Cardiovascular Dysautonomia in older adults. Aetiology, Diagnosis and Health related consequences

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Cardiovascular Dysautonomia in older adults

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Aetiology, Diagnosis and Health related consequences

Ekrem Yasa

LUND UNIVERSITY

DOCTORAL DISSERTATION

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Abstract

INTRODUCTION: The main regulator of heart rate, blood pressure, and maintenance of homeostasis during physiological stress is the cardiovascular part of autonomic nervous system (ANS). Cardiac dysautonomia means malfunctioning of ANS. ReflexsSyncope and orthostatic hypotension (OH) are the most common manifestations of cardiovascular dysautonomia for which the management is still not fully satisfactory.

METHODS AND RESULTS: In STUDY I we aimed to explore the association of hospital admissions due to unexplained syncope with OH and incident cardiovascular (CV) events and mortality. We analysed a population-based prospective cohort of Malmö Diet and Cancer Study consisting of 30 528 individuals (age, 58±8 years; males, 40%). Unexplained syncope admissions were associated with incident coronary events (HR: 1.85, 95% CI 1.49 to 2.30), heart failure (HR: 2.24, 95% CI 1.65 to 3.04), atrial fibrillation (HR: 1.84, 95% CI 1.50 to 2.26), aortic valve stenosis (HR: 2.06, 95% CI 1.28 to 3.32), all-cause (HR: 1.22, 95% CI 1.09 to 1.37) and CV mortality (HR: 1.72, 95% CI 1.23 to 2.42). Hospitalisations for OH were associated with incident stroke (HR: 1.66, 95% CI 1.24 to 2.23), heart failure (HR: 1.78, 95% CI 1.21 to 2.62), atrial fibrillation (HR: 1.89, 95% CI 1.48 to 2.41) and all-cause death (HR: 1.14, 95% CI 1.01 to 1.30),

In STUDY II, we aimed to assess the indications and outcomes of pacing therapy in The Syncope Study of Unselected Population in Malmö (SYSTEMA), a cohort of subjects with initially unexplained syncope. Of a total of 1666 unpaced patients investigated by carotid sinus massage, head-up tilt test (HUT) and ECG monitoring, 106 (6.4%; age, 65 ± 17 years) received a pacemaker. The indications for pacing were found by CSM in 30%, by HUT in 39%, by

implantable loop-recorder (ILR) in 13 % and in ECG in 18 %. Recurrent syncope and/or fall-related fractures were associated with treated hypertension (OR 2.45; 95% CI 1.00 to 6.0), reduced renal function (OR 1.63 per 10 mL/min GFR; 95% CI 1.22 to 2.19) and atrial fibrillation (OR 3.98; 95% CI 1.11 to 14.3).

In STUDY III we used the same study population as in study II and aimed to assess the cause of syncope or orthostatic intolerance in patients with pacemakers. Of 1,705 patients, 39 patients (2.3%; age 65.6 years; 39% women) had a cardiac implantable electronic device at the time of cardiovascular autonomic testing (CAT). A cause could be identified by CV autonomic tests in 36 of the 39 patients, of which OH (n = 16; 41%) and vasovagal syncope (n = 12; 31%) were most common.

In STUDY IV, we studied implantable cardiac monitors (ILR) which have an important role in diagnosing unexplained syncope. In this study we used the same study population as in studies II and III and assessed the outcomes of primary vs delayed ILR implantation after initial syncope evaluation. Patients who underwent CAT and ILR were grouped into those had been primarily implanted with ILR before CAT and those with post-CAT ILR implantation. Primary ILR implantation was associated with more positive CAT compared with delayed ILR implantation, but negative monitoring and pacemaker implantations were not different between the groups. ECG conduction disorders predicted subsequent pacemaker implantation.

CONCLUSIONS: Hospitalised patients with unexplained syncope or OH have higher risk of incident CV disease and death. CAT and prolonged ECG monitoring can identify pacing indications in unexplained syncope and CAT also to a high degree reveal the cause of recurrent syncope and/or orthostatic intolerance in paced patients, in whom OH and vasovagal syncope are common. Combined CAT and ILR monitoring may enhance the diagnostic findings in patients with unexplained syncope and without conduction disturbances on standard ECG, regardless of whether ILR is implanted prior to or after CAT.

Key words

Classification system and/or index terms (if any) Syncope, pacing, cardiovascular autonomic testing

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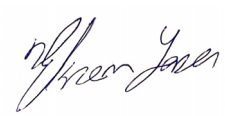
Signature  Date 2022-02-17

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II. Yasa, E., Ricci, F., Holm, H., Persson, T., Melander, O., Sutton, R., Hamrefors, V. & Fedorowski, A. Pacing therapy in the management of unexplained syncope: A tertiary care centre prospective study. Open Heart, 2019.

III. Yasa, E., Ricci, F., Holm, H., Persson, T., Melander, O., Sutton, R., Fedorowski, A. & Hamrefors, V. Cardiovascular Autonomic Dysfunction Is the Most Common Cause of Syncope in Paced Patients. Frontiers in Cardiovascular Medicine 2019 okt 25, I: 6, 154.

IV. Yasa, E., Intzilakis, T., Fabrizio, R., Melander, O., Hamrefors, V., Sutton, R., Fedorowski A. Outcome of primary vs delayed strategy of implanting a cardiac monitor for unexplained syncope: lessons from SYSTEMA cohort. Manuscript

Abbreviations

ANS	autonomic nervous system
HR	heart rate
BP	blood pressure
IST	inappropriate sinus tachycardia
OH	orthostatic hypotension
POTS	postural orthostatic tachycardia syndrome
VVS	vasovagal syncope
HF	heart failure
AF	atrial fibrillation
IHD	ischemic heart disease
HUT-T	head-up tilt test
CAD	coronary artery disease
ECG	electrocardiogram
ATP	adenosine triphosphate
ILR	implantable loop recorder
CAT	cardiac autonomic testing
PM	pacemaker
CIED	cardiac implantable electronic device

Introduction

In order to maintain homeostasis during physiological stress such as exercise and standing upright, the autonomic nervous system (ANS) regulates the heart rate (HR), vascular tone, and circulating blood volume, which results in appropriate control of central and peripheral blood pressure (BP) level (1-5). Thereby, the ANS constantly provides sufficient tissue perfusion with oxygenated blood and secures return of deoxygenated venous blood to the right atrium and ventricle, which, in turn is transported to the lungs(6). Cardiovascular dysautonomia with subsequent malfunction of cardiovascular hemostasis occurs when the ANS fails to function correctly causing maladaptation of the circulatory system. (7-11) (Figure 1).

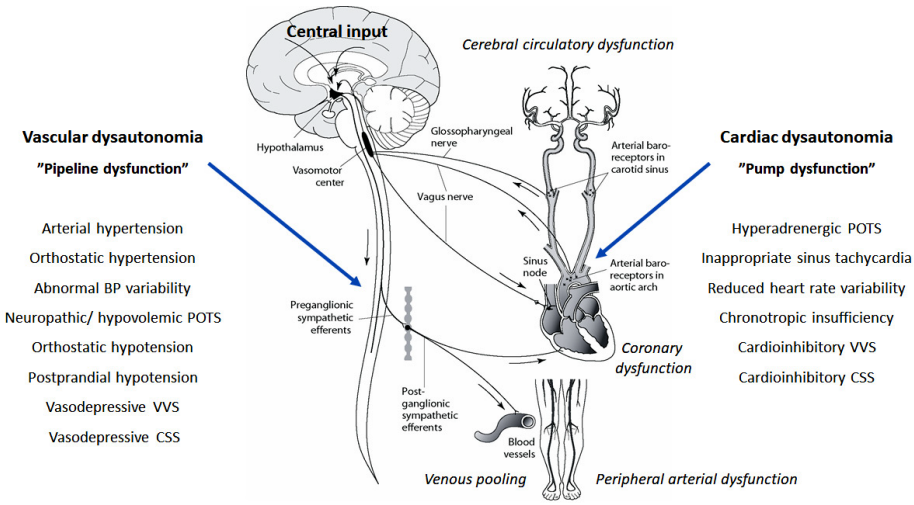

Figure 1. Cardiovascular dysautonomias. Adapted from Feigofsky S, Fedorowski A. Defining Cardiac Dysautonomia – Different Types, Overlap Syndromes; Case-based Presentations. J Atr Fibrillation 2020;13(1):2403. This work is licensed under a Creative Commons Attribution 3.0 Unported License.

Cardiovascular dysautonomia typically presents with various cardiovascular symptoms, fainting, dizziness, palpitations, rapid heartbeats, abnormally low or high BP, fatigue, or deconditioning, where the most common clinical syndromes are reflex syncope, inappropriate sinus tachycardia (IST), and syndromes of orthostatic intolerance: orthostatic hypotension (OH) and postural orthostatic tachycardia syndrome (POTS)(3, 8, 11-17). Some of cardiovascular symptoms are persistent,

such as a tendency to BP fall in OH or tachycardia in POTS, whereas other symptoms may be short-lived and abrupt onset such as reflex syncope of vasovagal type. Different cardiovascular dysautonomias may coexist; patients with OH may have chronotropic incompetence, whereas POTS patients may have IST and recurrent vasovagal syncope (VVS), as the major mechanism of sporadic syncope(13, 18-21). Further, dysautonomias may coexist with primary cardiac diseases. For instance, OH may coexist with heart failure (HF), atrial fibrillation (AF) and ischemic heart disease (IHD), complicating the appropriate management of these conditions, and worsening prognosis.(13, 22-28)

Many different methods can be employed to assess cardiovascular autonomic function such as head-up tilt test (HUT), prolonged ECG monitoring, 24-hour ambulatory BP monitoring, other autonomic tests such as active standing, exercise ECG, deep breathing test, carotid sinus massage or Valsalva maneuver (8, 11, 17, 29-33). These tests are usually available in dedicated units (syncope or dysautonomia units) or at centers where there is access to appropriate diagnostic modalities and expertise. Physicians, cardiologists in particular, are not always aware of cardiovascular dysautonomic disorders as their main clinical focus is usually on primary cardiac diseases such as HF, coronary artery disease (CAD), arrhythmias and hypertension, the latter not even seen as a dysautonomia, which hypertension is in fact, but rather as a potent cardiovascular risk factor(7, 9, 34-38). However, being alert to the possibility of cardiovascular dysautonomia is very important for cardiologists, internists and other specialties including primary care physicians, especially when dealing with patients presenting unusual symptoms and apparently normal vital parameters, laboratory tests, physical examination, and electrocardiogram (ECG). (8, 16, 17, 21, 39, 40)

Syncopal syndromes

Syncope is defined as a transient loss of consciousness due to cerebral hypoperfusion, with a rapid onset and total recovery (16). Syncope may be etiologically divided into three main groups:

-syncope due to vasovagal reflex or other cardiovascular reflexes such as carotid sinus reflex,

-cardiac syncope due to primary heart and great vessel disease, and

-syncope due to autonomic failure i.e. OH. (Figure 2)

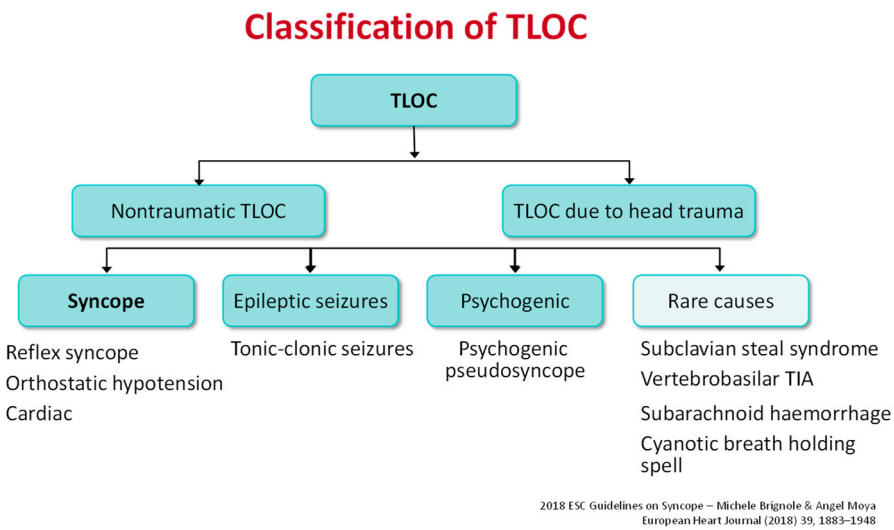

Figure 2. Classification of syncope. Reproduced from (16) with permission from the publisher.

In classical reflex syncope, cardiovascular reflexes become transiently inappropriate while in OH sympathetic efferent activity may be chronically impaired(3, 13, 41). OH is a major manifestation of autonomic failure, and is a frequent finding in the older population, with prevalence ranging between 10 and 35% (13, 42). OH prevalence increases with age and comorbidities, such as neurodegenerative, cardiovascular, metabolic, and renal diseases (13, 42, 43). The presence of OH is longitudinally associated with increased risk of mortality and cardiovascular disease(25, 42). Still, older adults who suffer from unexplained syncope, presyncope or present with signs of chronic cardiovascular dysautonomia, OH and/or reflex syncope are often neglected in epidemiological and interventional studies.(44, 45)

It is important to keep in mind that syncope differs from other forms of transient loss of consciousness (TLOC), which are:

-epilepsy,

-TLOC due to trauma, typically head trauma, and

-psychogenic pseudosyncope. (Figure 2)

The prognostic value of incident syncope and cardiovascular dysautonomia is not clear among otherwise healthy individuals and those with concurrent cardiovascular disease who have been affected by unexplained syncope, recurrent reflex syncope or symptoms of orthostatic hypotension. (46-49) Studies are sparse and often focused only on prognosis of patients with syncope diagnosis i.e. without a control

group unaffected by syncope, and the usual clinical setting is emergency department with all its attendant limitations.(46, 50) Likewise, studies on the prognostic value of recent hospitalization for symptomatic orthostatic hypotension are sparse(47), and larger epidemiological studies based on the discharge diagnosis of OH are lacking.(51) Thus, two major cardiovascular dysautonomic syndromes, reflex syncope and OH, have not been sufficiently studied in relation to how admissions for unexplained or inconclusively diagnosed syncope or OH impact the long-term prognosis, especially in middle-aged/older individuals where the risk of adverse events is higher.

In order to counteract bradycardia in syncope patients, either persistent or paroxysmal, pacemaker (PM) implantation is the most effective therapy (52-54). Current European Society of Cardiology Syncope Guidelines(16), corroborated by recent European pacing guidelines (55) recommend pacemaker therapy in older, medication-resistant patients (>40 years) with recurrent reflex syncope, history of syncope-related trauma, and lack of warning signs. (Figure 3).

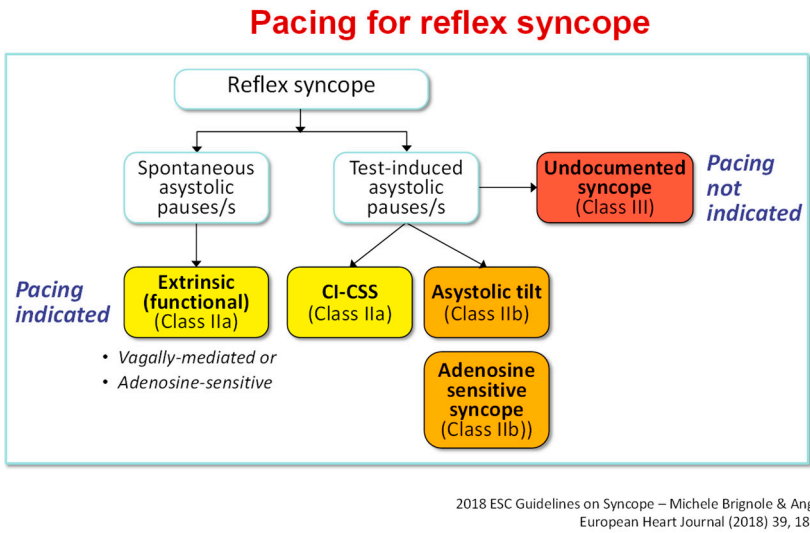

Figure 3. Pacing for reflex syncope. Reproduced from (16) with permission from the publisher.

To select appropriate candidates for pacing, a special stepwise algorithm is recommended, when investigation starts with cardiovascular autonomic tests (carotid sinus massage and head-up tilt testing with optional nitroglycerine provocation), followed by insertion of implantable loop recorder, in inconclusive or undiagnosed cases (Figure 4).

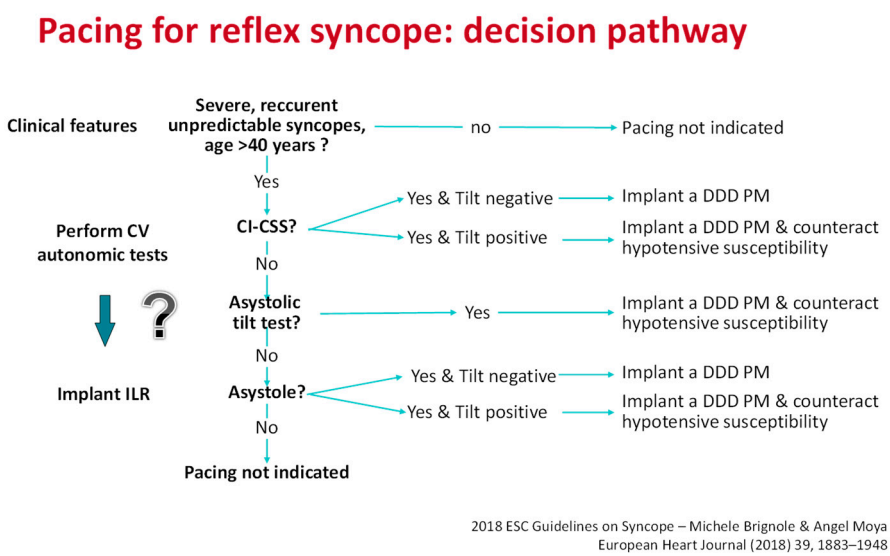

Figure 4. Algorithm for selection of syncope patients for pacemaker therapy. Reproduced from (16) with permission from the publisher.

Patients may experience syncope recurrences and fall injuries which are important clinical complications after PM implantation (56). Studies exploring causes of syncope in patients with implanted pacemakers are sparse. Syncope recurrence in pacemaker patients is today rarely due to pacemaker dysfunction but much more likely to be presentations of undetected cardiovascular autonomic dysfunction or substantially less common etiologies such as epilepsy. The question of recurrent syncope in patients who are paced has not received adequate attention in the literature to date with few studies available(57).

Considering pacemaker therapy in older patients with reflex syncope, one cannot avoid discussing the role of implantable loop recorders which have emerged since the end of 1990s as a new and now indispensable diagnostic tool, fully supported by recent syncope guidelines (Figures 5-6). The potential contribution of implantable loop recorders (ILR) in the diagnosis of unexplained syncope, although well-established in the current syncope guidelines, has not been fully explored.(16) It is hotly debated whether ILR implantation should be considered prior to or after cardiovascular autonomic testing (CAT) for patients with high risk of cardiac arrhythmic syncope. Currently, use of CAT as a first approach is rare due to unavailability in many centers or lack of comprehension of its potential including cost reduction. No clinical trials are published comparing the two approaches. Therefore, given that Lund University is well-placed to offer a retrospective comparison between these approaches, this was undertaken as pilot study to allow consideration of a later prospective, perhaps multicenter trial (16, 58-60).

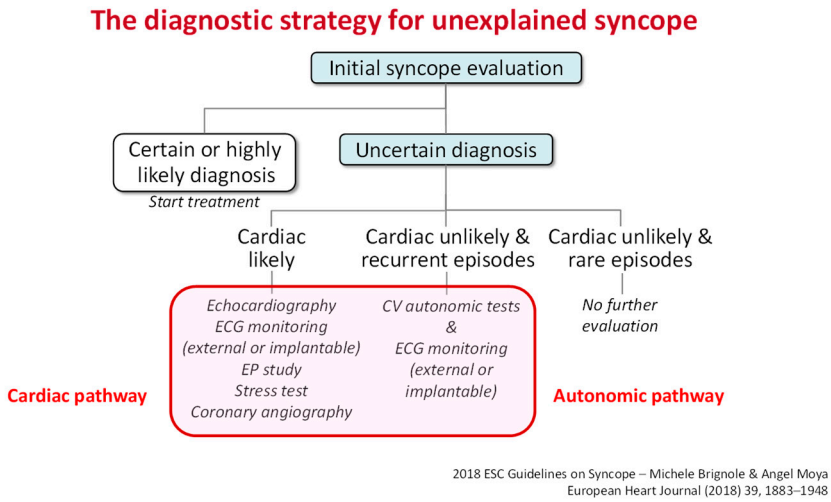

Figure 5. The diagnostic strategy for unexplained syncope. Adapted from (16).

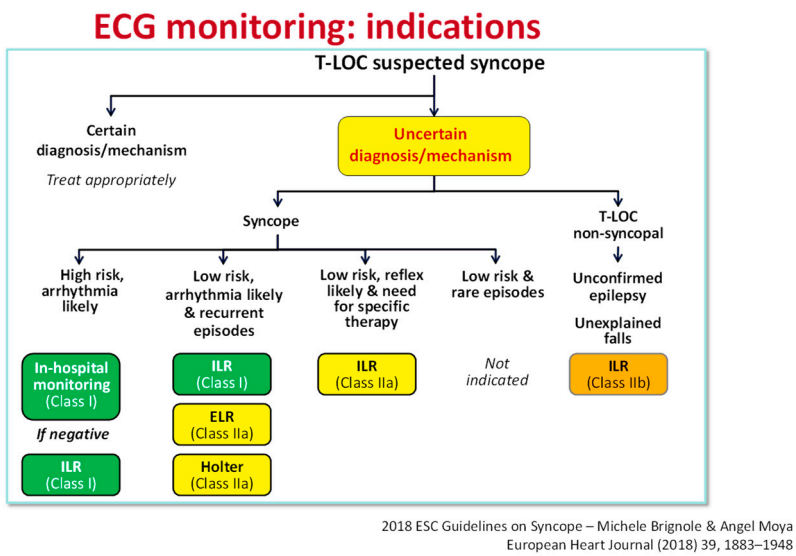

Figure 6. Indications for ECG monitoring. Reproduced from (16) with permission from the publisher.

Aims

- We aimed to identify the prognostic impact of hospitalization due to the main cardiovascular autonomic manifestations, syncope and orthostatic hypotension, on future cardiovascular events (Paper I)
- We aimed to explore the indications and assess the outcomes of pacemaker implantation following syncope evaluation (Paper II)
- We aimed to assess causes of recurrent syncope in patients with an implanted pacemaker after exclusion of pacemaker dysfunction (Paper III)
- We aimed to explore the results of monitoring from implantable loop recorders that were implanted prior to in comparison to after cardiovascular autonomic testing (Paper IV)

Material and methods

Study populations

Malmö Diet and Cancer Study cohort

The prospective Malmö Diet and Cancer Study (MDCS) is a cohort study in which men and women born between 1923 and 1950 from the city of Malmö, Sweden (total population: 330 000), were invited to participate.(58) The rate of participation was ~40%. A total of 30,528 inhabitants underwent a baseline examination between 1991–1996. The mean follow-up was 15±4 years. Full description of recruitment and screening procedures have been provided elsewhere.(58-60)

SYSTEMA study.

A specially designed project to systematically investigate and manage patients with unexplained syncope (Syncope Study of Unselected Population in Malmö; SYSTEMA) was initiated in 2008 in Malmö, Sweden (18, 61, 62). A total of 1705 patients with suspected syncope that is, unexplained transient loss of consciousness by initial evaluation, were referred to the tertiary Syncope Unit of Skåne University Hospital, Malmö, Sweden between August 2008 and December 2016. Prior to the primary syncope workup, other assessments may have been performed, containing exercise and external long-term ECG, echocardiography, coronary angiography, brain imaging and electroencephalogram, whenever appropriate. Next, the study participants underwent cardiovascular autonomic tests including carotid sinus massage (CSM) and HUT(61). Following cardiovascular autonomic assessment, patients were monitored by an ILR, if the syncope etiology could not be stated. Among study population of 1705 patients, 1666 were unpaced and in this group patients with implanted pacemaker were identified and detection methods of bradycardia, indications for PM implantation, and incidence of recurrent syncope, mortality and fall-related fractures were assessed.

Paper-specific methods

Paper I

Relationship between hospitalizations for syncope/orthostatic hypotension and incident cardiovascular disease (myocardial infarction, stroke, atrial fibrillation, and heart failure) in MDCS were assessed in a prospective approach. Individuals with prevalent or incident cardiovascular disease were excluded. A total number of approximately 1000 participants were identified in the cohort who met the criteria of index hospitalization after a preliminary analysis (Figure 7).

Adjusted Cox regression models were applied to assess the impact of unexplained syncope/OH hospitalizations on cardiovascular events and mortality, excluding subjects with prevalent cardiovascular disease.

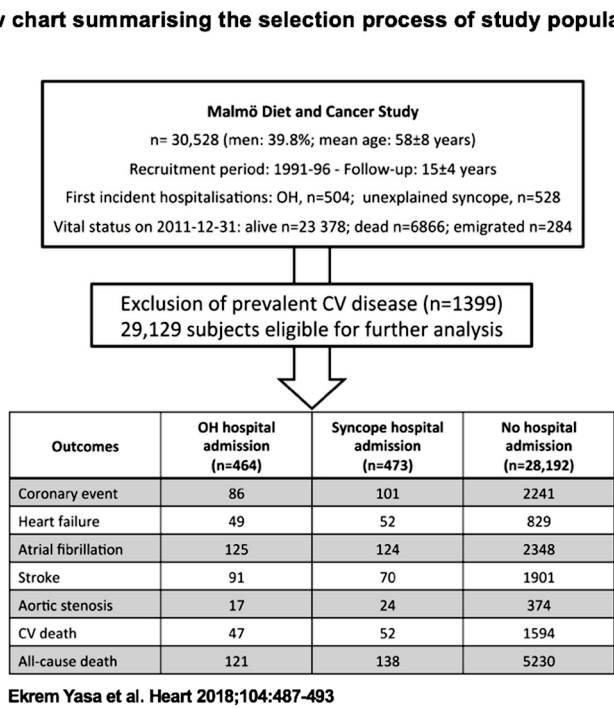

Figure 7. Study I population flowchart. Reprinted under the CC BY-NC.

Paper II

Among 1666 consecutive unpaced patients investigated in a tertiary syncope unit by CSM, HUT and ECG monitoring, 106 (6.4%; age, 65 ± 17 years) received a PM (Figure 8). The medical records were reviewed of all patients with PM implantation retrieving the following data: PM indication, date of PM implantation, syncope recurrence or unprovoked fall injury associated with low-energy fracture, as a possible syncope-proxy, and date and cause of death during follow-up period through 31 December 2017 (median, 4.3 years; range 1.2–9.3 years). Data and aetiologies of syncope recurrences and fall-related traumatic injuries were obtained by reviewing the medical records of the events, including history, PM settings and memory, any additional tests performed (such as orthostatic tests) as well as the final diagnosis by the responsible physician. VVS and OH were considered as aetiological factors when they were diagnosed in accordance with guidelines and in case of discrepancy between the diagnosis originally suggested by the responsible physician and the senior author who reviewed the records, the diagnosis was changed accordingly.

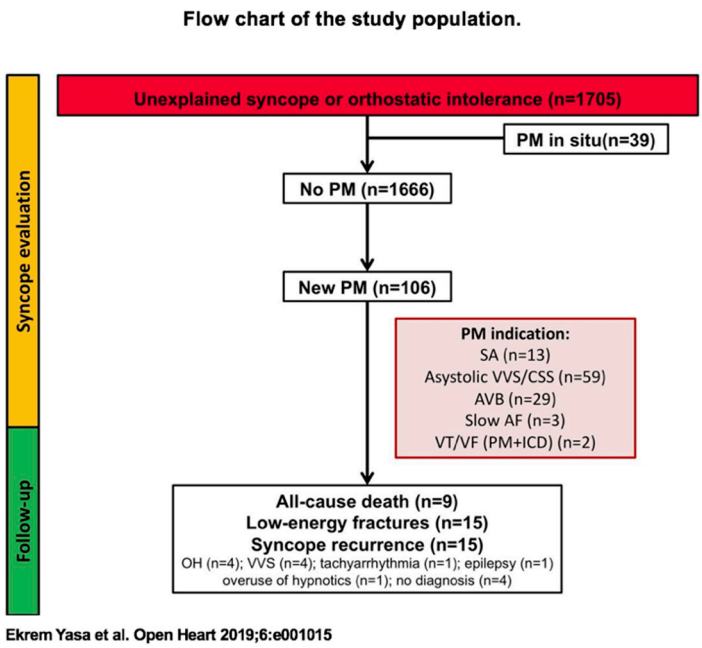

Figure 8. Study II population flowchart. Reprinted from Paper II under the CC BY-NC.

Paper III

In this study, the same study population was used as in paper II (Figure 9). The subset of patients who were investigated with already implanted pacemaker (n=39) was analyzed. Original pacemaker indications were retrieved from the medical records. The following diagnostic criteria were applied: a) reproduction of symptoms (dizziness, lightheadedness, pre-syncope and syncope), if patients were able to recall conditions preceding syncope, and b) conventional criteria of OH, carotid sinus syndrome (CSS), and VVS.

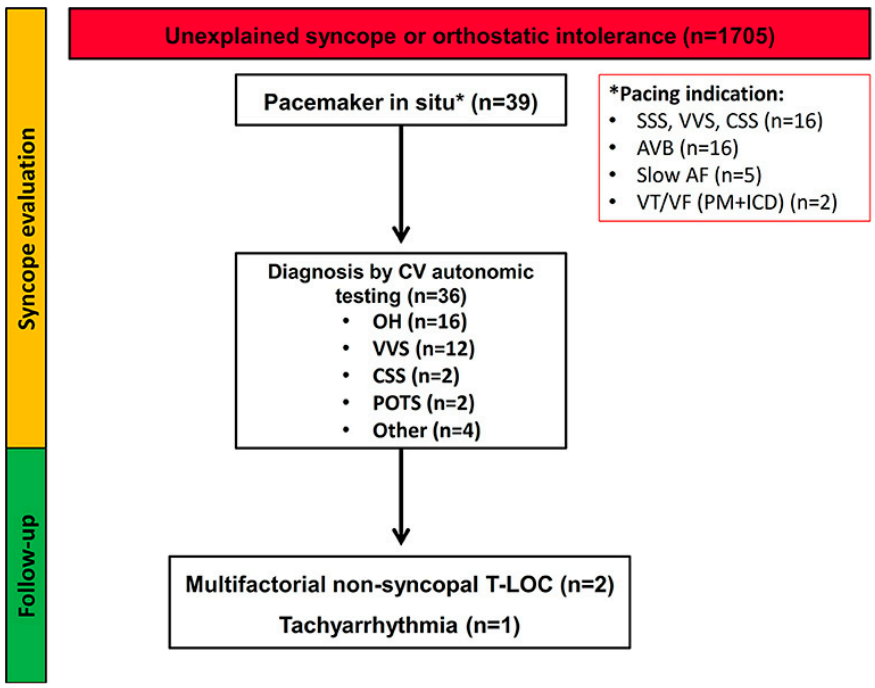

Figure 9. Study III population flowchart. Reprinted from Paper III under the CC BY.

Paper IV

Here, we analyzed all 1705 patients with unexplained syncope enrolled in the SYSTEMA cohort. We identified those who had ILR implanted either prior to or after CAT. Patients who underwent CAT and ILR were grouped into those referred to CAT after ILR implantation (primary ILR) and those in whom ILR was implanted after CAT (post-CAT ILR) (Figure 10).

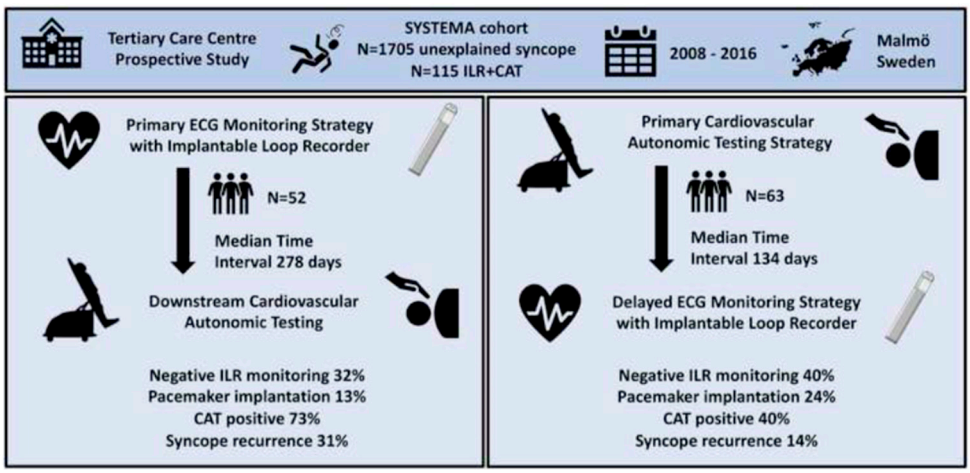

Figure 10. Unexplained syncope patients were compared regarding diagnostic findings in the two groups: primary ILR implantation and post-CAT ILR implantation. Panel A: CAT findings by diagnostic strategy. Panel B: ILR findings by diagnostic strategy.

Statistics

Paper I

Multivariate Cox proportional hazards analysis was used to calculate adjusted HRs for the coronary event, stroke, heart failure, new-onset atrial fibrillation and aortic valve stenosis associated with prior admission for unexplained syncope or OH. The same analytical approach was used to evaluate potential predictors of first-time hospital admission for unexplained syncope or OH.

Cumulative probabilities of all-cause and CV death stratified according to presence or absence of incident hospital admission for unexplained syncope or OH in the participant's history were calculated with Kaplan-Meier method, and quantified using the log-rank test. Cox proportional hazards analysis was applied to calculate adjusted HR for both all-cause and CV death associated with hospital admissions for OH or syncope. All tests were two sided; $p<0.05$ was considered statistically

significant. All calculations were performed using SPSS statistical software V.23 for Mac and GraphPad Prism V.6.0 for Mac (GraphPad Software, La Jolla, California, USA).

Paper II

Multivariate logistic regression models were applied to assess the relationship between the composite primary endpoints (recurrent syncope or low-energy fracture) and clinical patient characteristics. Associations between post-PM implantation mortality, recurrent syncope and fall injuries were analyzed with logistic regressions. The main characteristics of the study population are presented as mean and SD for continuous variables, and percentages for categorical variables. Group differences in continuous variables were compared using analysis of variance, and dichotomous variables were compared using Pearson's $\chi 2$ test. All tests were two-sided and p value <0.05 was considered statistically significant.

Paper III

The main characteristics of the study population were presented as mean and standard deviation for continuous variables, and percentages for categorical variables, unless otherwise specified. The Student's t-test was used to compare continuous variables between the groups. When the variables were not normally distributed, Mann-Whitney U-test was assessed. Pearson chi2 test was used to compare proportions among the groups.

All calculations were performed using IBM SPSS Statistics software version 25.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 6.00 (GraphPad Software, La Jolla, CA, USA, www.graphpad.com).

3.4 Paper IV

Baseline data, including syncope characteristics and past medical history were analysed. ANOVA and Mann-Whitney U-test were used to compare continuous variables between the syncope groups. Pearson's Chi-square test was assessed for categorical variables. All tests performed within the syncope workup, results of CAT and ILR monitoring outcomes were compared. Univariate and multivariate logistic regression models were used to explore predictors of pacemaker implantation. Data were analysed using IBM SPSS software version 27 (Armonk, New York) and GraphPad Prism V.6.00, GraphPad Software (La Jolla, CA, USA), www.graphpad. com. P-value of <0.05 was considered statistically significant. The data underlying this article will be shared on reasonable request to the corresponding author.

Manuscript specific results

Paper I

In the study population, 1028 subjects (3.4%) had at least one hospitalisation for unexplained syncope (n=524, 1.71%) or OH (n=504, 1.65%). Male gender, higher BMI and higher prevalence of hypertension, diabetes and history of CV disease were more common for those who were hospitalised for syncope/OH. Higher SBP, AHT and baseline CV disease predicted hospitalisations due to syncope whereas prevalent of diabetes predicted OH-related hospital admissions. Hospitalisation du to unexplained syncope was longitudinally associated with coronary events (HR: 1.85, 95% CI 1.49 to 2.30), heart failure (HR: 2.24, 95% CI 1.65 to 3.04), atrial fibrillation (HR: 1.84, 95% CI 1.50 to 2.26), aortic valve stenosis (HR: 2.06, 95% CI 1.28 to 3.32), all-cause mortality (HR: 1.22, 95% CI 1.09 to 1.37) and cardiovascular death (HR: 1.72, 95% CI 1.23 to 2.42). Hospitalisation due to OH was longitudinally associated with stroke (HR: 1.66, 95% CI 1.24 to 2.23), heart failure (HR: 1.78, 95% CI 1.21 to 2.62), atrial fibrillation (HR: 1.89, 95% CI 1.48 to 2.41) and all-cause mortality (HR: 1.14, 95% CI 1.01 to 1.30).

Three-hundred-fifty-four of 6866 deaths were preceded by hospitalization for unexplained syncope/OH. In this group, the CV and all-cause mortality rates were higher ($p<0.001$). In Cox regression models adjusted for traditional risk factors, previous syncope hospitalization was independently associated with both CV mortality (HR: 1.72, 95% CI 1.23 to 2.42, $p=0.002$) and all-cause mortality (adjusted HR: 1.22, 95% CI 1.09 to 1.37, $p=0.001$), whereas hospitalizations due to OH were independently associated with all-cause mortality (adjusted HR: 1.14, 95% CI 1.01 to 1.30, $p=0.032$), see Figure 11.

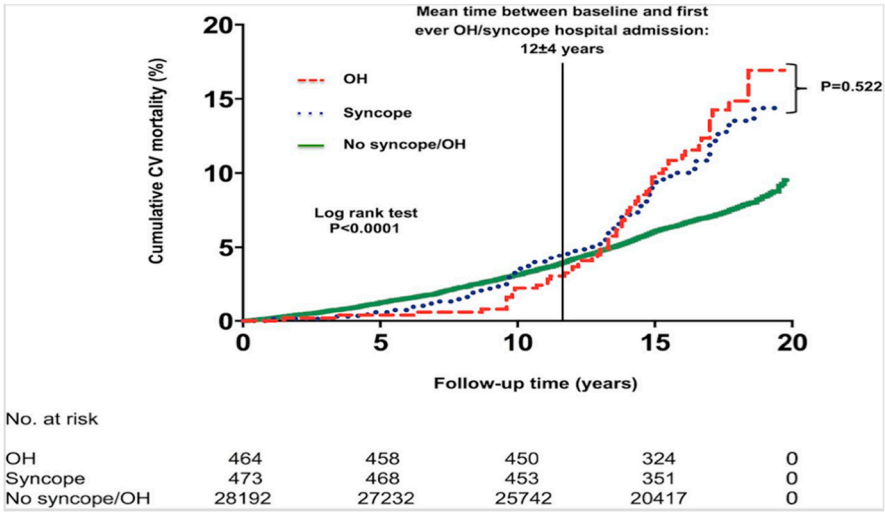

Figure 11. Kaplan-Meier curves with regard to CV mortality stratified according to incident syncope-related (blue) and OH-related (red) hospital admission: inpatients showed a significantly lower survival rate (Log-rank test p<0.001) compared with those never hospitalized for syncope or OH (green). Reprinted from paper I under the CC BY-NC.

Paper II

One-hundred-and-six participants (6,4 %) received a pacemaker where sinus arrest with asystole was the leading PM indication during CSM/HUT and ECG monitoring. Participants who received a PM were more likely to be male and were older compared to those who did not receive PM. During a follow-up time of 4 years, 15 patients (14%) had recurrent syncope episodes, 15 participants had fall-related fractures and 9 participants died. In logistic regression models, the recurrence of syncope and fall-related fractures was associated with hypertension (OR 2.45; 95% CI 1.00 to 6.0), reduced glomerular filtration rate (OR 1.63 per 10 mL/min↓; 95% CI 1.22 to 2.19) and atrial fibrillation (OR 3.98; 95% CI 1.11 to 14.3), Table 1. Nine participants who had received PM died during the follow up period in which none of the cases was related to PM or bradycardia. After adjustment for age and sex, logistic regression models demonstrated that the recurrence of syncope was associated increased mortality (OR 9.20; 95% CI 1.89 to 44.8). However, fall-related fractures were not associated with mortality (OR: 2.62; 95% CI, 0.52 to 13.3; p=0.25).

Table 1. Factors associated with the composite endpoint of syncope recurrence and fall-related low-energy fracture (n=28) among 106 patients who received pacemaker after completed syncope workup. Reprinted from paper II under the CC BY-NC.

	OR (95 % CI)	P value
Age, per year	1.03 (1.00 to 3.75)	0.081
Female sex	1.57 (0.66 to 3.75)	0.306
Hypertension	2.45 (1.00 to 6.00)	0.049
Use of thiazides and/or ARB	3.14 (1.16 to 8.49)	0.024
eGFR, per 10 mL/min decrease	1.63 (1.22 to 2.19)	0.001
Atrial fibrillation	3.98 (1.11 to 14.3)	0.034
Use of hypnotics	2.96 (0.40 to 22.1)	0.290
Diagnosis of OH	0.68 (0.26 to 1.73)	0.414
Diagnosis of VVS	0.54 (0.23 to 1.30)	0.168

- **ARBs, angiotensin receptor blockerOH, orthostatic hypotension ; VVS, vasovagal syncope; eGFR, estimated glomerular filtration rate according to Cockcroft Gault formula.**

Paper III

Thirty-nine (2,3%) participants in the SYSTEMA cohort had an PM implanted at the time of evaluation, Table 2. An etiology of syncope and/or symptoms of orthostatic intolerance in paced patients was found in 36 participants (92%). The most common diagnoses for PM implantation were OH (n = 16; 41%) and VVS (n = 12; 31%), sick-sinus syndrome (n=16), atrioventricular block (n=16) and AF with bradycardia (n=5). Prior to the CIED implantation, 22 (56%) participants had experienced syncope including 7 (32%) with OH and 9 (41%) with VVS.

In the group who had not experienced syncope before PM implantation, 9 (53%) had OH and 3 (18%) had VVS. In order to treat ventricular arrhythmias, 2 patients had been implanted with cardioverter-defibrillators.

Table 2. Patient characteristics (n = 1,705) at the time of initial evaluation stratified according to pacemaker status. Reprinted from paper III under the CC BY.

	Patients with pacemakers at the time of evaluation (*n* = 39)	**Rest of SYSTEMA cohort (*n* = 1,666)**	***P*-value**
Age, years	65.6 (19.9)	51.8 (21.8)	<0.001
Sex, % female	38.5	60.7	0.005
Reported history of			
Syncope, %	84.6	91.5	0.127
Dizziness, *n* %	74.4	72.6	0.811
Number of syncope episodes, md [range]	5 [0–250]	4 [0–1,350]	0.278[a]
Duration of symptoms, years, md [range]	6 [0–48]	3 [0–77]	0.058[a]
SBP, mmHg	132.8 (18.7)	131.4 (22.5)	0.71
DBP, mmHg	68.8 (9.1)	71.6 (10.2)	0.091
Resting heart rate, bpm	67.2 (8.1)	70.3 (12.6)	0.028
Hypertension, %	51.3	28.5	0.002
CAD, %	30.8	6.4	<0.001
Atrial fibrillation, %	33.3	6.6	<0.001
Heart failure, %	25.6	3.3	<0.001

[a] *P-value for Mann-Whitney U-test. Continuous variables were compared between groups using Student's t-test and dichotomous variables were compared according to group using Pearson chi^2 test, if not otherwise indicated. md, median; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery Idisease.*

Paper IV

In the SYSTEMA cohort, 115 (7%) participants received an ILR, including 52 patients (45%) in primary-ILR-group, and 63 (55%) in post-CAT ILR group. Participants with an ILR were older (p=0,002), had more syncopal episodes (6 vs 4; p<0.001), more traumatic falls (72% vs 53%; p<0.001), and less prodromal symptoms (40% vs 55%; p=0.005) compared to the group who did not receive ILRs. Within the follow-up period, the ILRs detected 13 (11.3%) cases of atrial fibrillation, 67 (58%) cases with normal sinus rhythm, 10 (8.7%) cases of sinus arrest, 10 (8.7%) cases of AV-block, 9 (7.8%) cases of supraventricular tachycardia, 4 (3.5%) cases of sinus tachycardia and 2 (1.7%) cases of ventricular tachycardia. In the primary-ILR-group, the CAT was more likely to be positive (p=0,007). Baseline differences between the groups are characterized in Table 3.

Table 3. Main study results: ILR findings in patients implanted before and after cardiovascular autonomic testing. In total,46 patients experienced syncope during monitoring period.

ILR finding	Total (n=115)	ISSUE	Primary ILR (n=52)	Post-CAT ILR (n=63)
Sinus arrest or sinus bradycardia <40 bpm	10	1A/2	3	7
AV block	10	1C	4	6
Normal sinus rhythm	67	3	33	34
Sinus tachycardia	4	4A	3	1
Atrial fibrillation	13	4B	4	9
SVT	9	4C	4	5
Ventricular tachycardia	2	4D	1	1
Pacemaker implantation	22		7	15*
Syncope without any of the above arrhythmias (normal sinus rhythm at syncope)	25	3	16	9
Negative (no arrhythmia and no syncope)	42	3	17	25

CAT, cardiovascular autonomic testing; ILR, implantable loop recorder; ISSUE, International Study of Syncope of Unknown Etiology Classification; AV, atrioventricular; SVT, supraventricular tachycardia; * including one implantable cardioverter-defibrillator and one VVIR pacemaker due to slow atrial fibrillation in post-test ILR group.

General discussion

This thesis has sought to enhance knowledge of the importance of two major forms of cardiovascular dysautonomia, reflex syncope and orthostatic hypotension (OH) in prognosis of general population, especially among older subjects, for patients with syncope considered for permanent pacing but without primary arrhythmic indications and for those patients who have been paced for syncope and present syncope recurrence. Finally, the strategy for initial investigation prior to pacing has been considered for patients with syncope but without a primary arrhythmic indication. Cardiovascular autonomic testing (CAT) first followed, if necessary, by long-term ECG monitoring by inserted loop recorder (ILR) versus ECG monitoring by ILR first followed by CAT.

Paper I

The first study set out to make a new assessment of the long-term cardiovascular (CV) risks in middle-aged patients who were hospitalised for unexplained syncope and orthostatic hypotension (OH). This aspect of syncope and OH has received little attention in the literature with syncope (unexplained) being frequently dismissed as benign. This aspect was felt to deserve more attention.

This is, notably, a large study with long follow-up. The study was drawn from a Malmö-area population base of approximately 30000 subjects in whom CV disease was absent at entry and took advantage of the high quality of Swedish registers where only <1% of hospital discharges lack an appropriate principal diagnosis(63). Furthermore, the validity of CV end-points is high (under annual quality-control review) with a low rate of misclassification, the combination offering strength to the study.

The findings of this study suggest that CV risks for these patients are important and, also, different between syncope and OH. Both groups of patients have been found to present high risk for all-cause mortality, heart failure and atrial fibrillation. Among syncope patients, coronary events, aortic valve stenosis and CV death was high, while in OH patients, risk for stroke was high.

The average rate of hospitalisations for syncope was 1.2 per 1000 person-years which is similar to those of epidemiological studies reporting 1-2 hospital

admissions for syncope per 1000 person-years from the general population. It is necessary to stress that only a minority of syncopes result in hospital admission, approximately 10%, and these are usually associated with older age combined with additional risks clearly requiring rapid assessment(16). Hospitalisation rates for OH were quite similar to those of syncope.

The prevalence of OH in adults older than 55 years was estimated to be 5-15% from previous studies (64, 65). When applied to this study population, it translates into around one in eight patients with OH being admitted at least once for this condition during follow-up. Admitted patients with OH are likely to be highly symptomatic as previous studies suggest that the majority of OH patients are asymptomatic (66). Prevalent CV disease, hypertension, antihypertensive treatment and use of diuretics in particular, were identified to predict syncope hospitalisations, paralleling the SPRINT study, where a more intensive treatment arm was associated with higher risk of syncope (67). History of CV disease also predicts hospital admission for syncope. This may be explained by the presentation of syncope revealing previously undetected CV disease, such as tendency to paroxysmal arrhythmia, or asymptomatic structural heart disease. Unexpectedly, antihypertensive treatment and prevalent CV disease had no impact on OH-related admissions, again paralleling the SPRINT trial. (67) This finding diverges from the commonly held belief that use of antihypertensive drugs is a major cause of OH (13). Diabetes, however, was predictive of OH-related admissions, as generally accepted.(68).

There remains no consensus whether a discharge diagnosis of syncope/OH without concurrent CV disease should be seen as a warning of future CV problems. A Framingham study report showed no increased risk of adverse CV outcomes among syncope patients although this report may be adversely affected by its inclusion of epilepsy as a form of syncope. (69) Moreover, one-third of syncopes had no defined aetiology with both higher mortality and CV morbidity. (69) A recent study, however, suggested hospitalisation for non-cardiac syncope in 'healthy' individuals might predict death, stroke, CV hospitalisation, device implantation and recurrent syncope.(48) Among patients presenting syncope at the emergency department, the probability of an adverse outcome within 2 years is approximately 25%, higher than in the general population.(50). Serious syncopal episodes, even if not associated at the time with CV disease, may prompt greater vigilance post-discharge with higher rates of detection of CV disease. Studies of the long-term prognosis after hospital admissions for OH are rare but, in large population-based cohorts, prevalent OH has been consistently linked with increased mortality and risk of CV events. (25, 70-72). Reports on hospital admissions due to worsening OH, typically as syncope and/or unexplained fall trauma, have not been previously reported.

As many as 30%–50% of patients with syncope, in many reports, leave hospital without a clear explanation of cause. (73) Older patients admitted due to the event being interpreted as unexplained syncope may have had an undetected CV condition, such as paroxysmal arrhythmia or underlying structural heart disease.

This unsatisfactory situation emphasises the role that implantable cardiac monitors should play in the post-discharge work-up of older patients with unexplained syncope, as proposed by Syncope Unit Project investigators.(74) It should also be borne in mind that vasovagal syncope may actually be a manifestation of an acute CV event such as pulmonary embolism (75) or coronary occlusion with a possible history of previous vasovagal syncope demonstrating an increased susceptibility.

As might be expected, patients discharged with a final diagnosis of OH demonstrated increased incidence of CV disease. These patients had confirmed, and symptomatic OH and should be anticipated to share the same prospective risks as the whole OH population. However, hospital admission due to OH might be seen as a marker of general frailty, comorbidities and higher CV risk compared with asymptomatic OH. The Lund group has previously reported that patients with syncopal OH show unfavourable neuroendocrine and procoagulatory changes (62, 76) and that OH is associated with structural cardiac changes.(22) Thus, patients with symptomatic OH constitute a vulnerable group in excess of the age-matched population in susceptibility to CV disease, in parallel with high-risk conditions such as hypertension and diabetes.

Study Limitations

This study has some important limitations. The majority of OH or syncope patients are not admitted to the hospital and are usually treated by general practitioners, alternatively they do not seek any medical advice. This means that there is possible selection bias in the study.

Although the Malmö diet and Cancer Study Cohort from which the data were derived was designed as prospective study, the database was studied in a retrospective analysis, meaning that there are attendant weaknesses. Further, we did not assess possible important clinical changes over time, such as blood pressure, changes in the antihypertensive drug regimen and electrocardiographic data at the index event. In this study population, there was a predominance of women, and female sex was an inverse predictor of syncope (HR: 0.81, 95% CI 0.66 to 0.98). It has been previously shown that female patients may be more prone to reflex syncope, although usually before middle-age (77). Additionally, individuals deemed likely to have reflex syncope are usually assessed as outpatients outside hospital. (78, 79)

Implications of the study

This study fills an important gap in knowledge suggesting syncope-related and OH-related admissions, without previous concomitant CV disease, have been seen as having a benign prognosis, However, when rigorously studied they show a high risk

of more serious CV events. Furthermore, it is necessary to underline the need for precise classification of syncope aetiology after admission to hospital as prognostic implications of unexplained syncope-related events and OH, although partly overlapping, differ in regard to type of CV event that may present.

Conclusions

Hospital admissions for syncope and OH in middle-aged adults are more common with advancing age and are associated with common comorbid conditions, diabetes and hypertension. Admission for syncope and OH predicts incident heart failure and atrial fibrillation. In addition, admission for syncope indicates higher risk of coronary events and aortic valve stenosis, whereas admission for OH is associated with a higher risk of stroke. Patients admitted for unexplained syncope have higher risk of both all-cause death and and CV death, whereas those with OH have higher all-cause mortality.

Paper II

This study was prompted by awareness of the literature on syncope recurrence in patients paced for unexplained syncope with a focus on the role of autonomic testing pre-implant in predicting such recurrences. The cardiovascular autonomic testing employed was head-up tilt-testing, carotid sinus massage (CSM) and insertable cardiac monitoring (ICM) also known as insertable ECG loop recorder.

The observations made were:

- pacing indications in patients presenting with unexplained syncope can be demonstrated in 70% of patients by laboratory cardiovascular autonomic tests (CSM, tilt testing) and in 13% by ICM;
- following pacemaker implantation, a considerable proportion of patients experience recurrent syncope or traumatic falls. These adverse outcomes seem to be over-represented in patients with hypertension taking antihypertensive therapy, atrial fibrillation and renal dysfunction and
- the patients with recurrent syncope after PM implantation have a higher mortality.

The pacing literature has mainly depended on ECG diagnosis for selection of patients for successful pacing, and this was reaffirmed by the 2021 ESC guidelines on pacing(55). Follow-up of paced patients, with clear ECG pacing indications, has dominantly been mainly for detection of technical faults and maximising battery life. As devices became increasingly reliable attention broadened to possible

problems of long-term pacing, for example, induction of heart failure by right ventricular apical pacing(80).

The problem of recurrent syncope has had less attention than it deserved, possibly because in patients with atrioventricular block syncope recurrence was low about 5% over 3 years (81). Early studies of recurrent syncope in PM recipients raised the possibility of autonomic causes, however the more extensive autonomic investigations, as used in our study, were not available then (82-84). With a prospective investigational protocol with cardiovascular autonomic tests, CSM and HUT, completed, when necessary, by ICM, we reveal insights into the aetiological and prognostic significance of syncope recurrence following the implantation of a pacemaker. Specifically, we show that syncope recurrence during follow-up is common in our cohort compared with AVB patients who are permanently paced (81, 85). Of note, sinus arrest was associated frequently with recurrent syncope (41%) in our patient group; thus, it may be that many of these patients have the 'extrinsic' form of sinus node disease where syncope may actually be reflex in origin (16, 84).

The study results emphasize the importance of a complete battery of diagnostic tests before implanting a pacemaker in patients, in whom a clear explanation for syncope is lacking. Such diagnostic testing may influence selection of pacing as required therapy, type of device to be implanted and the programming. Moreover, the concept of a "syncope unit" (86), in which resources and expertise can be concentrated, may be important for achieving optimal diagnostic and therapeutic efficacy when managing unexplained syncope. The availability of cardiovascular autonomic tests and the competence for their interpretation may be limited, meaning that competence may be concentrated in specific centers.

A distinct finding in this study is the association between hypertension and syncope recurrences. Hypertensive patients who are taking antihypertensive medications constitute a significant proportion of the population with pacemakers. Our results indicate that hypertensive patients are particularly prone to recurrent syncope, likely because of excessive antihypertensive therapy. This is in concordance with the results of the Systolic Blood Pressure Intervention Trial (SPRINT) and Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trials (67, 87), where hypotension and syncope was more common in the groups with more intensive-blood pressure treatment. This unwanted effect of antihypertensive therapy could also be explained by the higher prevalence of hypotensive susceptibility in our study population, subjects who are more sensitivity to antihypertensive drugs (88). Of note, it has been shown that hypertension as well as thiazide treatment are risk factors for re-hospitalisation following hip-fracture surgery (89). The recent North American hypertension guidelines recommend even stricter BP targets (BP <130/80 mm Hg), however our current findings should prompt a reserved approach in treating hypertensive patients with a history of syncope (90). This is in line agreement with the findings from Stop vasodepressor

drugs in reflex syncope (STOP-VD) trial (91), which showed that recurrent syncope and presyncope could be reduced by discontinuing/reducing antihypertensive therapy in the oldest that suffers from reflex syncope of vasodepressor type.

In addition to hypertension and antihypertensive therapy, renal failure and atrial fibrillation were associated with syncope recurrence and traumatic falls in our current cohort. These findings are consistent with a Danish nation-wide study, showing that atrial fibrillation and impaired renal predict recurrent syncope in patients with first-time syncope, especially in the younger (<65 years) participants (49, 92). An Irish group reported similar findings; in their study hypertension and atrial fibrillation were associated with increased fall propensity (93). Both renal failure and atrial fibrillation affect autonomic compensatory mechanisms; renal failure influences fluid homeostasis, whereas atrial fibrillation may lead to abnormal chronotropic response. Both these factors are important for the function of the baroreflex. Hypertension is associated with both reduced renal function and atrial fibrillation, prompting a vicious circle requiring careful judgement of risks and potential benefits of intensive BP reduction.

Intensive antihypertensive therapy may be important for improving long term cardiovascular prognosis, however syncopal recurrence has an important impact on quality of life and is associated with high healthcare costs, increased risk of injuries by falls and CV as well as all-cause mortality (49). Hip fractures are major consequences of syncope-related falls and are associated with approximately 25% reduction of life expectancy and institutionalisation rates of 8% - 34% in (94). It may be challenging to differentiate between falls and syncope, not least in older patients with cognitive impairment, even without such evidence amnesia for syncope is more common in the paced patient age group (95). Experience from dedicated syncope and fall facilities reinforces the evidence of an overlap between these two entities, which could often not be separated and are likely to be manifestation of the similar pathophysiology (96). Both falls and syncope are strongly associated with antihypertensive therapy and the number of cardiovascular conditions, such as atrial fibrillation (96). This overlap may possibly be explained by the reasoning that haemodynamic changes that are insufficient to cause critical cerebral hypoperfusion may still reduce cerebral perfusion so that it could play a part in traumatic falls, especially in older patients who may also suffer from gait and balance abnormalities combined with impaired protective reflexes. The results of our study indicate the need for future observational and interventional studies of chronic conditions that may affect the efficacy of pacemaker therapy for syncope.

Finally, although there were relatively few patients who died during the follow-up, recurrent syncope correlated distinctly with increased mortality, in line with previous data (46, 97). Thus, clinicians should be observant when meeting patients with recurrent syncope after pacemaker implantation, since this may indicate further cardiovascular and autonomic deterioration as well as signant increased risk of falls,

fractures, hospital admissions and other potentially life-threatening/quality of life reducing conditions.

Strengths and limitations

The principal strengths of this work were:

i. the study was prospective and conducted in a tertiary referral syncope unit, including the diagnostic modalities and therapeutic options that are recommended in guidelines and

ii. the length of the follow-up period

However, some limitations must be taken into account:

i. the study is an observational study done in one center, meaning that the results require confirmation in independent and larger samples;

ii. the study sample is small;

iii. the included cohort is a selected group of individuals that had been referred to a tertiary syncope unit. Thus, the study cohort may not reflect the general syncope population and

iv. patients who had implantation of a pacemaker for primary cardiac arrhythmia and in whom the indications were found prior to evaluation in the syncope unit were not included.

Conclusions

Cardiovascular autonomic testing and insertable cardiac monitors reveal indications for pacing in most patients that initially present with unexplained syncope. Prevalent hypertension associated with antihypertensive treatment, renal failure and atrial fibrillation may predict recurrent syncope and fall injury in syncope patients with pacemakers. Syncope recurrences in paced patients associated with increased mortality.

Paper III

The third study of this thesis was based on the same underlying cohort as in paper II, with the aim of investigating the causes of recurrent syncope in patients with an already implanted pacemaker at the time of syncope investigation.

This study has shown that:

I. The cause of both syncope and orthostatic intolerance in patients with pacemakers can be identified in a majority of cases, by using cardiovascular autonomic tests, including head-up-tilt test, carotid sinus massage (CSM) and Valsalva manoeuvre.

II. The most frequently occurring aetiologies of recurrent syncope among paced patients are orthostatic hypotension (most in older subjects) and vasovagal syncope (more in younger subjects). There were no patients with identified pacemaker dysfunction, as pacemakers were usually controlled after the syncopal event.

The literature on how to select patients for successful pacing has focused on symptoms and ECG diagnosis, whereas the clinical dilemma of recurrent syncope or orthostatic intolerance has been less studied. As previously mentioned, early studies raised the possibility of autonomic causes of syncope of paced patients, however the cardiovascular autonomic tests at the time were not as extensive as today (83, 84). By a prospective investigational protocol including cardiovascular autonomic tests in a syncope unit, we in this study have provided insights into the aetiology of recurrent syncope and/or orthostatic intolerance in patients with pacemakers. The most common causes were orthostatic hypotension and vasovagal syncope, which was identified as the underlying cause in seven out of ten patients. Of note, the prevalence of orthostatic hypotension was higher in these paced patients (41%) than in the remaining patients of the SYSTEMA cohort, which provides a broader perspective, (27%) and the proportion of patients in whom no cause could be identified during tilt was lower in the paced patients than in SYSTEMA (8% versus 22%).

Of interest, sick sinus syndrome was a common original pacing indication (41%) in the patients in whom vasovagal syncope was identified as the cause of recurrent syncope, thus, it should be considered that many of these paced patients may have the “extrinsic” form (84), implying a reflex syncope with a vasodepression (16). In paced patients with cardioinhibitory vasovagal syncope, conventional anti-bradycardia stimulation, a form of rate hysteresis, offers little to combat the vasodepressor component. This may have been underappreciated, even on tilt, if performed before implantation, by the dominant bradycardia/asystole (52). Performance of tilt testing prior to pacing must now be considered as a risk of syncope recurrence stratification tool, if positive, recurrence of syncope is

substantially more likely (88). Even if the initial pacing indications in our examined patients were in line with guidelines, not only does pacing offers little effect against the vasodepressor component of vasovagal syncope, it is also not helpful in orthostatic hypotension. This is the basis of recurrent syncope in these patients.

Of particular clinical relevance, the assessment of pacing function, which was done in all patients, showed no cases of dysfunction. Rather, this study stresses that the importance of a full diagnostic procedure according to the recent syncope guidelines (16, 98) and that this is also very pertinent in patients with pre-existing pacemakers presenting recurrent syncope and/or orthostatic intolerance.

Cardiovascular autonomic tests pointed out the aetiology of recurrent syncope in all eleven patients under 60 years of age, suggesting that cardiovascular autonomic testing may be particularly valuable younger patients. As was raised in relation to paper II, concentrating expertise in a dedicated facility ("Syncope Unit") (16) may be beneficial from a diagnostic and therapeutic point of view.

In this study, Closed Loop (CLS) pacing was used in minority of patients unlike the SPAIN trial (99). This type of pacemaker indirectly senses right ventricular volume by measuring its impedance. When a decrease in right ventricular volume is indicated, which is the case in vasovagal reflex syncope due to diminishing venous return, the pacemaker triggers pacing. This detected change in right ventricular volume occurs several minutes before the bradycardia/asystole in almost all vasovagal syncope (100, 101) thus, pacing can be triggered much earlier in the reflex than if the pacing was triggered by the later later occurring bradycardia. The favourable results of the SPAIN trial suggest that this means of triggering pacing may offer more benefit. The BIOSYNC study, a randomised controlled trial of CLS vs. standard DDD pacing has offered confirmation of benefit although a comparison between CLS pacing and rate hysteresis has not yet been undertaken (102).

Study Limitations

Some study limitations must be acknowledged. Firstly, as is the case for the second study of this thesis, this a small observational study done in a single center, warranting further confirmation of the results in other studies. Secondly, the group of patients is highly selected in that they have all been referred to a tertiary syncope unit, thus, it may not reflect the aetiological findings of a wider population with pacemakers that experiences recurrent syncope. Thirdly, the relatively low proportion of patients with an pre-implanted pacemaker at the time of entry into the cohort (2.3%) may be explained by the fact that only subjects with unexplained syncope and/or orthostatic had been referred to the syncope unit. Thus, the SYSTEMA cohort is a selected group in whom syncope aetiology could not readily be determined and/or the patient was not adequately managed at the initial contact with the the referring physician. Fourthly, the examination protocol used here did

not include additional autonomic tests such as the Valsalva manoeuvre or baroreceptor sensitivity testing in the whole patient population. When a clear cause of syncope recurrence was found these tests were not performed.

Conclusion

This study has shown that cardiovascular autonomic tests could identify the aetiology of syncope and/or orthostatic intolerance in the majority of patients with pacemakers. Orthostatic hypotension (40%) followed by vasovagal syncope (30%) are the most common diagnoses. The results emphasizes the clinical importance of a complete diagnostic work-up in accordance with guidelines also in paced patients with recurrent syncope or orthostatic intolerance.

Paper IV

This single-centre prospective study compared diagnostic yield and therapeutic implications of a primary ECG loop recorder implantation (ILR) strategy versus comprehensive cardiovascular autonomic testing denoted CAT (head-up tilt, active standing, and carotid sinus massage) and subsequent ILR loop implantation in a population of unexplained syncope patients. Our data demonstrate a nonsignificant difference in the number of final diagnoses achieved and the proportion of pacemaker implantations between the two strategies. However, as expected, the primary ILR implantation strategy resulted in a higher proportion of positive findings than CAT, although the primary ILR group was more extensively examined, prior to referral, with multiple investigations such as echocardiography, Holter ECG and brain imaging compared with those examined first with CAT. These are important observations because these two diagnostic strategies, ILR and CAT, both appear reasonable clinical options, in line with current syncope guidelines. However, there are other considerations than simply a choice between early ILR implantation, with possible additional CAT, and CAT with ILRs selected only when CAT yields no definite diagnosis. Assessment of cardiovascular autonomic function and reflex syncope susceptibility gives several distinct patient management advantages:

- confirmation of diagnosis by reproduction of spontaneous symptoms of VVS on tilt (30),
- patient education about prodromes and counter-pressure manoeuvres on tilt in VVS (30),
- a basis for pacemaker device selection in VVS (102),

- prognostic information with respect to future syncope recurrence, especially in the context of pacing therapy (103),
- a diagnosis of carotid sinus syndrome which may call for a different pacemaker programme (16),
- understanding of the role of the vasodepressor component in both CSS and VVS implying possible reduction in hypotensive medication or even addition of medication to support blood pressure (91),
- diagnosis of OH by active standing and delayed OH by tilt (17, 61).

Thus, the two approaches must be considered complementary, as supported by the comparison displayed in Figure 2. Neither positive nor negative CAT results predicted ILR outcome, which suggests that CAT identifies potential syncope mechanisms that

a) may exist in parallel to arrhythmic mechanisms but are not responsible for the syncope under investigation;

b) two or more mechanisms may exist in parallel and equally contribute to syncope. A similar observation was made regarding patients with positive vs negative ILR monitoring: in both groups, the proportion of positive CAT results was not different. This illustrates the complexity of unexplained syncope investigation: some patients had positive CAT only, some had positive ILR monitoring only, some had both, and a group of patients had neither positive CAT nor ILR, which is where the current challenge of syncope management lies. Consequently, a simple ILR strategy alone is inadequate, while a dual diagnostic strategy, CAT and ILR, offers the best available patient management. This method of investigation is fully compatible with ESC guidelines (16).

These data also support selection of ILR after CAT as there will be cost savings in less ILR use. Based on epidemiological data, around 70% of syncope aetiologies may be captured by CAT, whereas around 15% by long-term ECG monitoring. If the pre-test probability is very high for the latter, for instance in chronic conduction disorders and history of syncope suggesting a non-orthostatic sudden-onset scenario, primary-ILR strategy should be preferable, as the probability of recurrent arrhythmia in post-syncopal period is high. For the remaining patients, a CAT-first strategy should be preferred and be cost-effective. An exception to the dual approach could be made when the 12-lead ECG shows evidence of conduction disorders, especially left bundle branch block. Unsurprisingly, we found that these abnormalities were powerful predictors of the need for pacing. Recently, a meta-analysis has shown that ILR is a superior approach to both diagnostic electrophysiological study and immediate pacemaker implantation (104).

The issue of recurrent syncope after pacemaker implantation in patients for whom syncope was the main indication for pacing therapy has recently come into focus (57, 105). The report of Palmisano et al in 2020 (57) (ref. demonstrated the importance of autonomic status assessment before implantation to predict the likelihood of syncope recurrence after pacing, a subject also covered by the 2018 ESC guidelines (16). Further support to this concept, in the same cohort as in the current study, the most common causes of syncope recurrence in paced patients were orthostatic hypotension and vasovagal syncope (106), which are diagnosed by CAT. This serves to emphasise the use of the dual strategy in which CAT is preferably done prior to ILR implantation unless there are specific signs such as conduction abnormalities or high-risk settings suggesting cardiac arrhythmia which indicate primary ILR implantation. The yield of arrhythmia diagnosis with ILRs is clearly superior to CAT, which is supported by our data and, again, fully assimilated in guidelines (16).

Study Limitations

Some limitations must be acknowledged. Firstly, this is a small single-centre prospective study that has intrinsic limitations and obvious selection bias. Secondly, patients were not prospectively randomised to ILR as an initial strategy or CAT followed by ILR. Consequently, despite sharing many similar characteristics, the two populations cannot be held completely comparable. However, the findings fully support performance of a randomised clinical trial with appropriate patient selection. Finally, longer-term monitoring could have increased the diagnostic yield of ILR; indeed, when a strategy of prolonged monitoring is chosen, it should be maintained, even for several years, until a diagnosis is established (107).

Conclusions

A minority of patients with unexplained syncope requires monitoring with an implantable loop recorder. While early-ILR and CAT-first strategies are widely practised, primary CAT strategy offers a valuable and cost-effective approach in patient management, unlocking diagnoses of vasovagal syncope, orthostatic hypotension, and carotid sinus syndrome, and recurrent syncope prediction after pacing. The yield of ILR monitoring is cardiac arrhythmia in almost 50% of patients, sick sinus syndrome/sinus arrest being the most frequent event, even in a relatively short monitoring period. Around 20% of monitored patients will receive a pacemaker, strongly predicted by the presence of conduction disorders on resting ECG.

Final conclusions

This thesis composed of four studies has shown that the prognosis of healthy subjects who later require hospitalisation for syncope or orthostatic hypotension have a reduced prognosis. Patients that present with syncope without a primary arrhythmic diagnosis are better assessed by cardiovascular autonomic testing in addition to conventional ECG monitoring. Their prognosis for syncope recurrence will be revealed by this approach. Patients with pacemakers presenting syncope recurrence are best investigated by cardiovascular autonomic testing which reveals its cause in most and offers ways of avoiding further syncope. The strategy of testing of patients with syncope prior to pacing is currently practiced as ECG diagnosis with or without long-term ECG monitoring. This may be improved with respect to diagnosis made, prognosis and cost by employing cardiovascular autonomic testing first and ECG loop recording second. If the ECG diagnosis is highly likely, in conduction tissue disease, ECG loop recorder strategy first is to be preferred.

Summary in Swedish

Ett välfungerande samarbete mellan det kardiovaskulära, endokrina, and autonoma nervsystemen är nödvändigt för att upprätthålla adekvata puls- och blodtrycksnivåer, den så kallade hemodynamiska homeostasen. Kardiovaskulär dysautonomi innebär störningar i detta samarbete och orsakar en cirkulatorisk störning som i sin tur kan leda till hypotoni och nedsatt cerebralt flöde med symptom som suddig syn, trötthet, yrsel och eventuellt synkope. I den här avhandlingen har vi haft fyra olika arbeten där vi studerat kardiovaskulär dysautonomi med bl.a. den prognostiska betydelsen av synkopeinsjuknande avseende framtida kardiovaskulära händelser och mortalitet, utfallet av det Europeiska hjärtförbundets rekommenderade strategi för synkopeutredning och rollen av pacemakerbehandling hos oklara synkopepatienter. Vi har också tittat på orsak till synkope och ortostatisk intolerans hos patienter med pacemakerbehandling samt studerat utfallet av långtids-EKG-monitorering med implanterbar hjärtmonitor hos synkopepatienter.

I första studien siktade vi på att undersöka sambandet mellan sjukhusinläggningar på grund av oklar synkope och ortostatisk hypotension (OH) med efterföljande kardiovaskulära händelser och dödlighet. Vi analyserade en populationsbaserad prospektiv kohort av totalt 30 528 individer (åldern 58 ± 8 år, 40 %män 40) från Malmö. Våra resultat visade att patienter som skrivs ut med diagnosen oförklarlig synkope eller OH visade högre incidens av hjärt-kärlsjukdom och dödlighet.

I det andra projektet studerade vi en patientgrupp i Malmö (SYSTEMA) som blivit undersökta och behandlade på grund av oklar synkope. Mellan augusti 2008 och december 2016 remitterades 1705 patienter med misstänkt synkope till vår synkopeenhet vid Skånes universitetssjukhus, Malmö. Vi utvärderade bradykardidetekteringsmetoder, pacemaker-indikationer och undersökte förekomsten av återkommande synkope, fallrelaterade frakturer och dödlighet. Totalt 1666 patienter utan PM undersökts med sinus-carotismassage, head-up-lutningstest och EKG-övervakning, 106 (6,4 %; ålder, 65 ± 17 år) fick pacemaker. Våra resultat visade att kardiovaskulära autonoma tester och EKG-övervakning effektivt identifierar indikationer för pacemaker hos patienter med oförklarlig synkope. Återkommande synkope efter pacemaker förutsäger ökad dödlighet.

I den tredje artikeln syftade vi till att bestämma etiologin för synkope och/eller symtom på ortostatisk hypotoni hos patienter med existerande pacemakerbehandling. Bland 1 705 patienter med oklar synkope och/eller

ortostatisk hypotoni som undersöktes med kardiovaskulära autonoma tester, hade 39 patienter (2,3 %; ålder 65,6 år; 39 % kvinnor) en implanterbar enhet med pacemakerfunktion. Vi undersökte patienternas medicinska historik, diagnoser som hade hittats under kardiovaskulära autonoma tester och vidare utredningen, i händelse av negativ initial utvärdering. Våra resultat visar att kardiovaskulära autonoma tester avslöjar orsaken till synkope och/eller ortostatisk intolerans hos majoriteten av pacemakerbehandlade patienter. Den vanligaste diagnosen var ortostatisk hypotoni (40 %) följt av vasovagal synkope (30 %).

Implanterbara hjärtmonitorer (ILR) har en viktig roll för att diagnostisera oklar synkope. I vår sista studie bedömde vi resultaten av primär kontra fördröjd ILR-implantation efter initial synkopeutvärdering. Patienter som genomgick kardiovaskulär autonoma tester och fick ILR grupperades i de som fick ILR (primär ILR) innan respektive efter kardiovaskulära autonoma tester (fördröjd ILR-implantation). Primär ILR-implantation var associerad med oftare positiva fynd på kardiovaskulära autonoma tester jämfört med fördröjd ILR-implantation, men ILR-övervakning utan fynd och pacemakerimplantationer var inte olika mellan grupperna. Varierande blockeringar i vilo EKG förutspådde efterföljande behov av pacemakerimplantation.

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I started my residency at the Department of Cardiology in 2014. As a resident in Cardiology I have met many patients who suffer from syncope. I took part in syncope cases, examinations and following up of these patients. My curiosity regarding recurrent syncope led to more understanding of this medical condition and the effect it has on these patients lives. In clinical work I met my main advisor and syncope expert Assoc. prof. **Artur Fedorowski** and Assoc. prof. **Viktor Hamrefors**. We planned my research together. It has been a both challenging and improving work.

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I hope that my work will make a small contribution to this research area.

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Paper I

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ORIGINAL RESEARCH ARTICLE

Cardiovascular risk after hospitalisation for unexplained syncope and orthostatic hypotension

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ABSTRACT

Objective To investigate the relationship of hospital admissions due to unexplained syncope and orthostatic hypotension (OH) with subsequent cardiovascular events and mortality.

Methods We analysed a population-based prospective cohort of 30 528 middle-aged individuals (age 58±8 years; males, 40%). Adjusted Cox regression models were applied to assess the impact of unexplained syncope/OH hospitalisations on cardiovascular events and mortality, excluding subjects with prevalent cardiovascular disease.

Results After a median follow-up of 15±4 years, 524 (1.7%) and 504 (1.7%) participants were hospitalised for syncope or OH, respectively, yielding 1.2 hospital admissions per 1000 person-years for each diagnosis. Syncope hospitalisations increased with age (HR, per 1 year: 1.07, 95% CI 1.05 to 1.09), higher systolic blood pressure (HR, per 10 mm Hg: 1.06, 95% CI 1.01 to 1.12), antihypertensive treatment (HR: 1.26, 95% CI 1.00 to 1.59), use of diuretics (HR: 1.77, 95% CI 1.31 to 2.38) and prevalent cardiovascular disease (HR: 1.59, 95% CI 1.14 to 2.23), whereas OH hospitalisations increased with age (HR: 1.11, 95% CI 1.08 to 1.12) and prevalent diabetes (HR: 1.82, 95% CI 1.23 to 2.70). After exclusion of 1399 patients with prevalent cardiovascular disease, a total of 473/464 patients were hospitalised for unexplained syncope/OH before any cardiovascular event. Hospitalisation for unexplained syncope predicted coronary events (HR: 1.85, 95% CI 1.49 to 2.30), heart failure (HR: 2.24, 95% CI 1.65 to 3.04), atrial fibrillation (HR: 1.84, 95% CI 1.50 to 2.26), aortic valve stenosis (HR: 2.06, 95% CI 1.28 to 3.32), all-cause mortality (HR: 1.22, 95% CI 1.09 to 1.37) and cardiovascular death (HR: 1.72, 95% CI 1.23 to 2.42). OH-hospitalisation predicted stroke (HR: 1.66, 95% CI 1.24 to 2.23), heart failure (HR: 1.78, 95% CI 1.21 to 2.62), atrial fibrillation (HR: 1.89, 95% CI 1.48 to 2.41) and all-cause mortality (HR: 1.14, 95% CI 1.01 to 1.30).

Conclusions Patients discharged with the diagnosis of unexplained syncope or OH show higher incidence of cardiovascular disease and mortality with only partial overlap between these two conditions.

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INTRODUCTION

Syncope and orthostatic hypotension (OH) are frequently diagnosed in patients admitted to hospital due to transient loss of consciousness (T-LOC), and both have been associated with worse prognosis in population-based studies.[1 2]

The diagnosis of syncope (R55.9, International Classification of Diseases (ICD)-10) is often referred to as a synonym for reflex syncope, the most common cause of T-LOC, accounting for about 50%–60% of cases. Conversely, OH is believed to coexist with 10%–15% of T-LOC episodes,[3] which are then defined as syncope due to OH or autonomic failure. It is universally accepted that recurrent reflex syncope and OH are different clinical manifestations of cardiovascular (CV) autonomic dysfunction. Reflex syncope is an intermittent condition with varying frequency; patients are asymptomatic and appear normal between attacks that may recur only after years.[3] In contrast, OH is a chronic underlying dysfunction of the autonomic nervous system, varying symptomatology and occasional syncope.[4] Although OH and reflex syncope may overlap, especially when orthostatic blood pressure (BP) fall induces a vasovagal reflex, characteristically in delayed OH,[3] these two conditions are seen as separate entities. Unfortunately, the ICD system does not offer a specific 'reflex syncope' code complicating discrimination of syncope aetiologies.

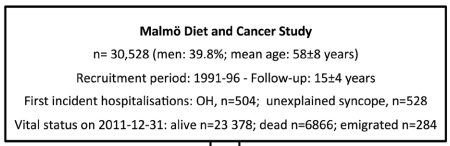
Population-based studies exploring incidence and consequences of hospitalisations where the final diagnosis was unexplained but most likely reflex syncope,[3 5] or more definitely OH, are very sparse. In consequence, discharged patients and their doctors may feel uncertain whether this index incident may imply future risk of CV disease. Moreover, OH is typically a demonstration of abnormal orthostatic BP response,[4] rather than syncope precipitating hospital admission with its prospective risks being based on screening data, including large numbers of asymptomatic subjects.

In this study, we assessed the occurrence of hospitalisations with a final discharge diagnosis of unexplained syncope or OH in a large population-based middle-aged cohort. We then explored the prognostic relationship of these hospitalisations to CV morbidity/mortality among study participants without prevalent CV disease at hospital discharge.

METHODS

Study cohort

The Malmö Diet and Cancer Study is a prospective cohort study in which all men born between 1923 and 1945 and women born between 1923 and 1950 from the city of Malmö, Sweden (total population: 330 000), were invited to participate. The participation rate was ~40%. Men and women,



Outcomes	OH hospital admission (n=464)	Syncope hospital admission (n=473)	No hospital admission (n=28,192)
Coronary event	86	101	2241
Heart failure	49	52	829
Atrial fibrillation	125	124	2348
Stroke	91	70	1901
Aortic stenosis	17	24	374
CV death	47	52	1594
All-cause death	121	138	5230

Figure 1 Flow chart summarising the selection process of study population. CV, cardiovascular; OH, orthostatic hypotension.

total of 30,528, underwent a baseline examination 1991–1996.[6] The average follow-up has been 15±4 years (figure 1). Full description of recruitment and screening procedures have been provided elsewhere.[7]

Definition of clinical characteristics

The participants underwent measurement of body weight and height and BP and filled a questionnaire on health, lifestyle and socioeconomic factors and medications. BP was measured using a mercury-column sphygmomanometer and properly sized right arm cuff after 10 min rest in supine position. Hypertension was defined, according to current guidelines, as systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg, or use of antihypertensive medications.[8] OH was assessed by the method subsequently published by a consensus group in 2011.[9] Baseline diabetes was defined as self-reported physician diagnosis of diabetes or use of antidiabetic medications. Baseline questionnaire recorded the smoking status. The study complied with the Declaration of Helsinki, and the protocol was approved by the regional ethics committee.

Ascertainment of clinical endpoints

All study participants were followed-up through 31 December 2011 by linking a unique 10-digit personal identification number with Swedish National Hospital Discharge Register (SNHDR), Swedish National Cause of Death Register (SNCDR) and Stroke Register of Malmö (STROMA). Event-free subjects (n=284; 0.9%) emigrating from Sweden before 31 December 2011 were assigned date of emigration as last follow-up date. We examined two primary outcomes: (1) first-time hospital admission for unexplained syncope or OH; and (2) first-ever CV event defined as coronary event, stroke, atrial fibrillation, heart failure and aortic valve stenosis. We also analysed two secondary outcomes: CV death and all-cause mortality. Data on the first-time hospitalisation for unexplained syncope or OH were based on primary or main secondary discharge diagnoses according to the ICD-9/10 system (syncope: ICD-9=780.2, and ICD-10=R550.9; OH: ICD-9=458 and ICD-10=I951) as retrieved from SNHDR, excluding cases with concurrent CV diagnoses identified as the primary cause of admission, such as acute coronary syndrome (myocardial infarction or unstable angina), stroke or transient ischaemic attack, cardiac arrhythmia, acute decompensated heart failure and valvular heart disease. In the case that the hospital admission was recorded for both unexplained syncope and OH, we classified the event as OH related, as in-hospital OH diagnosis warrants a positive orthostatic test.

Coronary event was defined as fatal or non-fatal myocardial infarction or death due to coronary heart disease on basis of ICD-9 and ICD-10 codes 410 and I21, respectively, in SNHDR and codes 410, 412 and 414 (ICD-9) or I21–I23 and I25 (ICD-10) in SNCDR. The register-based diagnosis of coronary event in SNHDR has been found to be highly valid.[10]

Fatal or non-fatal stroke was defined according to ICD9 and ICD10 as cases coded 430, 431, 434 and 436 or I60, I61, I63 and I64, respectively. STROMA was used for case retrieval. In addition, SNHDR and SNCDR were used for retrieval of patients who moved out of Malmö. As in previous studies, the outcome of atrial fibrillation was defined as either a diagnosis of atrial fibrillation or atrial flutter and ascertained using diagnosis codes 427.92 for ICD-8, 427D for ICD-9 and I48 for ICD-10. Heart failure (HF) was defined using codes 429 for ICD-9 and I50 and I11.0 for ICD-10. The primary diagnosis of HF in SNHDR has been shown to have an accuracy of 95%.[11] Aortic valve stenosis was defined using codes 424.1 for ICD-9 and I35.0 for ICD-10, including both discharge and surgical diagnoses. In subjects with more than one specific CV event, only the first event was used for analysis.

Statistical analysis

Group differences in continuous variables were compared using Student's t-test. Dichotomous variables were compared using Pearson's χ^2 test. Clinical determinants of syncope and OH-related hospital admissions were analysed using a multivariable-adjusted Cox regression model, controlling for conventional risk factors.

After exclusion of all cases that were preceded by prevalent CV disease at baseline, we further assessed the risk for incident CV events associated with syncope or OH-related hospitalisations. Recorded outcomes were first related to different covariates in an unadjusted model. Thereafter, a Cox proportional hazards analysis was used to calculate adjusted HRs for the coronary event, stroke, heart failure, new-onset atrial fibrillation and aortic valve stenosis associated with prior admission for unexplained syncope or OH. Age, sex, systolic blood pressure, use of antihypertensive therapy, current smoking, diabetes, body mass index (BMI) and use of hypolipidaemic agents were forced to enter the final model. We fitted two different Cox models, each including antihypertensive treatment or different classes of antihypertensive medications, with all other covariates remaining stable. We used the same analytical approach to evaluate potential predictors of first-time hospital admission for unexplained syncope or OH, here including also prevalent CV disease and cancer prior to the assessed event.

Thereafter, cumulative probabilities of all-cause and CV death stratified according to presence or absence of incident hospital admission for unexplained syncope or OH in the participant's history were calculated using the Kaplan-Meier method, and quantified using the log-rank test. Thereafter, Cox proportional hazards analysis was applied to calculate adjusted HR for both all-cause and CV death associated with hospital admissions for OH or syncope.

Two baseline variables had missing values: BMI and systolic BP (SBP). These were always <0.2% of the sample (n<60) and were

Table 1 Baseline characteristics of study population stratified by incident hospital admission for OH or unexplained syncope during follow-up

Characteristic	No OH/syncope hospitalisation n=29 500	OH hospitalisation n=504	Unexplained syncope hospitalisation n=524	p Value
Age (years)	57±8	63±7	62±7	<0.001
Sex (male, %)	37.5	47.4	50.0	<0.001
Body mass index (kg/m^2)	26±4	26±4	27±4	<0.001
Systolic BP (mm Hg)	141±20	147±21	148±21	<0.001
Diastolic BP (mm Hg)	86±10	87±10	88±10	<0.001
Hypertension (%)	61.0	70.6	74.4	<0.001
AHT (%)	17.1	24.8	27.7	<0.001
Diabetes (%)	3.4	7.4	5.6	<0.001
Current smoking (%)	28.4	24.6	25.1	0.053
Prevalent CVD (%)	4.4	7.9	9.7	<0.001
Prevalent cancer (%)	6.2	6.9	5.2	0.48

AHT, antihypertensive treatment; BP, blood pressure; CVD, cardiovascular disease; OH, orthostatic hypotension.

replaced by the average of remaining determinations. There were no missing values in any outcome. All tests were two sided; $p<0.05$ was considered statistically significant. All calculations were performed using SPSS statistical software V.23 for Mac and GraphPad Prism V.6.0 for Mac (GraphPad Software, La Jolla, California, USA).

RESULTS

The mean age of study population was 58±8 years; 40% were men; 61% (n=18 706) had hypertension at baseline (table 1). A total of 1028 patients (3.4%) had at least one hospitalisation for either unexplained syncope (n=524, 1.71%) or OH (n=504, 1.65%).

The average time between baseline and first admission for syncope/OH was 12.3±4.5 years, and the mean age at first hospitalisation was 74.4±7.6 years (range, 50–88 years).

Patients hospitalised for syncope/OH were older, more often male, had higher BMI and higher proportions of hypertension, diabetes and history of CV disease (table 1).

Hospitalisations for syncope were predicted by higher SBP, antihypertensive treatment, in particular use of diuretics, and baseline CV disease, whereas OH-related hospital admissions were predicted by history of diabetes, but not by antihypertensive treatment (table 2).

During follow-up, first-ever coronary event occurred in 2851, stroke in 2307, new-onset heart failure in 1207, atrial fibrillation in 2824 and aortic valve stenosis in 489 persons. Prevalence of CV disease at baseline plus prior to first incident hospitalisation for unexplained syncope/OH was 4.6% (n=1399), yielding 29 129 participants eligible for further analyses. Nine hundred and thirty-seven patients were hospitalised due to unexplained syncope (n=473) or OH (n=464) prior to any CV event, that is, first CV event or diagnosis was recorded at least 7 days after hospital discharge. The average time between first admission for syncope/OH and first-ever CV event was 3.6±3.5 years.

In Kaplan-Meier survival analysis, both incidence of coronary events and stroke were significantly higher among patients who had been hospitalised for OH or unexplained syncope. Patients with syncope-related hospital admission showed a near-significant trend (log-rank test, p=0.061) towards higher rate of coronary events compared with those having incident OH-related admissions (figure 2A). In contrast, OH-related hospitalisation was associated with significantly higher incident risk of stroke (log-rank test, p=0.017) (figure 2B). Multivariable-adjusted Cox regression analyses showed history of syncope hospitalisation was associated with higher risk of incident coronary events, heart failure, atrial fibrillation and aortic valve stenosis, while history of OH hospitalisation predicted incident stroke, heart failure and atrial fibrillation (figure 3).

Table 2 Multivariable-adjusted analysis evaluating potential predictors of recorded outcomes

	OH hospitalisation n=504		Unexplained syncope hospitalisation n=524	
Covariate at baseline	Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Female gender	0.82 (0.67 to 1.01)	0.061	0.81 (0.66 to 0.98)	0.033
Mean BMI, 1-unit increase	0.97 (0.94 to 1.00)	0.025	1.03 (1.00 to 1.05)	0.033
Mean age, 1 year increase	1.11 (1.08 to 1.12)	<0.001	1.07 (1.05 to 1.09)	<0.001
Current cigarette smoking	0.99 (0.77 to 1.26)	0.93	1.10 (0.87 to 1.38)	0.426
Diabetes	1.82 (1.23 to 2.70)	0.003	1.20 (0.79 to 1.84)	0.386
Prevalent CVD	1.30 (0.89 to 1.89)	0.183	1.59 (1.14 to 2.23)	**0.007**
Prevalent cancer	0.73 (0.48 to 1.11)	0.147	0.75 (0.50 to 1.13)	0.167
Systolic BP, 10 mm Hg increase	1.05 (0.99 to 1.10)	0.099	1.06 (1.01 to 1.12)	0.024
ACE-inhibitor	1.06 (0.65 to 1.73)	0.828	0.80 (0.49 to 1.31)	0.378
Beta-blocker	1.17 (0.87 to 1.58)	0.293	0.92 (0.69 to 1.23)	0.584
Calcium channel blocker	0.74 (0.48 to 1.14)	0.177	1.10 (0.77 to 1.57)	0.589
Diuretic	1.06 (0.74 to 1.53)	0.741	1.77 (1.31 to 2.38)	<0.001
AHT*	1.14 (0.89 to 1.46)	0.304	1.26 (1.00 to 1.59)	**0.050**

*Excluding the four classes of antihypertensive drugs from the model.
AHT, antihypertensive treatment; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; OH, orthostatic hypotension.

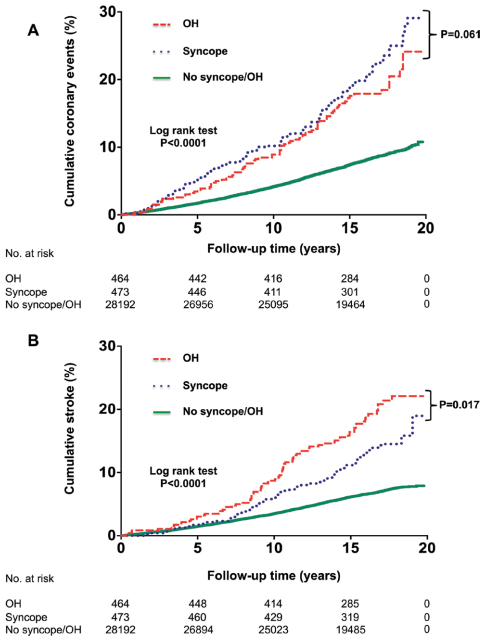


Figure 2 Long-term cumulative incidence of coronary events and stroke according to incident unexplained syncope- and orthostatic hypotension (OH)-related hospital admission *(n=29129)*. Kaplan-Meier curves with regard to coronary events (A) and stroke (B) stratified according to incident syncope-related (blue) and OH-related (red) hospital admissions: in both cases showing significantly lower event-free survival rate (Log-rank test: p<0.001) compared with patients never hospitalised for syncope or OH (green). Patients with a first-ever incident syncope-related hospital admission showed a near-significant trend (Log-rank test: p=0.061) towards higher coronary event rate compared with incident OH-related admission. OH-related hospitalisation was associated with a significantly higher risk of stroke (Log-rank test: p=0.017).

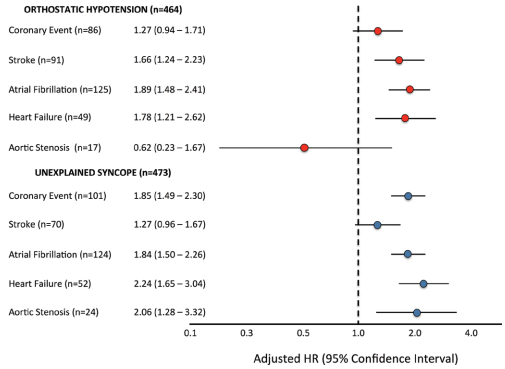


Figure 3 Risk estimation of incident cardiovascular (CV) events in Malmö Diet and Cancer Study cohort (n=29129) associated with history of orthostatic hypotension (OH)-related or unexplained syncope-related hospitalisation during follow-up. Multivariable-adjusted (age, sex, BMI, systolic BP, antihypertensive treatment, diabetes and current smoking) Cox regression model was applied by entering incident hospitalisation for OH or syncope prior to first-ever incident CV event (ie, coronary event, stroke, atrial fibrillation, heart failure and aortic valve stenosis) as an independent variable after exclusion of prevalent CV disease. Results are presented as adjusted HRs with 95% CIs. BMI, body mass index; BP, blood pressure.

Six thousand and eight hundred sixty-six patients (22.5%) died and 354 deaths were preceded by hospitalisation for unexplained syncope/OH. In Kaplan-Meier survival analysis, CV and all-cause mortality rates were significantly higher among patients who had been hospitalised for unexplained syncope (p<0.001) compared with individuals never being hospitalised for syncope/OH (figure 4). In multivariable-adjusted Cox proportional hazard model, adjusting for conventional risk factors, history of syncope hospitalisation was an independent predictor of both CV mortality (adjusted HR: 1.72, 95% CI 1.23 to 2.42, p=0.002) and all-cause mortality (adjusted HR: 1.22, 95% CI 1.09 to 1.37, p=0.001), whereas OH-related hospital admission independently predicted all-cause mortality (adjusted HR: 1.14, 95% CI 1.01 to 1.30, p=0.032) with a trend towards significance for CV mortality (adjusted HR: 1.33, 95% CI 0.93 to 1.92, p=0.124) (table 3).

DISCUSSION

Our study reports that hospital admissions for syncope and OH in middle-aged adults increase with age and convey independent prognostic information with important differences between the two groups. While admissions for either syncope or OH predict all-cause mortality, heart failure and atrial fibrillation, diagnosis of syncope indicates higher risk of coronary events, aortic valve stenosis and CV death. In contrast, admission for OH indicates higher risk of stroke.

Strengths and weaknesses of this study

Our study has several strengths. First, we analysed the prognostic implications of hospital admissions attributed to unexplained syncope and OH in a population-based cohort of approximately 30 000 middle-aged individuals without prevalent CV disease during a particularly long follow-up. Second, Swedish registers are subjected to annual quality control to ascertain completeness of information, and less than 1% of hospital admissions lack a proper discharge record with at least one principal diagnosis.[12] Third, the validity of CV endpoints ascertained in our registers is high, indicating only a small impact of case misclassification bias.

Our study has some important limitations. Most patients with OH or syncope are not admitted to hospital for investigation and are either treated by general practitioners or fail to seek any medical advice. Our study material is therefore selected, and results may reflect a selection bias. Although the broad study from which these data were derived was designed as prospective, we conducted a database retrospective analysis, with its usual weaknesses. Furthermore, in the absence of a rescreening programme, we acknowledge the lack of important clinical information, such as blood pressure, changes in the antihypertensive drug regimen and electrocardiographic data at index event. Finally, in our study population, there was a predominance of women, and female sex was an inverse predictor of syncope (HR: 0.81, 95% CI 0.66 to 0.98). It has been previously reported that female patients may be more prone to experience reflex syncope.[13] Nonetheless, individuals deemed likely to have reflex syncope are usually evaluated as outpatients without hospitalisation.[14]

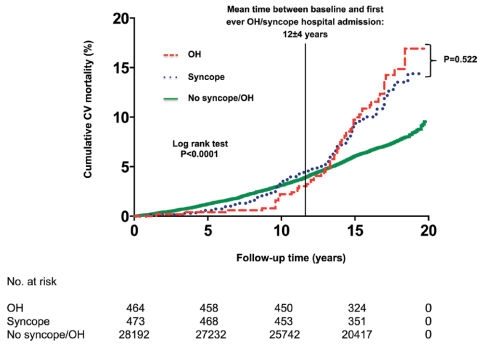


Figure 4 Long-term cumulative incidence of cardiovascular (CV) mortality rates according to incident syncope-related and OH-related hospital admission (n=29 129). Kaplan-Meier curves with regard to CV mortality stratified according to incident syncope-related (blue) and OH-related (red) hospital admission: inpatients showed a significantly lower survival rate (Log-rank test p<0.001) compared with those never hospitalised for syncope or OH (green). The black vertical line at 12 years is a landmark point indicating mean time between baseline and first-ever OH/syncope hospital admission. Thereafter, survival curves for OH/syncope-related hospital admission and non-hospitalised patients begin and continue to diverge. OH, orthostatic hypotension.

Strengths and weaknesses in relation to other studies

The average rate of hospital admissions for syncope was 1.2 per 1000 person-years, which is consistent with the epidemiological data reporting between one and two syncope-related admissions per 1000 person-years in the general population. Patients referred to hospitals constitute only a minority (≈10%) of those who seek medical assistance due to unexplained loss of consciousness. They are usually older and present with features of high-risk syncope that require rapid evaluation.[3] Interestingly, admission rate for OH was very similar.

The estimated prevalence of OH in adults older than 55 years may be extrapolated from previous studies and is approximately 5%–15%.[10 15] If applied to our study population, it would mean that about one in eight patients with OH had been admitted at least once for this condition during follow-up. Admitted patients with OH were most likely more symptomatic: previous studies suggest that majority of patients with OH are unaware of their problem.[16] Apart from age, we identified prevalent CV disease, hypertension, antihypertensive treatment and use of diuretics in particular, as predictors of syncope hospitalisations, in line with recent SPRINT study, where a more intensive treatment arm was associated with higher risk of syncope.[17]

A history of CV disease was also predictive of admission for syncope; a possible explanation is that syncope may have revealed an undetected CV condition, such as paroxysmal cardiac arrhythmia, or that prevalent CV disease predisposed to circulatory collapse by its negative impact on the heart and vessels, for example, via postinfarction cardiomyopathy, valvular heart disease or atrial fibrillation. Unexpectedly, antihypertensive treatment and prevalent CV disease had no impact on OH-related admissions, also in line with the results of SPRINT.[17] This is at variance from the common belief that use of antihypertensive drugs is a major cause of OH.[4] In contrast, diabetes was predictive of OH-related admissions, as is generally accepted.[18]

There is no consensus whether discharge diagnoses of syncope/OH without specific concurrent CV disease should be seen as warning of future CV complications. A report from Framingham showed no increased risk of adverse CV outcomes among patients with vasovagal and orthostatic syncope.[19] However, one-third of syncope aetiology was not defined, and this subgroup demonstrated both higher mortality and CV morbidity. A more recent study suggested hospitalisation for non-cardiac syncope in 'healthy' individuals might predict death, stroke, CV hospitalisation, device implantation and recurrent syncope.[2] Furthermore, among patients presenting syncope at emergency department, the probability of adverse outcome within 2 years is approximately 25%, higher than in general population.[20] However, it cannot be excluded that a serious episode of syncope, even if not associated with detectable CV disorder during hospitalisation, may lead to postdischarge diagnostic vigilance and higher rate of CV disease detection.

Regarding OH, studies exploring long-term prognosis associated with hospital admissions for OH are very sparse. In large population-based cohorts, prevalent OH has been consistently linked with increased mortality and risk of CV events.[1 21–23] However, the occurrence of hospital admissions due to worsening OH, typically syncope and/or unexplained fall trauma, has not been previously reported.

It has been reported that 30%–50% of patients with syncope leave hospital without a clear explanation of cause.[14 24] Older patients admitted due to the event interpreted as unexplained syncope may have had an undetected CV condition, such as paroxysmal cardiac arrhythmia with or without underlying structural heart disease. These results emphasise the role of implantable cardiac monitors in the postdischarge work-up of older patients with unexplained syncope, as proposed by Syncope Unit Project investigators.[25] Moreover, a recent study of patients admitted for a first episode of syncope demonstrated that one in six cases showed evidence of pulmonary embolism as the likely syncope aetiology,[26] rarely considered as a possible diagnosis. It should be also remembered that the presence of vasovagal syncope in a patient's history might be a marker of susceptibility to a coronary event. We have previously reported that history of vasovagal syncope indicates higher likelihood of prevalent myocardial infarction in middle-aged adults.[27]

As expected, patients discharged with a final diagnosis of OH demonstrated increased incidence of CV disease. These patients

Table 3 Risk estimation of cardiovascular (CV) death and all-cause death associated with history of orthostatic hypotension-related or unexplained syncope-related hospitalisation during follow-up in the Malmö Diet and Cancer Study cohort (n=29 129) individuals without prevalent CV disease)

	CV death			All-cause death		
Hospital admission	**Event (n)**	**aHR (95% CI)**	**p Value**	**Event (n)**	**aHR (95% CI)**	**p Value**
Unexplained syncope (n=473)	52	1.72 (1.23 to 2.42)	0.002	138	1.22 (1.09 to 1.37)	0.001
OH (n=464)	47	1.33 (0.93 to 1.92)	0.124	121	1.14 (1.01 to 1.30)	0.034

Model adjusted for age, sex, current smoking, body mass index, diabetes, systolic blood pressure, use of hypolipidaemic agents and antihypertensive treatment.
aHR, adjusted HR; OH, orthostatic hypotension.

had confirmed, and symptomatic OH and should share the same prospective risks as the whole OH population. However, hospital admission due to OH might be seen as a marker of general frailty, comorbidities and higher CV risk compared with asymptomatic OH. We have previously reported that patients with syncope triggered by OH show unfavourable neuroendocrine and procoagulatory changes[28 29] and that OH is associated with structural cardiac changes.[30] Thus, patients with symptomatic OH constitute a vulnerable group in excess of the age-matched population in susceptibility to CV disease, in parallel with high-risk conditions such as hypertension and diabetes.

Meaning of the study

Our study fills an important gap in knowledge suggesting syncope-related and OH-related admissions, without concomitant CV disease, previously seen as benign events, indeed herald higher risk of more serious CV events.

Furthermore, we underline the need for precise classification of syncope aetiology after admission to hospital as prognostic implications of unexplained syncope-related event and OH, although partially overlapping, differ in regard to type of CV event.

CONCLUSIONS

Hospital admissions for syncope and OH in middle-aged adults increase with advancing age and are associated with common comorbidities, diabetes and hypertension. Admission for syncope and OH predicts development of heart failure and atrial fibrillation. Moreover, admission for syncope indicates higher risk of coronary events and aortic valve stenosis, whereas admission for OH predicts stroke. Patients admitted for unexplained syncope have higher risk of both all-cause and CV death, whereas those admitted for OH demonstrate higher all-cause mortality.

Contributors EY: conception and study design, interpretation of data, manuscript drafting and approval of the version of the manuscript to be published. FR: statistical analysis and interpretation of data, manuscript drafting, critical revision of the article and approval of the version of the manuscript to be published. MM: conception and study design, manuscript drafting, critical revision of the article and approval of the version of the manuscript to be published. RS: conception and study design, manuscript drafting, critical revision of the article and approval of the version of the manuscript to be published. SG: interpretation of data, critical revision of the article and approval of the version of the manuscript to be published. RDC: interpretation of data, critical revision of the article and approval of the version of the manuscript to be published. OM: data collection, critical revision of the article and approval of the version of the manuscript to be published. AF: conception and study design, data collection, statistical analysis and interpretation of data, critical revision of the article and approval of the version of the manuscript to be published.

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Key messages

What is already known on this subject?
There is no evidence-based consensus about prognostic significance of hospital admission related to unexplained syncope and orthostatic hypotension (OH).

What might this study add?
Hospital admissions for unexplained syncope and OH, previously seen as benign events, herald higher risk of cardiovascular morbidity and all-cause mortality and convey independent prognostic information. Hospital admission for unexplained syncope indicates higher risk of coronary events (HR: 1.85, 95% CI 1.49 to 2.30) and cardiovascular death (HR: 1.72, 95% CI 1.23 to 2.42), whereas admission for OH significantly predicts stroke (HR: 1.66, 95% CI 1.24 to 2.23).

How might this impact on clinical practice?
Hospital admissions for unexplained syncope and OH should be regarded as a warning sign of future cardiovascular events.

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Heart

Cardiovascular risk after hospitalisation for unexplained syncope and orthostatic hypotension

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Paper II

openheart

Pacing therapy in the management of unexplained syncope: a tertiary care centre prospective study

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ABSTRACT

Objective Pacemaker (PM) therapy is effective when syncope is associated with bradycardia, but syncope recurrences and fall injuries after PM implantation may occur. We aimed to survey indications and outcomes of PM implantation, following evaluation of unexplained syncope.

Methods Among 1666 consecutive unpaced patients investigated in a tertiary syncope unit by carotid-sinus massage (CSM), head-up tilt test (HUT) and ECG monitoring, 106 (6.4%; age, 65 ± 17 years) received a PM. We assessed bradycardia detection methods, PM implantation indications, and explored incidence of recurrent syncope, fall-related fractures and mortality.

Results Indications for PM therapy were met in 32/106 patients (30%) by CSM, in 41/106 (39%) by HUT, in 14/106 patients (13%) by implantable loop-recorder (ILR) and in 19/106 (18%) by standard ECG. Sinus arrest with asystole was the predominant PM indication during CSM/HUT and external ECG monitoring, whereas ILR detected proportionally the same numbers o f asystole due to sinus arrest and atrioventricular block. During follow-up (median, 4.3 years), 15 patients (14%) had syncope recurrence, 15 suffered fall-related fractures and 9 died. Neither syncope recurrence nor fall-related fractures were dependent on initial PM indication. The composite endpoint of recurrent syncope/fall-related fracture was associated with treated hypertension (OR 2.45; 95% CI 1.00 to 6.0), reduced glomerular filtration rate (OR 1.63 per 10 mL/min↓; 95% CI 1.22 to 2.19) and atrial fibrillation (OR 3.98; 95% CI 1.11 to 14.3). Recurrent syncope predicted increased mortality (OR 9.20; 95% CI 1.89 to 44.8).

Conclusions Cardiovascular autonomic testing and ECG monitoring effectively identify pacing indications in patients with unexplained syncope. After PM implantation, treated hypertension, renal failure and atrial fibrillation predict syncope recurrence and fall-related injury. Recurrent syncope predicts increased mortality.

Key questions

What is already known about this subject?

- Recurrent syncope and unexplained injuries in paced patients are important clinical problems commanding prompt assessment.

What does this study add?

- Indications for pacing in patients presenting with unexplained syncope can be identified by cardiovascular autonomic tests alone in over two-thirds of cases.
- Paced patients presenting with recurrent syncope and fall-related injuries often suffer from reflex syncope susceptibility and orthostatic hypotension.
- Treated hypertension, atrial fibrillation and renal dysfunction are independent predictors of syncope recurrence and fall-related injuries in pacemaker patients.
- Recurrent syncope in paced patients predicts higher mortality.

How might this impact on clinical practice?

- Recurrent syncope in paced patients flags progressive deterioration of cardiovascular and autonomic nervous systems and is associated with adverse outcome.
- Additional research is needed to understand the role of comorbidities and polypharmacy on the efficacy of pacing therapy for syncope and prevention of low-energy fractures.

INTRODUCTION

Syncope is defined as transient loss of consciousness due to cerebral hypoperfusion, with a rapid onset, short duration and spontaneous complete recovery.[1 2] The vast majority of syncopal events is caused by abnormal behaviour of the circulatory system, where three main mechanisms may be encountered: reflex, autonomic failure or primary disease of the heart and great vessels.[2] In the latter, bradycardia is the predominant mechanism.[2]

Cardiac pacing has been the established method of treating bradycardia since 1958. Although very successful in cardiac syncope due to intrinsic atrioventricular block (AVB), with syncope recurrence rate of about 5% over 5 years,[3] pacemaker (PM) therapy in reflex syncope of cardioinhibitory type (asystole >3 s) is not as effective.[4] In the presence of hypotensive susceptibility indicated by a positive head-up tilt test (HUT),[5] syncope recurrence rate may be as high as 25%–50%, whereas negative HUT heralds pacing

efficacy very similar to that in AVB.[4 5] Thus, cardiac pacing is an effective treatment of syncope when applied in patients with either intrinsic AVB or in cardioinhibitory reflex syncope with a modest hypotensive susceptibility (so-called 'vasodepressor component'). This approach has been confirmed in the Syncope Unit Project-2,[6 7] which combined a thorough autonomic assessment with long-term ECG monitoring. The current European Society of Cardiology (ESC) syncope guidelines state that pacing the reflex form is recommended in patients >40 years of age with recurrent attacks, absence of prodrome and traumatic falls (Class IIA).[2] When syncope is unexplained, a stepwise algorithm has been proposed with cardiovascular autonomic assessment initially and prolonged ECG monitoring with implantable loop-recorder (ILR) to follow, if required.[2 6 7]

In this study, we explored the outcomes of the proposed strategy applied in a series of patients with unexplained syncope after initial evaluation. Further, we assessed the incidence of syncope recurrence and fall injury after PM implantation. Our study was performed in a tertiary referral centre with full access to all recommended diagnostic modalities and therapeutic options according to current syncope guidelines.[1 2]

METHODS

Study setting and population

The Syncope Study of Unselected Population in Malmö (SYSTEMA) project was initiated to investigate systematically and manage patients with unexplained syncope.[8] Between August 2008 and December 2016, 1705 patients with suspected syncope that is, unexplained transient loss of consciousness by initial evaluation, who were referred to the tertiary Syncope Unit of Skåne University Hospital, Malmö, Sweden, were enrolled and underwent cardiovascular autonomic assessment including carotid sinus massage (CSM) and HUT.[2] Following cardiovascular autonomic tests, patients were monitored using an ILR, if the aetiology of syncope could not be established. In addition to the main syncope workup, other tests may have been carried out, including exercise and external long-term ECG, echocardiography, coronary angiography, brain imaging and electroencephalogram, whenever appropriate.

Examination protocol

Cardiovascular autonomic tests included CSM, supine and upright, if appropriate, according to Newcastle protocol,[9] and tilt-table testing at 60°–70° plus optional nitroglycerin provocation according to the Italian protocol.[10] The patients were asked to take their regular medication and fast for 2 hours before the test, although they were allowed to drink water freely. Beat-to-beat blood pressure (BP) and ECG were continuously monitored using a non-invasive validated method (Nexfin monitor, BMEYE, Amsterdam, Netherlands), and subsequently analysed offline using a dedicated programme provided by the monitor manufacturer. In addition, the patients were asked to complete a questionnaire, which explored medical history, duration, frequency and features of syncope-related symptoms, smoking status, and current pharmacological treatment. The study complied with the Declaration of Helsinki, the Regional Ethical Review Board in Lund, Sweden accepted the study protocol (ref no 82/2008), and all study participants gave their written informed consent.

Diagnostic criteria of orthostatic hypotension, carotid sinus syndrome and reflex syncope

The following diagnostic criteria were applied: (a) reproduction of symptoms (dizziness, lightheadedness, presyncope and syncope), if patients were able to recall conditions preceding syncope, and (b) conventional criteria of orthostatic hypotension (OH), carotid sinus syndrome (CSS) and vasovagal reflex syncope (VVS).[2] Briefly, OH was defined as sustained decrease in systolic BP (SBP) ≥20 mm Hg and/or decrease in diastolic BP (DBP) ≥10 mm Hg or SBP <90 mm Hg, CSS as a fall in SBP ≥50 mm Hg and/or asystole >3 seconds with reproduction of syncope/symptoms while VVS as a reproduction of syncope associated with a characteristic pattern of pronounced hypotension with or without bradycardia/asystole.[2] The cardioinhibitory Vasovagal International Study (VASIS) IIB type of VVS was defined as asystole >3 seconds.[11]

Post-test workup

All patients were informed of test results, instructed how to cope with attacks, and complementary pharmacological and non-pharmacological interventions were applied according to current guidelines.[2] Patients with asystolic cardioinhibitory reflex (VASIS IIB on CSS or VVS) and recurrent, traumatic or unexpected syncopal attacks, especially if aged >40 years, were offered pacing therapy without further ILR monitoring. For patients younger than 40 years, an individual risk assessment and open discussion with the patient preceded the decision to pace. If the tests results were inconclusive or syncope, diagnosis could not be established after first-line evaluation using autonomic tests, patients with little or no prodrome, recurrent and traumatic attacks received an ILR. ILR patients who had positive non-asystolic HUT and/or CSM were instructed how to counteract the hypotensive reflex tendency according to current guidelines.[2] Those who showed asystole >3 s during a symptomatic episode were offered PM therapy, regardless of HUT/CSM results. In selected cases, where the autonomic tests were negative or inconclusive, and resting ECG demonstrated bifascicular block or significant bradycardia <40 bpm, patients were offered PM therapy based on their clinical characteristics such as advanced age, comorbidities and history of unpredictable syncope associated with serious trauma, as recommended by current guidelines.[2] This decision was reached by consensus between syncope expert (AF) and PM implanting specialist (TP). In a subset of patients, if

autonomic tests were performed during hospitalisation, and in-hospital external ECG monitoring (telemetry or Holter-monitoring) detected significant arrhythmia, PM was implanted without ILR monitoring.

The standard PM programming was dual chamber pacemaker (DDD) mode in a range 50–60 to 120–160/min. In selected cases of HUT-induced asystolic reflex with strong vasodepressor component preceding asystole, PM was programmed in DDD mode with closed-loop stimulation (CLS) (Biotronik, Berlin, Germany), and in patients with permanent atrial fibrillation VVI mode was selected.

Follow-up evaluation

The first author (EY) reviewed the medical records of all patients with PM implantation retrieving the following data: date of PM implantation, PM indication, information on syncope recurrence or unprovoked fall injury associated with low-energy fracture, as a possible syncope-proxy,[12] and date and cause of death during follow-up period through 31 December 2017 (median, 4.3 years; range 1.2–9.3 years). Data and aetiologies of syncope recurrences and fall-related traumatic injuries were obtained by reviewing the medical records of the events, including history, PM settings and memory, any additional tests performed (such as orthostatic tests) as well as the final diagnosis by the responsible physician. VVS and OH were judged as aetiological factors when they were diagnosed in accordance with guidelines[1 2] and in case of discrepancy between the diagnosis originally suggested by the responsible physician and the senior author who reviewed the records, the diagnosis was changed accordingly. In case the diagnosis was uncertain, the endpoint was assessed by adjudication between the first (EY) and the senior author (AF). Following primary endpoints were considered in the analyses: first recurrent syncope, first fall-related low-energy fracture and composite endpoint of either recurrent syncope or low-energy fracture.

Statistical analysis

The main characteristics of the study population are presented as mean and SD for continuous variables, and percentages for categorical variables. Group differences in continuous variables were compared using analysis of variance, and dichotomous variables were compared using Pearson's χ^2 test.

Logistic regression model was applied to assess the relationship between the composite primary endpoint (recurrent syncope or low-energy fracture) and clinical patient characteristics. Moreover, we analysed relations between post-PM implantation mortality, recurrent syncope and fall injuries. All tests were two-sided and p value <0.05 was considered statistically significant. All calculations were performed using IBM SPSS Statistics software V.25.0 (SPSS, Chicago, IL, USA) and GraphPad Prism V.6.00, GraphPad Software (La Jolla, CA, USA), www.graphpad.com.

RESULTS

Patient characteristics

Of 1705 patients investigated, 39 (2.3 %) had a PM at the time of the evaluation and were excluded from the study. Of the remaining 1666 patients, 106 (6.4 %) received a new PM following evaluation (figure 1). Compared with the rest of the cohort, patients who received a PM following evaluation were older and more often men (table 1). The majority of patients that received a new PM (71%) were >60 years. Baseline characteristics stratified by age (over/under 60 years) are shown in online supplementary table S1.

Pacing indications and outcomes in patients with new PMs

The pacing indications and the diagnostic methods are reported in figure 2. In 73 of 106 patients (68.9%), the pacing indications were identified during cardiovascular autonomic tests, that is, CSM/HUT, whereas a smaller proportion of pacing indications (n=14) was found on ILR (13.2%). Abnormal resting ECG constituted 7.5%, whereas in-hospital ECG monitoring accounted for 10.4% of all PM indications.

Of all patients in the SYSTEMA cohort that were examined during the period of study, 32 of 215 patients with positive CSM (14.8%) received PM while among 933 patients with positive HUT (ie, VVS), only 41 (4.4%) were implanted with PM, of these seven with CLS-PM. There were three patients with asystolic vasovagal reflex and recurrent/traumatic falls who declined PM implantation (two women and one man, all >40 years). In the subset of patients investigated with ILR (n=128), the 14 patients who received PM constituted a minority (10.9%) of all monitored subjects.

Sinus arrest during CSM/HUT and external ECG monitoring was the predominant diagnosis leading to PM implantation. ILR detected proportionally the same numbers of sinus arrest without ventricular escape and AVB while intraventricular block dominated as indication obtained from resting ECG (table 2). Method of detection and pacing indications stratified according to age <60/>60 years are shown in (online supplementary tables S2, S3).

During follow-up (median 4.3 years; range 1.2–9.3 years), 15 patients (14.2 %) had syncope recurrence. The most common diagnoses in these patients were OH and VVS (table 3). Among patients in whom PM indications were detected by ILR, syncope reoccurred in 5 of 14 (36%). Of these, PM indications were sinus arrest in two and AVB in three patients. In four of these five patients, cardiovascular autonomic tests performed prior to ILR monitoring and PM implantation demonstrated non-cardioinhibitory CSS (n=2), vasovagal reflex without asystole (n=1) and OH (n=1), indicating a concurrent hypotensive susceptibility. Patients in whom PM indications were met during HUT had lower syncope recurrence rate; syncope reoccurred in 5/41 patients (12.2 %). The corresponding PM indications were asystolic VVS (n=3) and VVS-induced AVB (n=2), respectively. Of

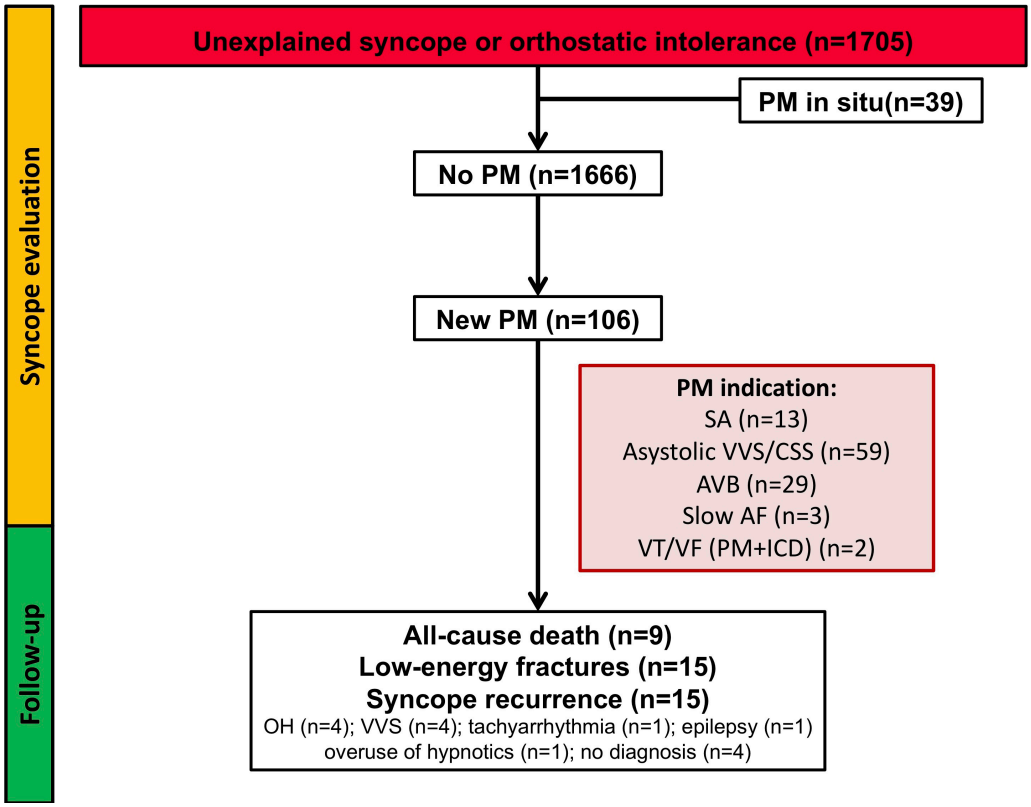

Figure 1 Flow chart of the study population. The diagram summarises the diagnostic workup and follow-up of patients presenting with unexplained syncope or symptoms of orthostatic intolerance. AF, atrial fibrillation; AVB, intraventricular/atrioventricular block; CSS, carotid sinus syndrome; ICD, implantable cardioverter defibrillator; OH, orthostatic hypotension; PM, pacemaker; SA, sinus arrest; VT/VF, ventricular tachycardia/ventricular fibrillation; VVS, vasovagal syncope.

note, among seven patients who received CLS-PM, there were no syncope recurrences. Among 32 paced patients diagnosed with cardioinhibitory CSS there were five recurrences of syncope (15.6%).

In all, 15 patients (14.2%) suffered unexplained fall-related fractures during follow-up. Of these, six fractures occurred among 41 patients (15%) in whom PM indication was found during HUT, 4 among 32 patients (13%) diagnosed during CSM, 2 among 11 patients (18%) diagnosed by ECG monitoring and 3 among 14 patients (21%) diagnosed by ILR.

Using the composite endpoint, 28 (26%) experienced either syncope or fall-related low-energy fracture during follow-up (15 syncope; 15 fractures, combined syncope/fracture in two patients; figure 1). The clinical factors identified at the time of evaluation, associated with the endpoint, were hypertension and concurrent antihypertensive treatment with either thiazides or angiotensin receptor blockers, or both, reduced renal function and atrial fibrillation (table 4). Results by age over/under 60 years are shown in Tables S4.

During follow-up, nine patients with newly implanted PM died: five patients with and four patients without preceding syncope recurrence. None of those deaths were PM or bradycardia related. Syncope recurrence was associated with mortality (OR 9.20; 95% CI 1.89 to 44.8; p=0.006) after adjustment for age and sex. Furthermore, three patients with fall-related fracture died, and in the remaining group there were accordingly six deaths. Fall-related fractures were not associated with increased mortality (OR: 2.62; 95% CI, 0.52 to 13.3; p=0.25).

DISCUSSION

In this study, we observed that (i) indications for pacing in patients presenting with unexplained syncope can be identified in 70% by cardiovascular autonomic tests, that is, CSM, head-up tilt testing and in 13% by insertable

Table 1 Patient characteristics (n=1666) at the time of initial evaluation stratified according to pacemaker status after completed syncope workup. Patients with previous pacemaker were excluded

	Patients with new pacemaker (n=106)	Patients without pacemaker (n=1560)	P value
Age, years	65.5 (16.8)	50.9 (21.8)	<0.001
Sex, % female	45.3	61.8	<0.001
Reported history of			
Syncope, %	98.1	91.0	0.014
Dizziness, n %	68.3	72.9	NS
Number of syncope episodes, md (range)	7 (0–100)	4 (0–1350	NS
Duration of symptoms, years, md (range)	7 (0–70)	3 (0–77)	<0.001
SBP, mm Hg	139.1 (22.2)	130.9 (22.4)	<0.001
DBP, mm Hg	71.4 (10.5)	71.6 (10.2)	NS
Resting heart rate, bpm	66.3 (11.6)	70.5 (12.6)	<0.001
eGFR, mL/min	79.3 (27.8)	96.4 (35.6)	<0.001
EF, %	54 (3)	54 (3)	0.418
Hypertension, %	39.4	27.8	0.011
Antihypertensive therapy, %	39.8	33.4	0.185
ACE inhibitors	10.7	9.6	0.721
ARB	16.5	9.2	0.014
Thiazides	10.7	6.4	0.090
Beta blockers*	14.6	18.5	0.322
CAD, %	7.8	6.3	NS
Atrial fibrillation, %	10.4	6.3	NS
Heart failure, %	6.8	3.1	<0.001

*Beta blockers were discontinued prior to the examination.
ARB, angiotensin II receptor blockers; CAD, coronary artery disease; DBP, diastolic blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate;SBP, systolic blood pressure.

cardiac monitors; (ii) recurrent syncope and traumatic falls following PM implantation are common and over-represented in patients with hypertension taking antihypertensive therapy, atrial fibrillation and renal dysfunction and (iii) recurrent syncope after PM implantation is associated with increased mortality.

The literature on pacing has hitherto largely focused on ECG diagnosis in order to select patients for successful pacing, reaffirmed by the 2013 ESC guidelines on pacing.[13] Follow-up of patients with clear ECG pacing indication has not been widely assessed, the emphasis being on technical faults and comorbidity, some induced by pacing, for example, heart failure. Recurrent syncope has had less attention than it deserved, being its relative rarity a partial explanation. Early series about recurrent syncope in PM recipients raised the possibility of autonomic causes, although a full battery of autonomic investigations was not available to those investigators.[14 15] Using a prospective investigational protocol including cardiovascular autonomic tests, CSM and HUT, completed, when necessary, by ILR, we have been able to provide insights into the aetiological and prognostic significance of syncope recurrence after PM implantation. In particular, we have shown that recurrence during follow-up is relatively common compared with the known data on AVB patients who are permanently paced.[3 16] Sinus arrest without ventricular escape was associated frequently with recurrent syncope aetiology in our patient group among those with recurrent syncope (41%); thus, it should be considered that many of these patients have the 'extrinsic' form of sinus node disease,[15] implying that these patients also have reflex syncope.[2]

Our results affirm the importance of a comprehensive diagnostic workup before a decision is made to implant a PM in patients without a clear explanation for syncope, as this may influence selection of pacing as therapy, type of device to be implanted and its programming. Moreover, concentrating resources and expertise in a dedicated facility—that is, syncope unit[17]—might be another important factor to achieve optimal diagnostic and therapeutic efficacy of unexplained syncope management. Our results seem to support this approach as cardiovascular autonomic tests are not widely available and cardiologists may have limited knowledge of test interpretation.

Another prominent aspect of this study is association between syncope recurrences and prevalent hypertension. Patients who are hypertensive and receiving antihypertensive medication tend to form a substantial part of the paced patient population. From our study, it appears that hypertensive patients are particularly vulnerable to recurrent syncope, likely due to excessive antihypertensive therapy. This is in line with the results of the Systolic Blood Pressure Intervention Trial (SPRINT) and Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trials,[18 19] where serious adverse events defined as hypotension and syncope occurred more frequently in the intensive-treatment group. The possible unwanted effect of antihypertensive therapy could be also explained by the higher prevalence of hypotensive susceptibility in our study population, which may offer greater sensitivity to BP-reducing drugs.[5] Interestingly, hypertension is a risk factor for rehospitalisation after hip-fracture surgery, in many cases due to traumatic fall as also is treatment with thiazides.[20] It should be kept in mind that recent North American hypertension guidelines recommend even lower therapeutic goals (BP <130/80 mm Hg), which should be considered reservedly when treating patients with history of syncope.[21] Notably, the Stop vasodepressor drugs in reflex syncope (STOP-VD) trial[22] has shown that recurrence of syncope and presyncope could be significantly reduced by discontinuing/reducing vasoactive therapy in most elderly patients affected by reflex vasodepressor syncope.

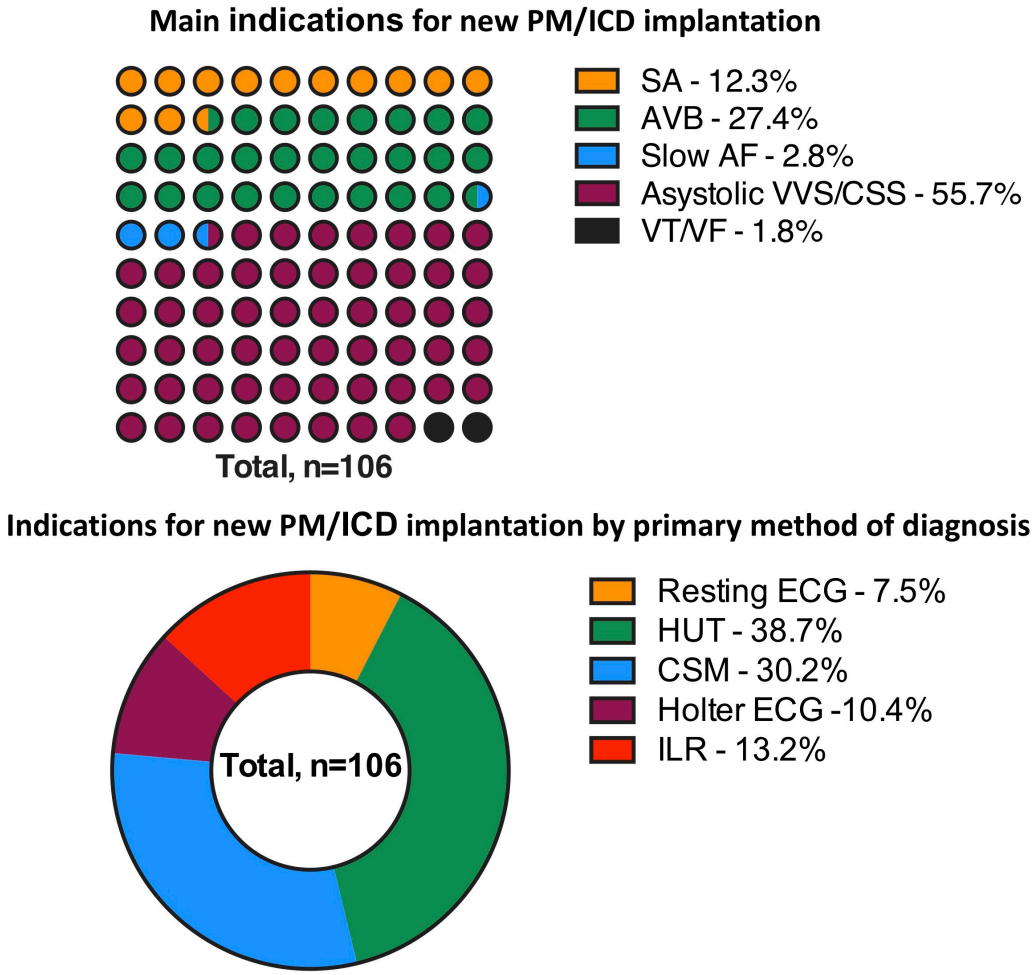

Figure 2 Main indications for new PM/ICD implantation and primary methods of diagnosis; 73 of the 106 patients (69 %) revealed a pacing indication during HUT or CSM: asystolic VVS/CSS in 59 (81%) cases, AVB in 13 (18%) and slow AF in 1 (1%). AF, atrial fibrillation; AVB, atrioventricular block; CSM, carotid-sinus massage; CSS, carotid sinus syndrome; HUT, head-up tilt test; ICD, implantable cardioverter defibrillator; ILR, implantable loop-recorder; PM, pacemaker; SA, sinus arrest; VT/VF, ventricular tachycardia/ventricular fibrillation; VVS, vasovagal syncope.

In our cohort, two other factors were associated with syncope recurrence and fall-related fractures after PM implantation: renal failure and atrial fibrillation. This is also in agreement with previous findings from a Danish nation-wide study of patients with first-time syncope where atrial fibrillation and impaired renal function were found to be independent predictors of recurrent syncope, especially in the youngest segment of the population, that is, <65 years.[23 24] Similar findings were reported by an Irish group, where hypertension and AF were associated with increased fall propensity.[25] Both conditions affect the compensatory mechanisms governed by autonomic and cardiovascular systems: renal failure hampers body fluid homeostasis, whereas atrial fibrillation portends a significant loss of autonomic control of chronotropic response, both crucial for baroreflex function. It is also plausible that hypertension is aetiologically associated with both reduced renal function and atrial fibrillation, leading to a vicious circle requiring careful judgement of risks and potential benefits of intensive BP reduction (figure 3).

While aggressive hypotensive therapy may serve to improve cardiovascular outcomes and other surrogate

Table 2 Pacing indications according to the method of diagnosis in patients with newly implanted pacemaker after completed syncope workup

	Resting ECG	HUT*	CSM*	External ECG monitoring	ILR	Total
SA or asystolic reflex*, n	1	33	26	6	6	72
Atrioventricular block, n	7	8	5	3	6	29
Slow AF, n	0	0	1	1	1	3
SA plus VT/VF, n	0	0	0	1	1	2
Total	8	41	32	11	14	106

*In the cases where HUT or CSM were applied, the diagnosis was asystolic (cardioinhibitory) reflex and the absence of p-waves.
AF, atrial fibrillation;CSM, carotid-sinus massage; HUT, head-up tilt test; ILR, implantable loop recorderSA, sinus arrest; VF, ventricular fibrillation; VT, ventricular tachycardia; VVS, vasovagal syncope.

endpoints of cardiovascular prognosis, there can be little doubt that syncopal recurrence has a significant impact on quality of life, remarkably debilitating in this age group, and is also associated with high healthcare costs, increased risk of fall-related injuries and cardiovascular and all-cause death.[24] Particularly, hip fractures are major consequences of syncope-related falls and are associated with approximately 25% reduction of life expectancy and institutionalisation rates ranging between 8% and 34% in community-dwelling patients.[26] Differentiation between falls and syncope is challenging, especially among elderly patients with cognitive impairment and experience from dedicated syncope and fall facilities reinforces the evidence of an overlap between these two entities, which are often indistinguishable and likely manifestation of the similar underlying pathophysiology.[27] Both non-accidental falls and syncope show strong association with antihypertensive treatment and number of prevalent cardiovascular conditions including atrial fibrillation.[27] A possible explanation for this overlap is that haemodynamic changes insufficient to cause critical cerebral hypoperfusion but sufficient to reduce cerebral perfusion play a part in falls and consequent low-energy fractures especially in older patients already compromised by gait and balance abnormalities and impaired protective reflexes. These results warrant further observational and interventional studies on the role of chronic conditions that may influence the efficacy of PM therapy in syncope.

Finally, although the number of patients who died during the follow-up period was relatively small, there was a distinct correlation between recurrent syncope and increased mortality, in concordance with our previous reports.[28 29] Thus, clinicians should be vigilant when syncope recurs as it may indicate further deterioration of cardiovascular and autonomic systems or be a red flag signalling increased risk of falls, fractures, hospital admissions and other potentially life-threatening conditions.

Strengths and limitations

The principal strengths of this work were (i) the prospective nature of the study conducted in a tertiary referral syncope unit with full access to all recommended diagnostic modalities and therapeutic options according to current syncope guidelines and (ii) length of follow-up.

We acknowledge some limitations of the present work: (i) this is a single-centre observational study and our

Table 3 The aetiology of syncope/T-LOC recurrence among patients who received pacemaker after completed syncope workup

	All (n=106)
No syncope recurrence, n (%)	91 (85.8)
Syncope recurrence, n (%)	15 (14.2)
Orthostatic hypotension, n (%)	4 (26.7)
Vasovagal syncope, n (%)	4 (26.7)
Tachyarrhythmia, n (%)	1 (6.7)
Epileptic seizure*, n (%)	1 (6.7)
Hypnotics overuse*, n (%)	1 (6.7)
No diagnosis, n (%)	4 (26.7)

*Not syncope by definition.
T-LOC, transient loss of consciousness.

Table 4 Factors associated with the composite endpoint of syncope recurrence and fall-related low-energy fracture (n=28) among 106 patients who received pacemaker after completed syncope workup

	OR (95 % CI)	P value
Age, per year	1.03 (1.00 to 3.75)	0.081
Female sex	1.57 (0.66 to 3.75)	0.306
Hypertension	2.45 (1.00 to 6.00)	0.049
Use of thiazides and/or ARB	3.14 (1.16 to 8.49)	0.024
eGFR, per 10 mL/min decrease	1.63 (1.22 to 2.19)	0.001
Atrial fibrillation	3.98 (1.11 to 14.3)	0.034
Use of hypnotics	2.96 (0.40 to 22.1)	0.290
Diagnosis of OH	0.68 (0.26 to 1.73)	0.414
Diagnosis of VVS	0.54 (0.23 to 1.30)	0.168

ARBs, angiotensin receptor blocker OH, orthostatic hypotension ; VVS, vasovagal syncope; eGFR, estimated glomerular filtration rate according to Cockcroft Gault formula.

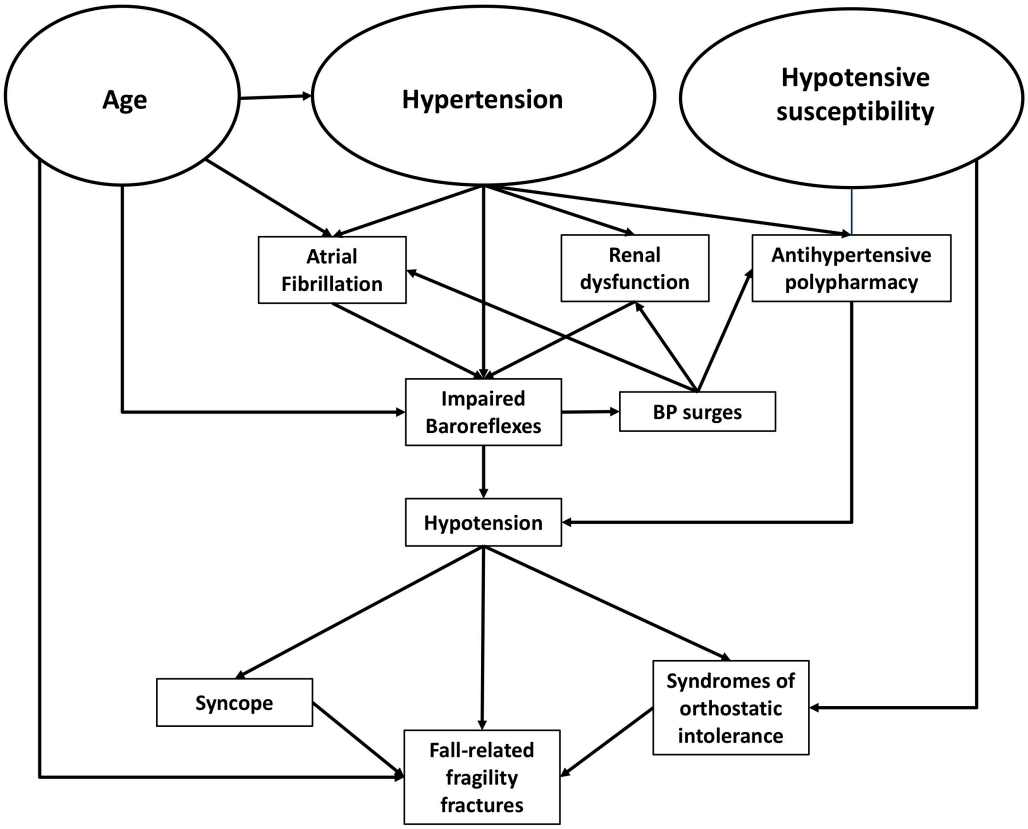

Figure 3 Pathophysiological mechanisms underlying impaired baroreflex function and recurrent syncope in paced patients.

results need confirmation in independent and larger samples; (ii) our study sample is small but in the light of our findings we felt that an early report is appropriate; (iii) our study sample reflects a selected population of individuals referred to a tertiary syncope unit and may not reflect the general syncope population and (iv) patients with PMs implanted due to primary cardiac arrhythmia detected prior to our evaluation in the syncope unit were not included.

Conclusions

Cardiovascular autonomic tests and insertable cardiac monitors reveal pacing indications in most patients presenting with unexplained syncope. In syncope patients with newly implanted PMs, prevalent hypertension associated with antihypertensive treatment, renal failure and atrial fibrillation may predict recurrent syncope and fall injury. Syncope recurrences in paced patients herald increased risk of death.

Contributors FR, AF, HH and EY had full access to all the data in the study and take responsibility of the data and accuracy of the data analysis. OM, AF, HH, VH and TP contributed to the study conception and design. OM and AF contributed to the acquisition of data. All authors analysed and interpreted the data. AF was the study supervisor. AF, FR and VH did the statistical analysis. EY, FR, AF and VH drafted the manuscript with critical revision for important intellectual content from all authors.

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Competing interests AF reports personal fees from Cardiome Corp. and a patent Thermofisher pending outside the submitted work; RS reports personal fees and other from Medtronic Inc., Abbott Laboratories Inc. outside the submitted work; RS performs consultancy for Medtronic Inc.; RS is a member of the speaker's Bureau of Abbott Laboratories Inc.; RS is shareholder in Boston Scientific Inc., Edwards Lifesciences Inc., and Astrazeneca PLC; no other relationships oractivities that could appear to have influenced the submitted work.

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Paper III

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ORIGINAL RESEARCH
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Cardiovascular Autonomic Dysfunction Is the Most Common Cause of Syncope in Paced Patients

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Introduction: Syncope and orthostatic intolerance in paced patients constitute a common clinical dilemma. We, thus, aimed to determine the etiology of syncope and/or symptoms of orthostatic intolerance in paced patients.

Methods: Among 1,705 patients with unexplained syncope and/or orthostatic intolerance that were investigated by cardiovascular autonomic tests, including Valsalva *maneuver,* active standing, carotid sinus massage, and tilt-testing, 39 patients (2.3%; age 65.6 years; 39% women) had a cardiac implantable electronic device (CIED). We explored past medical history, diagnoses found during cardiovascular autonomic tests, and the further clinical workup, in case of negative initial evaluation.

Results: An etiology was identified during cardiovascular autonomic tests in 36 of the 39 patients. Orthostatic hypotension (n = 16; 41%) and vasovagal syncope (n = 12; 31%) were the most common diagnoses. There were no cases of pacemaker dysfunction. The original pacing indications followed guidelines (sick-sinus-syndrome in 16, atrioventricular block in 16, atrial fibrillation with bradycardia in five). Twenty-two of the 39 patients (56%) had experienced syncope prior to the original *CIED* implantation. Orthostatic hypotension was diagnosed in seven (32%) and vasovagal syncope in nine (41%) of these patients. Of the 17 patients that had not experienced syncope prior to the original CIED implantation, nine patients (53%) were diagnosed with orthostatic hypotension and vasovagal syncope was diagnosed in three (18%). Of the 39 patients, two had implantable cardioverter-defibrillators to treat malignant ventricular arrhythmias diagnosed after syncopal episodes.

Conclusion: Cardiovascular autonomic tests reveal the etiology of syncope and/or orthostatic intolerance in the majority of paced patients. The most common diagnosis was orthostatic hypotension (40%) followed by vasovagal syncope (30%), whereas there were no cases of pacemaker dysfunction. Our results emphasize the importance of a complete diagnostic work-up, including cardiovascular autonomic tests, in paced patients that present with syncope and/or orthostatic intolerance.

Keywords: pacemaker, pacing, syncope, orthostatic intolerance, cardiovascular autonomic tests

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INTRODUCTION

Syncope is defined as transient loss of consciousness (T-LOC) due to cerebral hypoperfusion, with a rapid onset, short duration, and spontaneous complete recovery (1, 2). For most syncopal events, three main mechanisms may be encountered: reflex syncope, orthostatic hypotension, and cardiac syncope, the latter including bradyarrhythmia as the predominant mechanism (1, 2). Although cardiac pacing is usually very successful in cardiac syncope due to bradyarrhythmia, with syncope recurrence rate of about 5% over 5 years (3, 4), successful pacemaker therapy in reflex syncope of cardioinhibitory type, meaning an asystole longer than 3 s or bradycardia below 40 beats per min, may be challenging (5). In case of concurrent hypotensive tendency, which may be observed as a significant decrease in blood pressure in standing position during head-up tilt test (HUT) (6), the syncope recurrence rate may be as high as 25–50%. In contrast, normal blood pressure response during HUT (tilt-negative) heralds pacing efficacy being almost the same as in primary bradyarrhythmia (5, 6). Thus, cardiac pacing is an effective treatment against syncope when applied in patients with either primary cardiac bradyarrhythmia or in the cardioinhibitory form of reflex syncope, with only a modest hypotensive tendency or so-called "vasodepressor reflex component".

This approach has been confirmed in the Syncope Unit Project (SUP)-2 reports (7, 8) and current guidelines recommend pacing reflex syncope in selected patients >40 years with recurrent attacks, absence of prodrome and traumatic falls (1). When syncope is unexplained, a stepwise algorithm has been proposed with cardiovascular autonomic assessment as initial stage, and prolonged ECG monitoring by insertable cardiac monitor (ICM) as the next stage, if required (8). However, unexplained syncope and/or orthostatic intolerance in patients with an already implanted pacemaker constitutes a diagnostic and therapeutic challenge and studies addressing clinical management in such patients are sparse. In the current study we, thus, explored the etiology of unexplained recurrent syncope and/or orthostatic intolerance in paced patients.

MATERIALS AND METHODS

Study Setting and Population

The patients in the current study were all from The Syncope Study of Unselected Population in Malmö (SYSTEMA). SYSTEMA was initiated to investigate systematically and manage patients with unexplained syncope (9). Between August 2008 and December 2016, a total of 1,705 patients with suspected syncope i.e., unexplained T-LOC by initial evaluation, who were referred to the tertiary Syncope Unit of Skåne University Hospital, Malmö, Sweden, were enrolled. All 1,705 patients underwent cardiovascular autonomic assessment including carotid sinus massage (CSM), HUT and Valsalva maneuver (1, 2). Along with the main syncope workup, additional tests may have been carried out, including exercise, and external long-term ECG, echocardiography, coronary angiography, brain imaging, and EEG, whenever appropriate. If carotid bruits were detected during admission or hospitalization, a carotid duplex ultrasonography was performed ahead of autonomic tests to rule-out significant carotid artery stenosis.

Cardiovascular Autonomic Test Examination Protocol

The patients were asked to take their regular medication and fast for 2 h before the test, although they were allowed to drink water without restriction. Prior to examination, the patients were asked to complete a questionnaire, which explored past medical history, duration, frequency and features of syncope-related symptoms, smoking status, and current pharmacological treatment. The cardiovascular autonomic tests included CSM, if appropriate (i.e., if age $\geq$ 40 years and no contraindications), according to Newcastle protocol (10). In brief, CSM was performed in the supine position using firm longitudinal massage of the right carotid sinus at the site of maximal pulsation 5–10 s while observing symptoms, blood pressure and RR-intervals. If right CSM in the supine position was non-diagnostic (i.e., no asystole $>$ 3 s and no fall in SBP $>$ 50 mmHg), left CSM was performed in the supine position, and then right and left CSM in 70° head-up tilt position.

Head-up tilt-table test was performed at 60–70° including optional nitroglycerin provocation according to the Italian protocol (11). Thus, nitroglycerin (400 μg spray sublingually) was administered first after 20 min of passive HUT if syncope had not occurred and the hemodynamic parameters were stable that is no hypotension (SBP<90 mmHg). Beat-to-beat blood pressure (BP) and electrocardiogram (ECG) were continuously monitored using a non-invasive validated method (Nexfin monitor, BMEYE, The Netherlands), and subsequently analyzed offline using a dedicated program provided by the monitor manufacturer. The Regional Ethical Review Board in Lund, Sweden accepted the study protocol (ref no. 82/2008), and all study participants gave their written informed consent.

Diagnostic Criteria of Orthostatic Hypotension, Carotid Sinus Syndrome, and Reflex Syncope

The following diagnostic criteria were applied: a) reproduction of symptoms (dizziness, lightheadedness, pre-syncope and syncope), if patients were able to recall conditions preceding syncope, and b) conventional criteria of orthostatic hypotension (OH), carotid sinus syndrome (CSS), and vasovagal reflex syncope (VVS) (1, 2). Briefly, OH was defined as a sustained decrease in systolic BP (SBP) $\geq$ 20 mmHg and/or decrease in diastolic BP (DBP) $\geq$ 10 mm Hg, or systolic BP $<$ 90 mmHg, CSS as a fall in SBP $\geq$50 mmHg and/or asystole $>$3 s with reproduction of syncope/symptoms, while VVS as a reproduction of syncope associated with a characteristic pattern of pronounced hypotension with or without bradycardia/asystole (1, 2). Moreover, an assessment of initial OH was performed by active standing test if the clinical history was suggestive of this disorder.

TABLE 1 | Patient characteristics ($n = 1,705$) at the time of initial evaluation stratified according to pacemaker status.

	Patients with pacemakers at the time of evaluation ($n = 39$)	Rest of SYSTEMA cohort ($n = 1,666$)	*P*-value
Age, years	65.6 (19.9)	51.8 (21.8)	<0.001
Sex, % female	38.5	60.7	0.005
Reported history of			
Syncope, %	84.6	91.5	0.127
Dizziness, *n* %	74.4	72.6	0.811
Number of syncope episodes, md [range]	5 [0–250]	4 [0–1,350]	0.278[a]
Duration of symptoms, years, md [range]	6 [0–48]	3 [0–77]	0.058[a]
SBP, mmHg	132.8 (18.7)	131.4 (22.5)	0.71
DBP, mmHg	68.8 (9.1)	71.6 (10.2)	0.091
Resting heart rate, bpm	67.2 (8.1)	70.3 (12.6)	0.028
Hypertension, %	51.3	28.5	0.002
CAD, %	30.8	6.4	<0.001
Atrial fibrillation, %	33.3	6.6	<0.001
Heart failure, %	25.6	3.3	<0.001

[a]*P-value for Mann-Whitney U-test. Continuous variables were compared between groups using Student's t-test and dichotomous variables were compared according to group using Pearson chi^2 test, if not otherwise indicated. md, median; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery ldisease.*

Calculations

Following evaluation in the autonomic laboratory (including Valsalva maneuver, active standing, carotid sinus massage, and tilt-testing), the most likely etiology judged by the investigating physician was compiled for all patients. If no likely diagnosis was established during cardiovascular autonomic testing, additional information was retrieved from the medical records of the patients.

The main characteristics of the study population were presented as mean and standard deviation for continuous variables, and percentages for categorical variables, unless otherwise specified. Continuous variables were compared between groups using Student's *t*-test when normally distributed and with Mann-Whitney U-test if not. Proportions among groups were compared using Pearson chi^2 test. A P-value < 0.05 was considered significant. All calculations were performed using IBM SPSS Statistics software version 25.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 6.00 (GraphPad Software, La Jolla, CA, USA, www.graphpad.com).

RESULTS

Of the 1,705 patients that were investigated due to unexplained syncope and/or orthostatic intolerance, 39 (2.3%) already had an implanted pacemaker at the time of the evaluation. The original pacing indications in these patients were sick-sinus-syndrome (SSS) in 16 (41%), atrioventricular block in 16 (41 %) and atrial fibrillation with bradycardia in five (12.8%). Twenty-two of the 39 patients (56%) had experienced syncope prior to the original pacemaker implantation. Two patients (one female and one male, aged 81 and 17 years, respectively) had implantable cardioverter-defibrillators due to malignant ventricular arrhythmias. Both these patients had experienced syncope prior to the implantation. Compared with the rest of the SYSTEMA cohort, the patients with a pre-existing pacemaker were older, more often men and were more likely to have cardiovascular disease (**Table 1**).

Following evaluation in the autonomic laboratory (including Valsalva maneuver, active standing, carotid sinus massage, and tilt-testing), an etiology was identified in 36 of the 39 patients, of which OH was the predominant diagnosis (**Figure 1**). Regarding the three patients in whom no etiology could be identified during tilt, further work-up demonstrated ventricular tachyarrhythmia in one; in another, vertigo, dementia and neurodegenerative changes were found and in the third, balance/gait disorder without haemodynamic basis, was considered causative.

Among the 22 patients that had experienced syncope prior to the original device implantation, orthostatic hypotension was diagnosed in seven (32%) and vasovagal syncope in nine (41%) patients. Of the 17 patients that had not experienced syncope prior to the original pacemaker implantation, nine patients (53%) was diagnosed with orthostatic hypotension whereas vasovagal syncope was diagnosed in three (18%). Statistical power calculations indicated insufficient power to detect any statistically significant differences in diagnoses between the 22 patients with prior syncope and the 17 patients without prior syncope.

All patients underwent pacemaker interrogation as an initial part of their assessment. There were no cases of pacemaker dysfunction. No paced patient received an ICM for diagnosis.

Most patients (28/39) were aged 60 years or more. In these patients, orthostatic hypotension was diagnosed in 50%, whereas vasovagal syncope was dominant in patients under 60 years of age. Cardiovascular autonomic tests indicated the etiology in all patients under 60 years of age. Results stratified according to age over/under 60–years appear in **Tables S1–S3**.

DISCUSSION

In the current study we have shown that:

I. A likely etiology of syncope and/or orthostatic intolerance in patients with pacemakers can be successfully identified by cardiovascular autonomic tests, including head-up-tilt, carotid sinus massage and Valsalva maneuver.
II. The most common etiologies in the unexplained group are orthostatic hypotension (preferentially in older subjects) and vasovagal syncope (preferentially in younger subjects). There were no cases of pacemaker dysfunction in our cohort.

The pacing literature has focused on symptoms and ECG diagnosis in order to select patients for successful pacing therapy. Recurrent syncope or orthostatic intolerance in paced patients has had less attention. Early series raised the possibility of autonomic causes, although a full range of autonomic

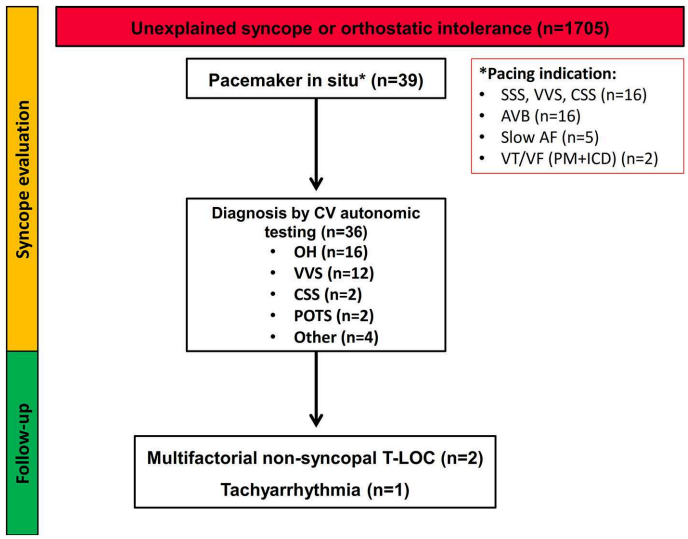

FIGURE 1 | Flow-chart of the study population. The diagram summarizes the diagnostic work-up and follow-up of patients presenting with unexplained syncope or symptoms of orthostatic intolerance. SSS, sick sinus syndrome; VVS, vasovagal syncope; CSS, carotid sinus syndrome; POTS, postural orthostatic tachycardia syndrome; AVB, atrioventricular block; AF, atrial fibrillation; VT, ventricular tachycardia; VF, ventricular fibrillation; PM, pacemaker; ICD, implantable cardioverter defibrillator; T-LOC, transient loss of consciousness.

investigations was not available to those investigators (12, 13). Using a prospective investigational protocol including cardiovascular autonomic tests, we have been able to provide insights into analysis of the etiology of recurrent syncope and/or orthostatic intolerance in paced patients. Orthostatic hypotension or vasovagal syncope was the etiology in seven of ten patients. Notably, orthostatic hypotension was more common among paced patients (41%) than in the rest of the SYSTEMA cohort (27%) and the proportion of patients in whom no cause could be identified during tilt was lower (8% compared with 22%). Regarding the finding of vasovagal syncope, sick sinus syndrome was a common original pacing indication (41%), thus, it should be considered that many of these paced patients show the "extrinsic" form (13), implying a reflex mechanism for syncope with a vasopressor component (1). Importantly, in paced patients with cardioinhibitory vasovagal syncope, the anti-bradycardia stimulation cannot treat the vasodepressor component, which was undetected, even on tilt if performed before implantation, by the severe bradycardia/asystole. Performance of tilt prior to pacing must now be considered as a risk of syncope recurrence tool, if positive, recurrence of syncope is substantially more likely (6). While the initial pacing indications followed guidelines in all patients, pacing offers little or no help for the vasodepressor component of vasovagal syncope and in orthostatic hypotension, thus constitutes the basis of recurrent syncope.

Of note, assessment of pacing function (performed in all patients) revealed no cases of dysfunction. Rather, our study affirms the importance of a comprehensive diagnostic work-up according to recent syncope guidelines (1, 2) also in patients with pre-existing pacemakers that present with recurrent syncope and/or orthostatic intolerance. Interestingly, cardiovascular autonomic tests indicated the etiology in all eleven patients under 60 years of age, suggesting that cardiovascular autonomic test may be particularly valuable in this age group. Concentrating expertise in a dedicated facility ("Syncope Unit") (1) offers increased diagnostic and therapeutic efficacy, as cardiovascular autonomic tests are not widely available and cardiologists may have limited knowledge of test interpretation.

In this study, we did not use Closed Loop pacing as was done in the SPAIN trial (14). This pacemaker senses right ventricular volume indirectly by measuring its impedance. When impedance increases by decrease in right ventricular volume, as occurs in vasovagal syncope due to diminishing cardiac output and venous return, pacing is triggered. This detected change precedes bradycardia/asystole in almost all vasovagal syncope, thus, the trigger for pacing is earlier in the reflex than waiting for later occurring bradycardia. The favorable results of the SPAIN trial suggest that this means of triggering pacing may offer more benefit. The BIOSYNC study, a randomized controlled trial of CLS vs. standard DDD pacing has almost completed recruitment (15).

We acknowledge some study limitations. Firstly, this is a single-center observational study with limited sample size, requiring our results to be confirmed. Secondly, our study is of a selected group referred to a tertiary syncope unit, thus, it may not reflect the etiology of a wider syncope population. The relatively low proportion of patients with an existing pacemaker at the time of entry into the cohort (2.3%) may be explained by the fact that only subjects with unexplained syncope and/or orthostatic had been referred to the syncope unit. Thus, the SYSTEMA population is a selected group in whom syncope etiology could not readily be determined and/or the patient adequately managed by the referring physician. Thirdly, our examination protocol did not include additional autonomic tests such as the Valsalva maneuver or baroreceptor sensitivity test in all patients.

CONCLUSION

In conclusion, we have shown that cardiovascular autonomic tests indicate the etiology of syncope and/or orthostatic intolerance in the majority of paced patients. The most common diagnosis is orthostatic hypotension (40%) followed by vasovagal syncope (30%), which emphasizes the importance of a full diagnostic work-up in paced patients that present with recurrent syncope and/or orthostatic intolerance.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Regional Ethical Review Board in Lund, Sweden (ref no. 82/2008). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EY, RS, AF, and VH: concept and design. EY, FR, HH, TP, OM, RS, AF, and VH: data analysis, interpretation, drafting article, critical revision of article, and approval of article. AF and VH: statistics. OM, AF, and VH: funding secure. EY, TP, and AF: data collection. FR, HH, and TP: other.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2019.00154/full#supplementary-material

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