**SUPPLEMENTARY DATA**

## METHODS

### Study protocol

Patients were systematically managed according to the local clinical protocol, which is based on the recommendations of the European Society of Cardiology (ESC) syncope guidelines.[1,2]

In summary, the diagnostic protocol for syncope in this population is based on 3 phases or steps. Step 1, prior to the patients' inclusion in the study, consists of the initial assessment in the emergency department. A clinical history and physical examination are performed in a systematic manner, including testing for orthostatic hypotension and carotid sinus massage (if not contraindicated), general bloodwork, chest x-ray and 12-lead ECG, as well as 12-24-hour telemetry monitoring and a transthoracic echocardiogram (in cases where no prior echocardiogram from the last 6 months is available). Those patients with no definitive or highly probable diagnosis are then considered unexplained syncope, and these patients are admitted to the hospital with continuous ECG monitoring. Other complementary diagnostic tests such as exercise stress testing, myocardial perfusion gamma scan or cardiac magnetic resonance imaging are carried out at the treating clinician's discretion in line with the suspected diagnosis and applicable recommendations. Step 2 involves hospital admission with continuous ECG monitoring and an invasive electrophysiology study. Step 3 involves implanting an ICM with subsequent clinical monitoring.

### Treatment and clinical follow-up

The syncope was treated according to the clinical practice guidelines in line with the confirmed etiology.[1] In patients with syncope secondary to a conduction disorder, the implantation of a cardiac stimulation device was indicated. In patients with syncope secondary to ventricular tachycardia, defibrillator implantation was indicated. The device type (pacemaker, defibrillator, or resynchronizer), as well as treatments such as ablation, antiarrhythmic drugs or angioplasty were discussed within the Heart Team and were individualized according to the patient's functional status, the prior degree of heart failure, and patient preferences. In addition, all patients were educated on syncope and lifestyle changes to prevent and treat reflex syncope. After hospital discharge, patients were followed up in the outpatient cardiology clinic at least twice a year, and those who had received a cardiac device were also followed up with the corresponding remote function.

**Electrophysiology study**

Two femoral venous accesses were gained and 2 tetrapolar catheters (Supreme, Abbott, St Jude Medical, St Paul, Minnesota) were used for basic measurements, atrial stimulation, and ventricular stimulation. Sinus node recovery time was obtained after 30 sec of atrial pacing at 600 and 500 milliseconds (msec), and the highest value was corrected by baseline heart rate. The programmed ventricular stimulation protocol used up to 3 extrastimuli delivered after 8 paced ventricular cycle lengths at 600, 500 and 400 msec from the right ventricular apex and outflow tract in the event that no sustained VT was induced prior to this.

In patients with baseline conduction disturbances where the HV interval was < 70 msec, a class I drug (procainamide 10 mg/kg or flecainide 2 mg/kg intravenously) was administered. Continuous monitoring of the HV interval and atrial pacing were performed during the class I drug infusion and for 10 minutes after the infusion.

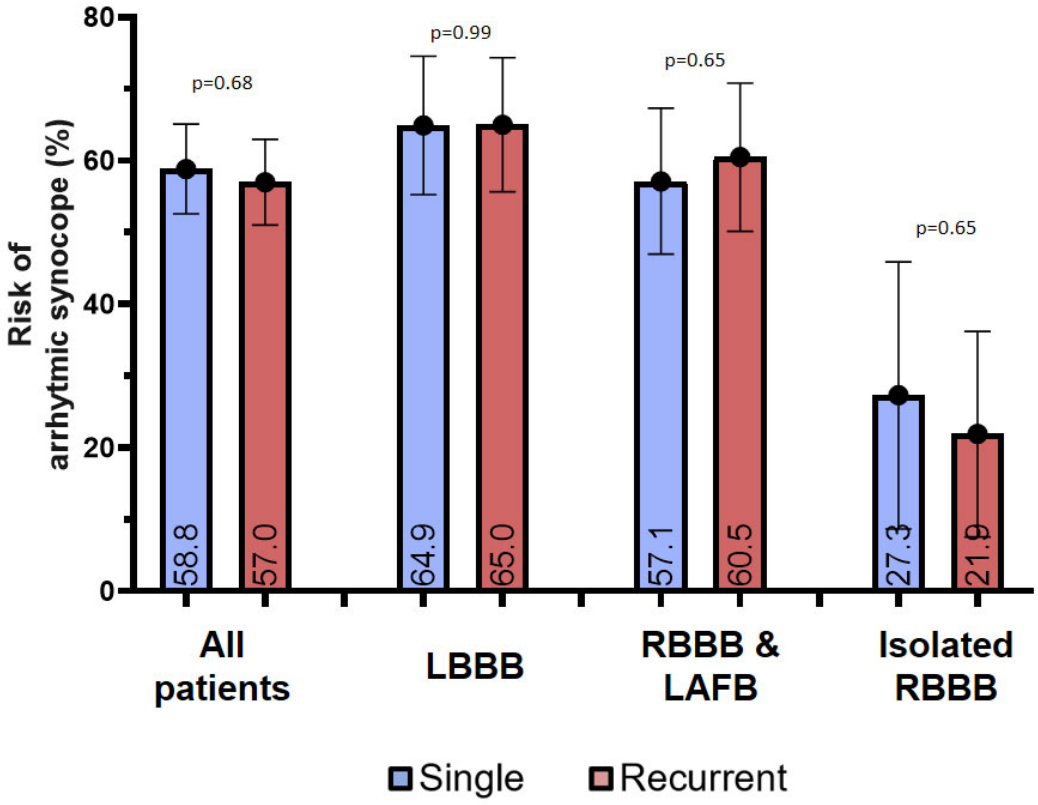
EPS was considered positive according to current ESC guidelines[1] in the following cases: *a)* baseline HV interval ≥ 70 msec or ≥ 100 msec after class I drug administration; *b)* second or third-degree infra- or intra-Hisian block (with pacing cycle length above 400 msec) before or during incremental atrial pacing or after class I drug administration; *c)* induction of sustained VT.

**Monitoring with implantable cardiac monitor**

In step 3, a Reveal XT (in patients included before 2014) or Linq (Medtronic, Inc, United States) device was implanted. The implantation was performed under local anesthetic at the primary site recommended by the manufacturer (fourth left intercostal space). The patients were instructed on how to use it and were provided with a device for remote monitoring (Medtronic Carelink,' United States). The ICM was programmed with the settings for syncope.

ICM monitoring was considered diagnostic in the event of being able to correlate recurrence of syncope or presyncope with the electrocardiographic trace of the ICM, or when the following rhythm disorders were documented in an asymptomatic patient: complete or advanced AV block, asystole lasting > 3 seconds while the patient was awake, or the presence of sustained VT.

**Figure 1 of the supplementary data.** Risk of arrhythmic syncope according to the type of complete bundle branch block and by groups.




LAFB, left anterior fascicular block; LBBB, left bundle branch block; RBBB, right bundle branch block.

**Table 1 of the supplementary data.** Definitions of etiology of syncope

| Syncope diagnosis [1] | Definition | |
|---|---|---|
| *Vasovagal syncope* | Certain | Precipitated by emotional distress or orthostatic stress and associated with typical prodrome |
| | Highly probable | Associated with typical prodrome but without a clear trigger, or associated with a typical trigger with minimal prodrome<br><br>or<br><br>ECG recording in the ICM suggestive of reflex origin (type 1A, 1B,2 of the ISSUE classification) |
| *Carotid sinus hypersensitivity* | Certain | Syncope is reproduced in the presence of asystole > 3 seg and/or fall in systolic BP > 50 mmHg during CSM |
| | Highly probable | Presence of asystole > 3 seg and/or fall in systolic BP > 50 mmHg during CSM without reproducing the syncope |
| *Orthostatic syncope* | Certain | Occurs after standing up and there is documentation of symptomatic orthostatic hypotension (OH) in active standing test |
| | Highly probable | Occurs after standing up and there is documentation of asymptomatic OH in the active standing test<br><br>or<br><br>Occurs after standing and the ECG recording in the ICM is compatible with OH response (type 3 or type 4A of ISSUE classification) |
| *Arrhythmic syncope* | Certain | Clear correlation between arrhythmic event and syncope, or diagnostic findings in the EPS: HV interval ≥ 70 msec or ≥ 100 msec after class I drug challenge, advanced AV block, induction of VT, or SVT that reproduces the symptoms |
| | Highly probable | Documentation of asymptomatic advanced AV block, asystole > 3 secs (except during sleep), SVT or VT. SNRTc > 525 ms in the EPS+ documented sinus pauses on ECG monitoring |
| *Advanced AVB/severe conduction disturbances* | Certain | Correlation between type II 2nd degree, 3rd degree or high-grade AVB event and syncope, or diagnostic findings in the EPS: HV interval ≥ 70 msec or ≥ 100 msec after |

| | | |
|---|---|---|
| | | class I drug challenge, intra-Hisian or infra-Hisian block |
| | Highly probable | Documentation of asymptomatic type II 2nd degree, 3rd degree or high-grade AVB |
| *Sinus node dysfunction* | Certain | Clear correlation between sinus pause and syncope |
| | Highly probable | SNRTc > 525 ms in the EPS+ documented sinus pauses on ECG monitoring. Asystole > 3 secs (except during sleep) |
| *Acute coronary syndrome* | Highly probable | Occurs during the acute phase of an ACS, with typical chest pain, acute ischemic ECG changes and/or troponin rise |
| *Exercise low cardiac output* | Highly probable | Occurs during intense exercise such as fast walking, running or dancing in the presence of a ventricular outflow obstruction (like aortic stenosis), without criteria for previous diagnosis |

ACS, acute coronary syndrome; AV, atrio-ventricular; BP, blood pressure; CSM, carotid sinus massage; EPS, electrophysiology study; OH, orthostatic hypotension; SNRTc, corrected sinus node recovery time; SVT, Supraventricular tachycardia; VT, ventricular tachycardia.

**Table 2 of the supplementary data.** Etiological diagnosis achieved in each step of the diagnostic protocol

| | TOTAL | | | | STEP 2 | | | | STEP 3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diagnosis | All patients (n = 503) | Single episode (n = 238) | Recurrent episodes (n = 265) | *P* | All patients (n = 503) | Single episode (n = 238) | Recurrent episodes (n = 265) | *P* | All patients (n = 222) | Single episode (n = 103) | Recurrent episodes (n = 119) | *P* |
| Unknown | 131 (26.0) | 64 (26.9) | 67 (25.3) | .682 | 222 (44.1) | 103 (43.3) | 119 (44.9) | .713 | 131 (59.0) | 64 (62.1) | 67 (56.3) | .378 |
| aAVB/sCD | 258 (51.3) | 126 (52.9) | 132 (49.8) | .483 | 223 (44.3) | 108 (45.4) | 115 (43.4) | .655 | 35 (15.8) | 18 (17.5) | 17 (14.3) | .515 |
| Orthostatic | 43 (8.6) | 15 (6.3) | 28 (10.7) | .088 | 22 (4.4) | 10 (4.2) | 12 (4.5) | .858 | 21 (9.5) | 5 (4.9) | 16 (13.5) | .029 |
| SND | 22 (4.4) | 11 (4.6) | 11 (4.2) | .797 | 3 (0.6) | 1 (0.4) | 2 (0.8) | .627 | 19 (8.6) | 10 (9.7) | 9 (7.6) | .569 |
| Reflex | 17 (3.4) | 9 (3.8) | 8 (3.0) | .637 | 10 (2.0) | 6 (2.5) | 4 (1.5) | .417 | 7 (3.2) | 3 (2.9) | 4 (3.4) | .849 |
| Low cardiac output | 10 (2.0) | 4 (1.6) | 6 (2.3) | | 10 (2.0) | 4 (1.7) | 6 (2.3) | | 0 | 0 | 0 | |
| VT | 7 (1.4) | 2 (0.8) | 5 (1.9) | | 6 (1.2) | 2 (0.8) | 4 (1.5) | | 1 (0.5) | 0 (0) | 1 (0.8) | |
| Fast SVT/AF | 4 (0.8) | 1 (0.4) | 3 (1.1) | | 1 (0.2) | 1 (0.4) | 0 (0) | | 3 (1.4) | 0 (0) | 3 (2.5) | |
| CSH | 3 (0.6) | 1 (0.4) | 2 (0.8) | | 3 (0.6) | 1 (0.4) | 2 (0.8) | | 0 | 0 | 0 | |
| Other | 8 (1.6) | 5 (2.1) | 3 (1.1) | | 3 (0.6) | 2 (0.8) | 1 (0.4) | | 5 (2.3) | 3 (2.9) | 2 (1.7) | |

aAVB/sCD, advanced atrioventricular block or severe conduction disturbances; AF, atrial fibrillation; CSH, carotid sinus hypersensitivity; SND, sinus node disfunction; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

Values are expressed as No. (%).

**Table 3 of the supplementary data.** Type of cardiac device implanted to treat the syncope

| Type of device | Total | Single syncope | Recurrent syncopes |
|---|---|---|---|
| | (n = 295) | (n = 141) | (n = 154) |
| VVI pacemaker | 90 (30.5) | 44 (31.2) | 46 (29.9) |
| DDD pacemaker | 181 (61.4) | 81 (57.5) | 100 (64.9) |
| CRT-pacemaker | 9 (3.1) | 5 (3.6) | 4 (2.6) |
| Single chamber ICD | 3 (1.0) | 1 (0.7) | 2 (1.3) |
| Dual chamber ICD | 3 (1.0) | 3 (2.1) | 0 (0) |
| CRT-ICD | 9 (3.1) | 7 (5.0) | 2 (1.3) |

CRT, cardiac resynchronization therapy; ICD, implantable cardiac defibrillator.

Values are expressed as No. (%).

**Table 4 of the supplementary data.** Baseline characteristics of patients with and without arrhythmic syncope

| Variable | Total (n = 503) | nonarrhythmic syncope (n = 212) | Arrhythmic syncope (n = 291) | *P* |
|---|---|---|---|---|
| *Age, y* | 77.9 [71.0-83.2] | 78.3 [70.3-73.3] | 77.5 [71.6-83.1] | .953 |
| *Age >75 y* | 314 (62.4) | 127 (59.9) | 187 (64.3) | .319 |
| *Female* | 185 (36.8) | 84 (39.6) | 101 (34.7) | .259 |
| *Hypertension* | 391 (77.7) | 162 (76.4) | 229 (78.7) | .544 |
| *Diabetes* | 171 (34.0) | 69 (32.6) | 102 (35.1) | .558 |
| *Dyslipidemia* | 300 (59.6) | 124 (58.5) | 176 (60.5) | .653 |
| *No SHD* | 380 (76.2) | 168 (80.0) | 212 (73.4) | .086 |
| *Ischemic heart disease* | 110 (21.9) | 41 (19.3) | 69 (23.7) | .241 |
| *Old ST-elevation infarction* | 35 (7.0) | 19 (9.0) | 16 (5.5) | .132 |
| *Nonischemic dilated cardiomyopathy* | 22 (4.4) | 8 (3.8) | 14 (4.8) | .578 |
| *History of atrial fibrillation* | 98 (19.5) | 39 (18.4) | 59 (20.3) | .599 |
| *Use of negative chronotropic drugs* | 170 (34.8) | 70 (33.5) | 100 (35.8) | .590 |
| *Recurrent syncope* | 265 (52.7) | 114 (53.8) | 151 (265) | .676 |

| | | | | |
|---|---|---|---|---|
| *Total number of previous syncope* | | | | |
| 0 | 238 (47.3) | 98 (46.2) | 140 (48.1) | .347 |
| 1 | 107 (21.3) | 52 (34.7) | 55 (28.2) | |
| 2 | 63 (12.5) | 29 (2.8) | 34 (19.5) | |
| 3 | 51(10.1) | 18 (15.5) | 33 (19.1) | |
| ≥ 4 | 44 (8.8) | 15 (7.1) | 29 (10.1) | |
| **Characteristics of the syncope** | | | | |
| *Prodrome* | 202 (40.4) | 91 (43.1) | 111 (38.4) | .288 |
| *Severe trauma* | 209 (41.8) | 94 (44.6) | 115 (39.8) | .287 |
| **Echocardiogram** | | | | |
| *EDD, mm* | 47 [43-52] | 47 [43-52] | 47 [43-52] | .401 |
| *ESD, mm* | 30 [26-36] | 30 [25-35] | 31 [27-36] | .044 |
| *Interventricular septum, mm* | 13 [11-15] | 13 [11-14] | 13 [11-15] | .423 |
| *LVEF, %* | 58 [50-62] | 58 [52-62] | 57 [50-62] | .316 |
| *LVEF < 45%* | 78 (16.5) | 30 (15.2) | 48 (17.3) | .543 |
| **ECG on admission** | | | | |
| *Heart rate, bpm* | 70 [60-80] | 75 [65-80] | 70 [60-80] | < .001 |
| *Atrial fibrillation* | 84 (16.8) | 36 (17.1) | 48 (16.7) | .907 |
| *Long PR* | 178 (41.1) | 54 (29.7) | 124 (49.4) | < .001 |
| *QRS duration, msec* | 140 [130-152] | 140 [130-150] | 140 [130-158] | .006 |
| *LBBB morphology* | 194 (38.7) | 68 (32.2) | 126 (43.5) | .011 |
| *Long PR and LBBB* | 57 (11.3) | 11 (5.2) | 46 (15.8) | < .001 |
| *RBBB morphology* | 287 (57.2) | 136 (64.5) | 151 (51.9) | .005 |
| *Isolated RBBB* | 54 (11.1) | 41 (19.9) | 13 (4.6) | < .001 |
| *RBBB and LAFB* | 177 (35.2) | 73 (34.4) | 104 (35.7) | .762 |
| *Long PR and RBBB* | 109 (21.8) | 41 (19.3) | 68 (23.4) | .279 |
| *Long PR, RBBB, and LAFB* | 78 (15.5) | 28 (13.2) | 50 (17.2) | .2214 |

bpm, beats per minute; msec, milliseconds; EDD, end-diastolic diameter; ESD, end-systolic diameter; LAFB, left anterior fascicular block; LBBB, left bundle branch block; RBBB, right bundle branch block; LVEF, left ventricular ejection fraction; SHD, structural heart disease.

Values are expressed as No. (%). The quantitative variables are expressed as medians [interquartile range].

**Table 5 of the supplementary data.** Cox proportional hazards multivariate model to assess the association between recurrent syncopal episodes and the risk of an arrhythmic syncope

| | Factor | HR | HR 95%CI | *P* |
|---|---|---|---|---|
| *Unadjusted* | | | | |
| | *Recurrent syncope* | 0.92 | 0.73-1.16 | .500 |
| | | | | |
| *Adjusted** | | | | |
| | *Recurrent syncope* | 1.06 | 0.81-1.38 | .674 |
| | Female sex | 0.75 | 0.56-1.00 | .056 |
| | Age> 75 years | 1.26 | 0.96-1.66 | .099 |
| | Hypertension | 1.01 | 0.72-1.43 | .934 |
| | Diabetes | 1.00 | 0.75-1.33 | .992 |
| | IHD | 1.17 | 0.84-1.61 | .347 |
| | LVEF< 45% | 1.08 | 0.75-1.57 | .665 |
| | Atrial fibrillation | 1.14 | 0.76-1.72 | .520 |
| | LBBB | 1.66 | 1.27-2.18 | < .001 |
| | Long PR interval | 1.88 | 1.44-2.46 | < .001 |

CI, confidence interval; HR, hazard ratio; IHD, ischemic heart disease; LAFB, left anterior fascicular block; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; RBBB, right bundle branch block.

* Possible interactions between pairs of explanatory variables were checked, and no statistically significant results were found.

**Table 6 of the supplementary data.** Mechanism of syncope recurrence after the diagnosis and appropriate treatment.

| Mechanism | Total | Single syncope | Recurrent syncopes |
|---|---|---|---|
| | (n = 35a) | (n = 13) | (n = 22) |
| Orthostatic | 20 (57.1) | 7 (53.9) | 13 (59.1) |
| Reflex | 3 (8.6) | 2 (15.4) | 1 (4.6) |
| aAVB/sCD | 2 (5.7) | 0 (0) | 2 (9.1) |
| Low cardiac output | 1 (2.9) | 1 (7.8) | 0 (0) |
| VT | 2 (5.7) | 1 (7.7) | 1 (4.6) |
| Fast SVT/AF | 3 (9.6) | 0 (0) | 3 (13.6) |
| SND | 0 | 0 | 0 |
| CSH | 0 | 0 | 0 |
| Pacemaker dysfunction | 2 (5.7) | 1 (7.7) | 1 (4.6) |
| Other | 1 (2.9) | 1 (7.8) | 0 (0) |
| Unknown | 1 (2.9) | 0 (0) | 1 (4.6) |
| Total arrhythmic causes | 7 (20.0) [b] | 1 (7.7) [b] | 6 (27.3) [b] |

aAVB/sCD, advanced atrio-ventricular block or severe conduction disturbances; AF, atrial fibrillation; CSH, carotid sinus hypersensitivity; SND, sinus node disfunction; SVT, supraventricular tachycardia; VT, ventricular tachycardia.
[a] 32 of the 35 patients had a pacemaker implanted.
[b] Comparation between SSG and RSG. *P* = .161.

## REFERENCES

1 Brignole M, Moya A, de Lange FJ, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J* 2018;39:1883-1948.

2 Moya A, Rivas-Gandara N, Perez-Rodón J, et al. Syncope and bundle branch block: Diagnostic approach. Herzschrittmacherther Elektrophysiol. 2018;29:161-165.