3%)	2 (1.2%)	23 (4.0%)

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Table 2. Burden of Diagnostic Test by Age and Gender

Subject Characteristics	Male <65 Years (N = 136)	Female <65 Years (N = 141)	Male ≥65 Years (N = 128)	Female ≥65 Years (N = 165)	Total Subjects (N = 570)
Total no. of tests, median	13	14	13	11	13
25th–75th percentile	10–22	9–22	8–19	8–18	9–20
Previous diagnostic tests performed before Reveal implant					
No tests performed	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.2%)
Standard ECG	134 (98.5%)	140 (99.3%)	124 (96.9%)	158 (95.8%)	556 (97.5%)
Orthostatic blood pressure measurements	59 (43.4%)	73 (51.8%)	66 (51.6%)	77 (46.7%)	275 (48.2%)
Carotid sinus massage	57 (41.9%)	44 (31.2%)	51 (39.8%)	53 (32.1%)	205 (36.0%)
Basic laboratory tests	120 (88.2%)	120 (85.1%)	110 (85.9%)	138 (83.6%)	488 (85.6%)
Ambulatory Holter monitoring	86 (63.2%)	101 (71.6%)	86 (67.2%)	109 (66.1%)	382 (67.0%)
Tilt test	51 (37.5%)	61 (43.3%)	45 (35.2%)	44 (26.7%)	201 (35.3%)
Electrophysiology testing	34 (25.0%)	35 (24.8%)	38 (29.7%)	37 (22.4%)	144 (25.3%)
Exercise testing	81 (59.6%)	78 (55.3%)	72 (56.3%)	66 (40.0%)	297 (52.1%)
Echocardiography	113 (83.1%)	123 (87.2%)	114 (89.1%)	140 (84.8%)	490 (86.0%)
External loop recording	18 (13.2%)	20 (14.2%)	8 (6.3%)	21 (12.7%)	67 (11.8%)
In-hospital ECG monitoring	74 (54.4%)	71 (50.4%)	72 (56.3%)	94 (57.0%)	311 (54.6%)
Coronary angiography	37 (27.2%)	27 (19.1%)	40 (31.3%)	29 (17.6%)	133 (23.3%)
Electroencephalography	57 (41.9%)	68 (48.2%)	49 (38.3%)	48 (29.1%)	222 (38.9%)
MRI/CT scan	75 (55.1%)	66 (46.8%)	61 (47.7%)	65 (39.4%)	267 (46.8%)
Neurological or psychiatric evaluation	72 (52.9%)	71 (50.4%)	62 (48.4%)	65 (39.4%)	270 (47.4%)
Other test(s) performed	9 (6.6%)	19 (13.4%)	19 (14.8%)	20 (12.1%)	67 (11.7%)
Diagnostic tests resulted in a (suspected) diagnosis					
Standard ECG	21 (15.4%)	22 (15.6%)	22 (17.2%)	28 (17.0%)	93 (16.3%)
Orthostatic blood pressure measurements	12 (8.8%)	12 (8.5%)	15 (11.7%)	18 (10.9%)	57 (10.0%)
Carotid sinus massage	12 (8.8%)	8 (5.7%)	9 (7.0%)	13 (7.9%)	42 (7.4%)
Basic laboratory tests	16 (11.8%)	11 (7.8%)	16 (12.5%)	15 (9.1%)	58 (10.2%)
Ambulatory Holter monitoring	23 (16.9%)	15 (10.6%)	20 (15.6%)	23 (13.9%)	81 (14.2%)
Tilt test	11 (8.1%)	12 (8.5%)	10 (7.8%)	10 (6.1%)	43 (7.5%)
Electrophysiology testing	6 (4.4%)	10 (7.1%)	8 (6.3%)	11 (6.7%)	35 (6.1%)
Exercise testing	14 (10.3%)	11 (7.8%)	10 (7.8%)	5 (3.0%)	40 (7.0%)
Echocardiography	16 (11.8%)	13 (9.2%)	16 (12.5%)	16 (9.7%)	61 (10.7%)
External loop recording	2 (1.5%)	3 (2.1%)	0 (0.0%)	4 (2.4%)	9 (1.6%)
In-hospital ECG monitoring	13 (9.6%)	13 (9.2%)	12 (9.4%)	18 (10.9%)	56 (9.8%)
Coronary angiography	9 (6.6%)	3 (2.1%)	6 (4.7%)	5 (3.0%)	23 (4.0%)
Electroencephalography	8 (5.9%)	13 (9.2%)	9 (7.0%)	4 (2.4%)	34 (6.0%)
MRI/CT scan	11 (8.1%)	7 (5.0%)	11 (8.6%)	9 (5.4%)	38 (6.7%)
Neurological or psychiatric evaluation	16 (11.8%)	16 (11.3%)	12 (9.4%)	13 (7.9%)	57 (10.0%)
Other test(s) performed	3 (2.2%)	0 (0.0%)	2 (1.6%)	3 (1.8%)	8 (1.4%)

Abbreviations: CT, computed tomography; ECG, electrocardiography, MRI, magnetic resonance imaging.

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muscle spasms" were equally common in men and women (3.3% and 2.6%, respectively). More men than women visited a neurologist, at all or as the last specialist in their care pathway before the ILR implant (53% vs 43%, $P = 0.023$ and 6% vs 2%, $P = 0.031$, respectively). These figures also imply that diagnoses other than neurological causes were found in the majority of patients and/or that a specialist other than a neurologist eventually referred the patient for an ILR (Table 2). Palpitations (17% vs 10%, $P = 0.013$) and dyspnea (9% vs 3%, $P = 0.003$) were more common in women than in men, especially in women <65 years. Similarly, spasms and grand mal seizures were reported more frequently, and a neurologist was more often the first visited specialist in patients <65 years of age.

Syncope Recurrence and Diagnostic Yield of the Implantable Loop Recorder

Recurrent syncope occurred in 218 patients (38%) during follow-up. Women tended to have a lower risk of recurrence during the first year after the ILR implant than men (hazard ratio: 0.75, 95% confidence interval [CI]: 0.56–1.01). There was no difference between men and women in the time from implant to recurrence with a diagnosis (Figure 2). The recurrence rates were 36% and 35% vs 44% and 38% in patients <65 years and ≥65 years old, respectively.

Specific Treatment Based on ILR-Captured Information

Most but not all diagnoses resulted in some kind of specific treatment. Within the 218 patients with recurrence of syncope, a permanent pacemaker was implanted less often in patients <65 years old, with no difference between men and women (Table 3). In patients ≥65 years old, a permanent pacemaker was more frequently implanted in men than in women (39% vs 21%). Drug therapy for syncope was more common in women than in men (10.2% vs 2.2%, $P = 0.034$) and in both age groups. "No specific treatment" was more common in patients <65 years old than in older patients (40% vs 25%, $P = 0.029$), with no difference between men and women.

Discussion

Patients with unexplained syncope had clinically important age- and gender-related differences in their baseline characteristics and clinical presentation of syncope, how many and what kind of physicians they saw, and the type of tests they underwent. The only gender or age-related difference in the treatments prescribed was that drug therapy for syncope was more common in women. "No specific treatment" was equally common in women and men, but was more common in patients <65 years old. The high prevalence of an arrhythmic cause in each gender and age category may be explained by the continuous ECG monitoring during a syncope event.

Unexplained syncope was more common in patients ≥65 years old with no difference between men and women, possibly because a blunted response from the autonomic nervous system could make syncope from benign causes less common by increasing age. Prodromes such as palpitations, dizziness, and sweating were more common at a younger age, suggesting that the syncope episode developed more slowly in younger patients. Notably, 8% of patients with recurrent syncope had documented vasovagal and/or orthostatic mechanisms that had not been detected initially.[15]

Reflex syncope is twice as common in patients under 40 years of age than at 60 years old and above, and most triggers and prodromal signs are more common in younger patients and in women.[12] In a cross-sectional survey of 1925 randomly selected residents of Olmstead County, 45 years of age or older, the estimated prevalence of syncope was 19% and was more common in women (22% vs 15%, $P < 0.001$).[10] The age-specific rates were similar in patients 45 to 54 (20%), 55 to 64 (20%), 65 to 74 (15%), and >75 (21%) years of age. Even when the cause of syncope is known, age-dependent differences in presentation may be found, such as in 1060 consecutive patients with tilt-positive vasovagal syncope, where older persons were less likely to give a typical history, including total loss of consciousness or palpitations, and more likely to present with unexpected falls.[9] When the age and etiology in new-onset syncope were investigated in 502 patients, divided into groups of 36 to 60, 61 to 75, and >75 years of age, clinical features were similar. Syncope recurrence was more common and more often unexplained in the elderly age group (54% vs 37% and 43% in the older and middle-aged groups, $P < 0.01$).[8] In patients with unexplained syncope, the likeliness of a positive response to a tilt test did not change with age or gender, but older patients had an increased frequency of a pure vasodepressor response.[24]

Comorbidities were significantly more common in patients ≥65 years old. By comparison, in a large cohort of women, autonomic dysfunction was more common than in men, and most common in the 15- to 45-year-old range.[7] Symptoms included migraine, chronic fatigue syndrome, gastroparesis, interstitial cystitis, orthostatic hypotension, postural orthostatic tachycardia syndrome, and autonomic neuropathy. A Danish nationwide observational study of 127 508 patients hospitalized for a first-time syncope included patients with a median age of 65 years, 53% of whom were females and were older but with the same proportion of women as in our study population.[25] Cardiovascular disease was present in 28% and was associated with hospital admission for syncope (age 0–29 years: odds ratio [OR]: 5.8, 95% CI: 5.2–6.2; age 30–49 years: OR: 4.4, 95% CI: 4.2–4.6) and age above 80 years (OR: 2.0, 95% CI: 1.9–2.0).

Patients <65 years old more often met an electrophysiologist ($P = 0.046$) as the last specialist before ILR implant, and patients ≥65 years old, especially males, more often visited the emergency room ($P = 0.045$). Males in both age groups visited a neurologist more often than women as the last specialist before the ILR implant. Younger patients underwent a tilt test, an exercise test, and/or electroencephalography (EEG) more frequently. The median number of tests was 13 (IQR, 9–22) and 12 (IQR, 8–18) in the age groups <65 and ≥65 years, respectively ($P = 0.019$). No test was consistently less often prescribed to women, except coronary angiography that was more common in men in both age groups.

Muscle spasms (1- or 2-sided), grand mal, and "other muscle spasms" were more common in patients <65

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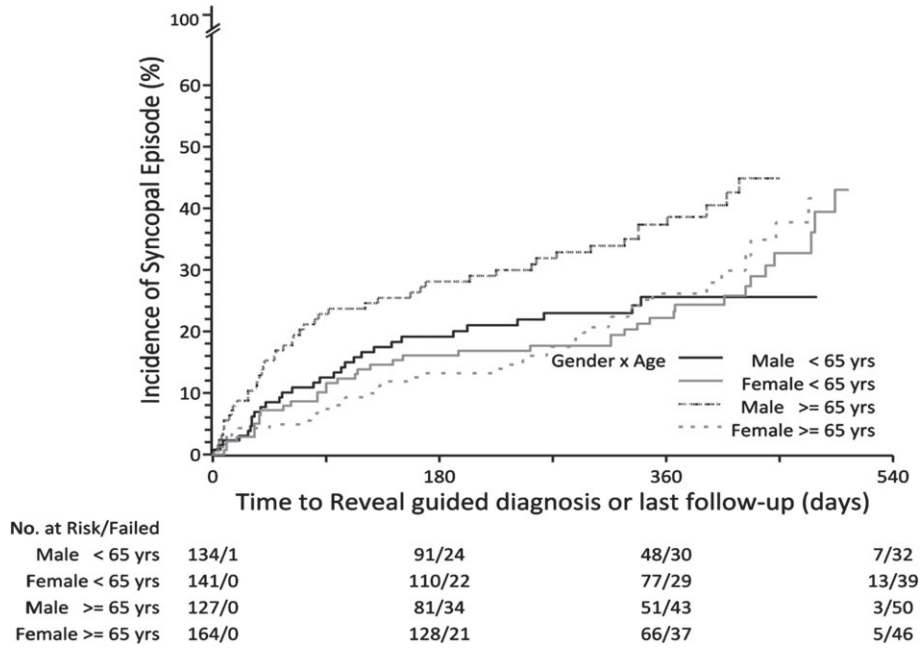

Figure 2. Kaplan-Meier curve showing the time to an implantable loop recorder-guided diagnosis in men and women <65 and ≥65 years of age.

Table 3. Clinical Decisions Made by Age and Gender

Subject Characteristics	Male <65 Years (N = 49)	Female <65 Years (N = 50)	Male ≥65 Years (N = 57)	Female ≥65 Years (N = 62)	Total Subjects (N = 218)
No treatment	21 (42.9%)	17 (34.0%)	9 (15.8%)	18 (29.0%)	65 (29.8%)
PM implant, dual chamber + rate drop response	5 (10.2%)	7 (14.0%)	9 (15.8%)	6 (9.7%)	27 (12.4%)
PM implant, dual chamber	5 (10.2%)	13 (26.0%)	22 (38.6%)	13 (21.0%)	53 (24.3%)
PM implant , single chamber	3 (6.1%)	0 (0.0%)	6 (10.5%)	3 (4.8%)	12 (5.5%)
ICD implant	3 (6.1%)	2 (4.0%)	2 (3.5%)	3 (4.8%)	10 (4.6%)
Antiarrhythmic drug therapy	2 (4.1%)	1 (2.0%)	2 (3.5%)	4 (6.5%)	9 (4.1%)
Catheter ablation	1 (2.0%)	3 (6.0%)	2 (3.5%)	2 (3.2%)	8 (3.7%)
Drug therapy for syncope	2 (4.1%)	4 (8.0%)	1 (1.8%)	7 (11.3%)	14 (6.4%)
Education to use counter pressure maneuvers	2 (4.1%)	2 (4.0%)	0 (0.0%)	2 (3.2%)	6 (2.8%)
Counselling (no specific therapy)	2 (4.1%)	3 (6.0%)	2 (3.5%)	4 (6.5%)	11 (5.0%)
Other	4 (8.2%)	4 (8.0%)	5 (8.8%)	3 (4.8%)	16 (7.3%)

Abbreviations: ICD, implantable cardioverter defibrillator; PM, pacemaker.
Multiple responses are possible.

years old, and EEG was more often performed in these patients. These symptoms were more common in men of both age groups than in women, but EEG was most frequently prescribed in women <65 years old, whereas magnetic resonance imaging/computed tomography and visits to a neurologist/psychiatrist were equally distributed between sexes and age groups. In at least 2 patients a manually activated ECG recording showed the characteristic tonic/clonic muscle contractions of an epileptic seizure. The lesson to learn is to routinely program both activation modes to "on" and to encourage family members and possible bystanders to trigger a recording at the time of symptoms when the patient may be unable to do it.[17]

There was a borderline statistically significant association between age and the risk of syncope recurrence ($P = 0.051$) when tested in a multivariate model with adjustment for covariates. After allowing for imputation of missing values, the association became statistically significant, implying that older patients may have a higher risk of having a recurrence. Using the same analysis technique, no association was found between age and the time to ILR-guided diagnosis. In the clinical decision making, a diagnosis primarily made on ILR

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data was significantly more common in patients ≥65 years old ($P = 0.026$). In another report, the diagnostic yield and rate of ILR-guided therapy of an ILR was higher in patients ≥65 years of age (42% vs 20%) during a 14-month follow-up.[19]

Limitations

This prospective, observational study reflected the patient selection by many physicians that includes some bias, whereas it is representative of real world management of unexplained syncope. A randomized study designed to follow current guidelines might have been scientifically interesting and might have yielded different information. The present study showed that current guidelines were not followed to a great extent, supporting that efforts to make them known and implemented are justified. Also, the results would most probably have been different if the patients in this completely observational study had instead undergone systematic evaluation at a specialized syncope unit. The battery longevity of the ILR models used in this study was 14 months to 3 years, which precluded an analysis of the ILR findings in relation to outcome parameters like all-cause mortality.

Conclusions

Women and men differed in baseline characteristics and clinical presentation of syncope, with women more often having an event standing or during activity than men. There was no gender-related difference in the diagnostic pathway and subsequent treatment of syncope. Regardless of gender and age, the likeliness of an arrhythmia mechanism was high, with an increasing diagnostic yield over time after implant of an ILR. The likelihood of treatment being based on ILR data was highest in patients ≥65 years old.

References

1. Kapoor W, Snustad D, Peterson J, et al. Syncope in the elderly. *Am J Med.* 1986;80:419–428.
2. Cooke J, Carew S, Costelloe A, et al. The changing face of orthostatic and neurocardiogenic syncope with age. *QJM.* 2011;104:689–695.
3. Park J, Jang SY, Yim HR, et al. Gender difference in patients with recurrent neurally mediated syncope. *Yonsei Med J.* 2010;51:499–503.
4. Sheldon R, Hersi A, Ritchie D, et al. Syncope and structural heart disease: historical criteria for vasovagal syncope and ventricular tachycardia. *J Cardiovasc Electrophysiol.* 2010;21:1358–1364.
5. Task Force for the Diagnosis and Management of Syncope; European Society of Cardiology (ESC); European Heart Rhythm Association (EHRA); Heart Failure Association (HFA); Heart Rhythm Society (HRS), Moya A, Sutton R, Ammirati F, et al. Guidelines for the diagnosis and management of syncope (version 2009). *Eur Heart J.* 2009;30:2631–2671.
6. Soteriades ES, Evans JC, Larson MG, et al. Incidence and prognosis of syncope. *N Engl J Med.* 2002;347:878–885.
7. Ulas UH, Chelimsky TC, Chelimsky G, et al. Comorbid health conditions in women with syncope. *Clin Auton Res.* 2010;20:223–227.
8. Roussanov O, Estacio G, Capuno M, et al. New-onset syncope in older adults: focus on age and etiology. *Am J Geriatr Cardiol.* 2007;16:287–294.
9. Duncan GW, Tan MP, Newton JL, et al. Vasovagal syncope in the older person: differences in presentation between older and younger patients. *Age Ageing.* 2010;39:465–470.
10. Chen LY, Shen W-K, Mahoney DW, et al. Prevalence of syncope in a population aged more than 45 years. *Am J Med.* 2006;119:1088.e1–7.
11. Romme JJCM, van Dijk N, Boer KR, et al. Diagnosing vasovagal syncope based on quantitative history-taking: validation of the Calgary Syncope Symptom Score. *Eur Heart J.* 2009;30:2888–2896.
12. Romme JJCM, van Dijk N, Boer KR, et al. Influence of age and gender on the occurrence and presentation of reflex syncope. *Clin Auton Res.* 2008;18:128–133.
13. Kazemi B, Haghjoo M, Arya A, et al. Predictors of response to the head-up tilt test in patients with unexplained syncope or presyncope. *Pacing Clin Electrophysiol.* 2006;29:846–851.
14. Sud S, Klein GJ, Skanes AC, et al. Predicting the cause of syncope from clinical history in patients undergoing prolonged monitoring. *Heart Rhythm.* 2009;6:238–243.
15. Edvardsson N, Frykman V, van Mechelen R, et al. Use of an impantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry. *Europace.* 2011;13:262–269.
16. Sun BC, Hoffman JR, Mangione CM, et al. Older age predicts short-term, serious events after syncope. *J Am Geriatr Soc.* 2007;55:907–912.
17. McGavigan AD, Hood S. The influence of sex and age on response to head-up tilt-table testing in patients with recurrent syncope. *Age Ageing.* 2001;30:295–298.
18. Kanjwal K, Karabin B, Kanjwal Y, et al. Differentiation of convulsive syncope from epilepsy with an implantable loop recorder. *Int J Med Sci.* 2009;6:296–300.
19. Kanjwal K, Kanjwal Y, Karabin B, et al. Clinical symptoms associated with asystolic or bradycardic responses on implantable loop recorder monitoring in patients with recurrent syncope. *Int J Med Sci.* 2009;6:106–110.
20. Brignole M, Menozzi C, Maggi R, et al. The usage and diagnostic yield of the implantable loop-recorder in detection of the mechanism of syncope and in guiding effective antiarrhythmic therapy in older therapy. *Europace.* 2005;7:273–279.
21. Entem FR, Enriquez SG, Cobo M, et al. Utility of implantable loop recorders for diagnosing unexplained syncope in clinical practice. *Clin Cardiol.* 2009;32:28–31.
22. Task Force members, Brignole M, Vardas P, Hoffman E, et al. Indications for the use of diagnostic implantable and external ECG loop recorders. *Europace.* 2009;11:671–687.
23. Armstrong VL, Lawson J, Kamper AM, et al. The use of an implantable loop recorder in the investigation of unexplained syncope in older people. *Age Ageing.* 2003;32:185–188.
24. Galizia G, Abete P, Mussi C, et al. Role of early symptoms in assessment of syncope in elderly people: results from the Italian Group for Study of Syncope in the Elderly. *J Am Geriatr Soc.* 2009;57:18–23.
25. Huth Ruwald M, Lock Hansen M, 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.

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