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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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 \(\geq 65\) 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 \(\geq 65\) years. There were no age- or gender-related differences in the diagnostic yield of the ILR, whereas patients \(\geq 65\) 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, some of which occur more frequently in 1 of the sexes or at a certain age in life. 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, is likely to explain the cause of syncope. However, despite even extensive evaluation, about one-third of patients do not receive a diagnosis, and their syncope is then called unexplained.

The Place of Reveal In the Care pathway and Treatment of patients with Unexplained Recurrent syncope (PICTURE) 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
Comorbidities were more common in patients without prodrome, which was more common in older patients. The average follow-up time was 10 ± 17 years. There were differences in the level of activity between age and body position or activity at the beginning of a syncope episode. The body position at the beginning of a syncope episode was different in men and women (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.

2-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. 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
Table 1. Patient Characteristics by Age and Gender

| Clinical features of syncope                              | Male <65 Years (N = 136) | Female <65 Years (N = 141) | Male ≥65 Years (N = 128) | Female ≥65 Years (N = 165) | Total Subjects (N = 570) |
|-----------------------------------------------------------|---------------------------|----------------------------|--------------------------|---------------------------|--------------------------|
| Hospitalized because of syncope                           | 86 (63.2%)                | 91 (64.5%)                 | 96 (75.0%)               | 126 (76.4%)               | 399 (70.0%)               |
| Any severe trauma (e.g., 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%)                   | 2 (1.6%)                 | 0 (0.0%)                  | 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%)               |
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

| Condition                        | Male <65 | Female <65 | Male ≥65 | Female ≥65 | Total Subjects |
|----------------------------------|----------|------------|----------|------------|----------------|
| 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 | Male <65 Years (N = 136) | Female <65 Years (N = 141) | Male ≥65 Years (N = 128) | Female ≥65 Years (N = 165) | Total Subjects (N = 570) |
|--------------------------------------------------------|--------------------------|----------------------------|--------------------------|----------------------------|--------------------------|
| 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

| Profession             | Male <65 Years (N = 136) | Female <65 Years (N = 141) | Male ≥65 Years (N = 128) | Female ≥65 Years (N = 165) | Total Subjects (N = 570) |
|------------------------|--------------------------|----------------------------|--------------------------|----------------------------|--------------------------|
| 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

| Profession             | Male <65 Years (N = 136) | Female <65 Years (N = 141) | Male ≥65 Years (N = 128) | Female ≥65 Years (N = 165) | Total Subjects (N = 570) |
|------------------------|--------------------------|----------------------------|--------------------------|----------------------------|--------------------------|
| 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%)                |
| 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

| Diagnostic Tests                                               | Male <65 Years (N = 136) | Female <65 Years (N = 141) | Male ≥65 Years (N = 128) | Female ≥65 Years (N = 165) | Total Subjects (N = 570) |
|---------------------------------------------------------------|--------------------------|-----------------------------|--------------------------|---------------------------|-------------------------|
| 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

| Diagnostic Tests                                               | Male <65 Years (N = 136) | Female <65 Years (N = 141) | Male ≥65 Years (N = 128) | Female ≥65 Years (N = 165) | Total Subjects (N = 570) |
|---------------------------------------------------------------|--------------------------|-----------------------------|--------------------------|---------------------------|-------------------------|
| 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.
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%, \( P < 0.001 \)). 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 likelihood 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 years old.
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, single chamber | 5 (10.2%)  | 13 (26.0%) | 22 (38.6%) | 13 (21.0%) | 53 (24.3%)  |
| ICD implant             | 3 (6.1%)              | 2 (4.0%)                | 2 (3.5%)              | 3 (4.8%)                | 12 (5.5%)              |
| 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.\textsuperscript{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
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 likelihood 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.

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