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ESC GUIDELINES

2018 ESC Guidelines for the diagnosis and management of syncope

The Task Force for the diagnosis and management of syncope of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA)

Endorsed by: European Academy of Neurology (EAN), European Federation of Autonomic Societies (EFAS), European Federation of Internal Medicine (EFIM), European Union Geriatric Medicine Society (EUGMS), European Society of Emergency Medicine (EuSEM)

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The disclosure forms of all experts involved in the development of these Guidelines are available on the ESC website http://www.escardio.org/guidelines.

For the Supplementary Data which include background information and detailed discussion of the data that have provided the basis for the Guidelines see https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehy037#supplementary-data

Click here to access the corresponding chapter in ESC CardioMed - Section 39 Syncope

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Abbreviations and acronyms

ABPM	Ambulatory blood pressure monitoring
AF	Atrial fibrillation
ARVC	Arrhythmogenic right ventricular cardiomyopathy
ATP	Adenosine triphosphate

AV	Atrioventricular
AVID	Antiarrhythmics versus Implantable Defibrillators trial
BBB	Bundle branch block
BNP	B-type natriuretic peptide
BP	Blood pressure
b.p.m.	Beats per minute
CI	Confidence interval
CI-CSS	Cardioinhibitory carotid sinus syndrome
CPG	Committee for Practice Guidelines
CRT-D	Cardiac resynchronization therapy defibrillator
CSM	Carotid sinus massage
CSS	Carotid sinus syndrome
DCM	Dilated cardiomyopathy
DDD-PM	Dual chamber pacemaker
ECG	Electrocardiogram/electrocardiographic
ED	Emergency department
EEG	Electroencephalogram
EFAS	European Federation of Autonomic Societies
EFIM	European Federation of Internal Medicine
EHRA	European Heart Rhythm Association
ENS	European Neurological Society
EPS	Electrophysiological study
ESC	European Society of Cardiology
EUGMS	European Union Geriatric Medicine Society
EuSEM	European Society of Emergency Medicine
HBPM	Home blood pressure monitoring
HCM	Hypertrophic cardiomyopathy
HR	Heart rate
ICD	Implantable cardioverter defibrillator
ILR	Implantable loop recorder
ISSUE	International Study on Syncope of Unknown Etiology
L-DOPA	L-3,4-dihydroxyphenylalanine
LOC	Loss of consciousness
LQTS	Long QT syndrome
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
NYHA	New York Heart Association
OH	Orthostatic hypotension
PC-Trial	Physical Counterpressure Manoeuvres Trial
PCM	Physical counter-pressure manoeuvres
PNES	Psychogenic non-epileptic seizures
POST	Prevention of Syncope Trial
POTS	Postural orthostatic tachycardia syndrome
PPS	Psychogenic pseudosyncope
RCT	Randomized controlled trial
SCD	Sudden cardiac death
SNRT	Sinus node recovery time
SU	Syncope unit
SUP	Syncope Unit Project
SVT	Supraventricular tachycardia
TIA	Transient ischaemic attack
t.i.d.	Ter in die (three times daily)
TLOC	Transient loss of consciousness
TNG	Trinitroglycerin
VA	Ventricular arrhythmia
VF	Ventricular fibrillation
VT	Ventricular tachycardia
VVS	Vasovagal syncope

1. Preamble

Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in selecting the best management strategies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision making of health professionals in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of guidelines have been issued in recent years by the European Society of Cardiology (ESC), as well as by other societies and organisations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines). ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC, including representation from its relevant ESC sub-specialty groups, in order to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management of a given condition according to ESC Committee for Practice Guidelines (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined in *Tables 1* and *2*.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (http://www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period were notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new Guidelines. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions the Guidelines are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the *European Heart Journal*. The Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC Guidelines also includes the creation of educational tools and implementation programmes for the recommendations including condensed pocket guideline versions, summary slides, booklets with essential messages, summary cards for non-specialists and an electronic version for digital applications (smartphones, etc.).

Table 1 Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

These versions are abridged and thus, if needed, one should always refer to the full-text version, which is freely available via the ESC website and hosted on the EHJ website. The National Societies of the ESC are encouraged to endorse, translate and implement all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines, disseminating them and implementing them into clinical practice.

Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic, or therapeutic medical strategies. However, the ESC Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

2. Introduction

The first ESC Guidelines for the management of syncope were published in 2001, with subsequent versions in 2004 and 2009. In March 2015, the ESC CPG considered that there were enough new data to justify the production of new Guidelines.

The most important aspect characterizing this document is the composition of the Task Force, which is truly multidisciplinary. Cardiologists form a minority of the panel; experts in emergency medicine, internal medicine and physiology, neurology and autonomic diseases, geriatric medicine, and nursing cover all aspects of management of the various forms of syncope and transient loss of consciousness (TLOC).

Compared with the previous versions of these Guidelines, the 2018 document contains Supplementary Data as an integral part. While the print text mainly aims to give formal evidence-based recommendations according to the standardized rules of the ESC, this new web-only feature allows expansion of the content to practical issues, and aims to fill the gap between the best available scientific evidence and the need for dissemination of these concepts into clinical practice *('We have the knowledge, we need to teach it')*. Thanks to the Supplementary Data further explanation on specific points is given, and thanks to the Web Practical Instructions advice is given on how to evaluate patients with loss of consciousness (LOC), and how to perform and interpret tests properly; whenever possible, we provide tracings, videos, flow charts, and checklists.

The document aims to be patient-orientated and focused on therapy, and to reduce the risk of recurrence and the life-threatening consequences of syncope recurrence. For this purpose, even in the absence of strong evidence from trials, we give as much advice as possible on the most appropriate therapy based on the practical expertise of the members of the Task Force *('Our patients seek solutions, not only explanations')*. When possible, we provide therapeutic and decision-making algorithms.

Finally, we recognize that one major challenge in syncope management is the reduction of inappropriate admissions and inappropriate use of tests while maintaining the safety of the patient. We give strong focus to pathways and organizational issues *('We have the knowledge; we need to apply it')*. In particular, we propose a care pathway for the

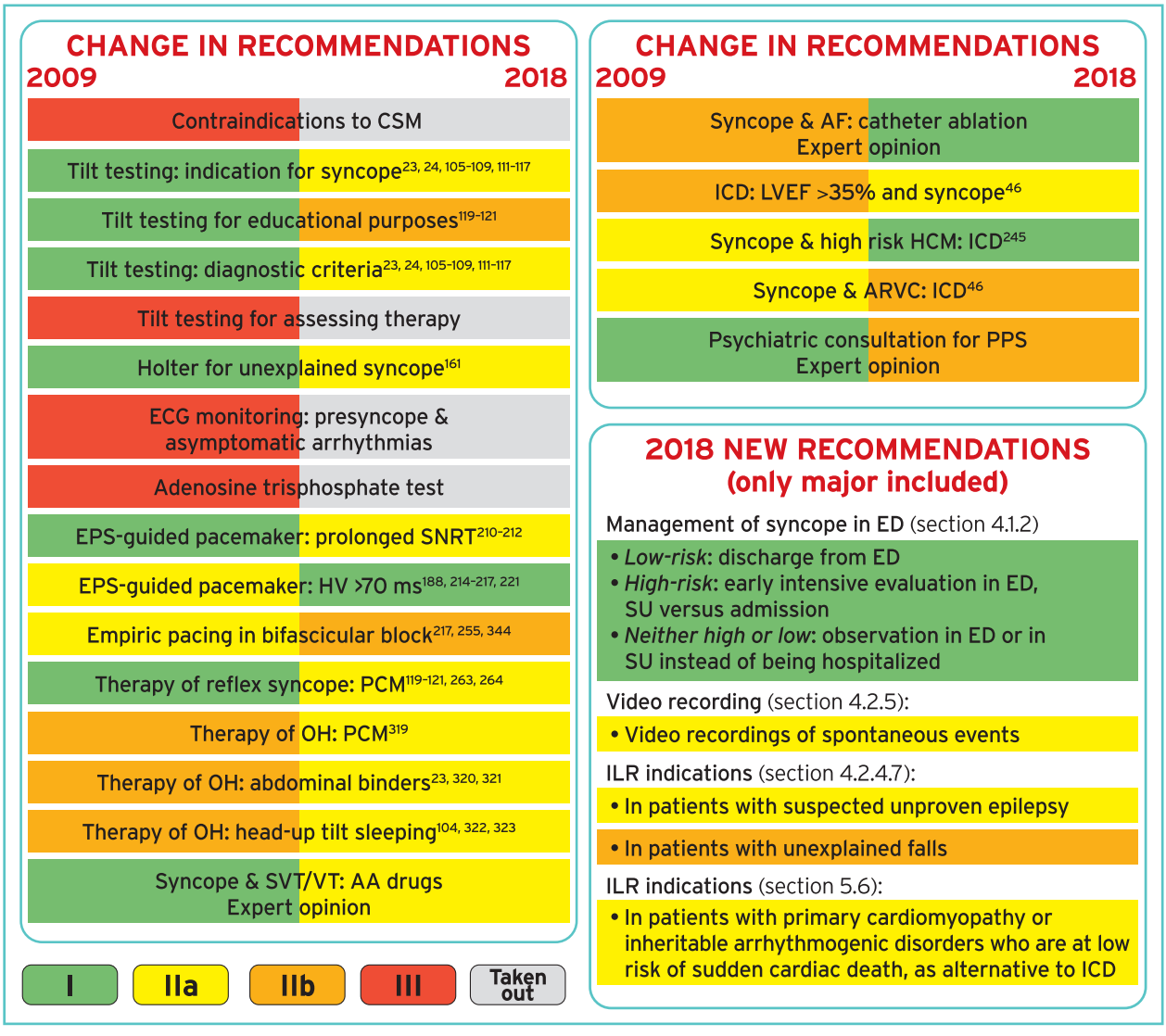
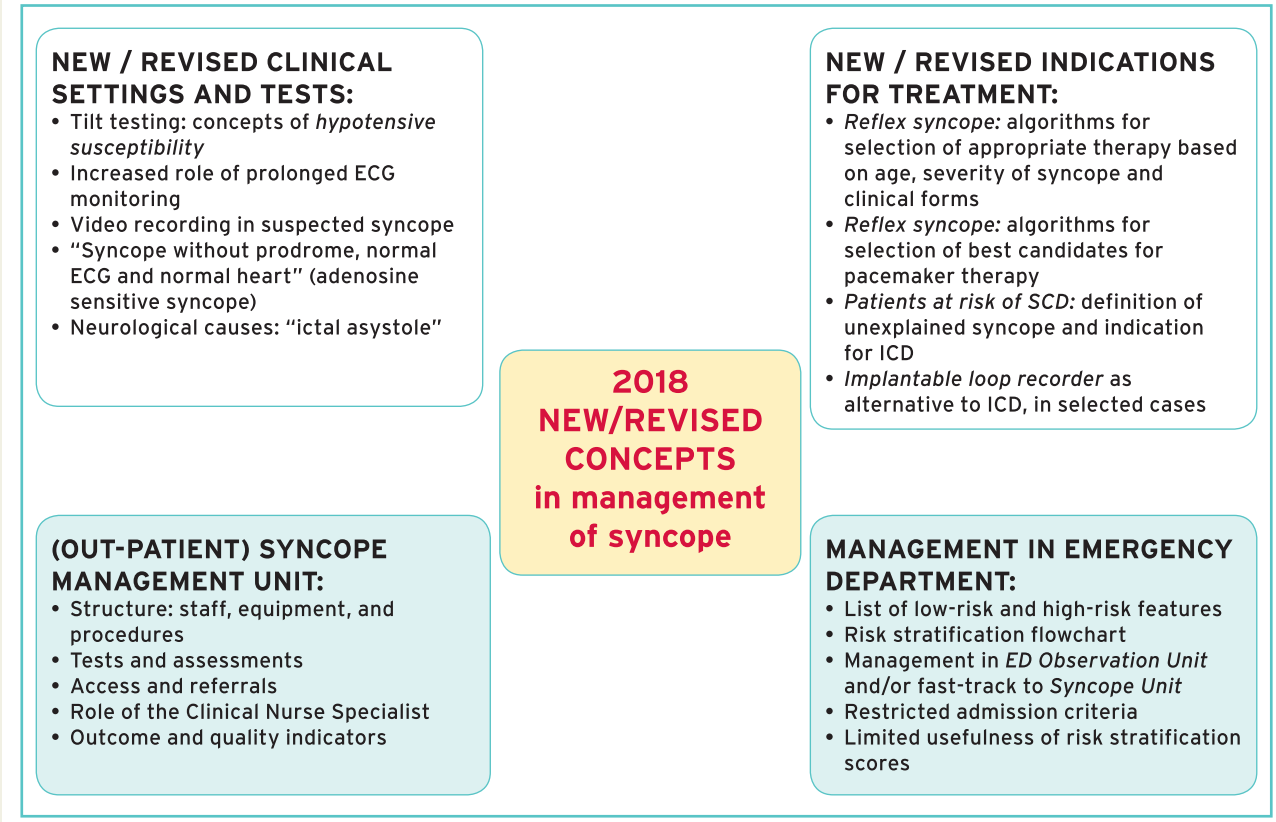


Figure 1 What is new in the 2018 syncope Guidelines? AA = antiarrhythmic; AF = atrial fibrillation; ARVC = arrhythmogenic right ventricular cardiomyopathy; CSM = carotid sinus massage; ECG = electrocardiogram; ED = emergency department; LVEF = left ventricular ejection fraction; EPS = electrophysiological study; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; OH = orthostatic hypotension; PCM = physical counter-pressure manoeuvres; POTS = postural orthostatic tachycardia syndrome; PPS = psychogenic pseudosyncope; SNRT = sinus node recovery time; SU = syncope unit; SVT = supraventricular tachycardia; VT = ventricular tachycardia.



Central illustration New/revised concepts in the management of syncope. ECG = electrocardiogram; ED = emergency department; ICD = implantable cardioverter defibrillator; SCD = sudden cardiac death.

management of patients with TLOC from their arrival in the emergency department (ED), and give practical instructions on how to set up outpatient syncope clinics (syncope units) aimed at reducing hospitalization, under- and misdiagnoses, and costs.

2.1 What is new in the 2018 version?

The changes in recommendations made in the 2018 version compared with the 2009 version, the new recommendations, and the most important new/revised concepts are summarized in *Figure 1*.

3. Definitions, classification, and pathophysiology

3.1 Definitions

- *Syncope* is defined as TLOC due to cerebral hypoperfusion, characterized by a rapid onset, short duration, and spontaneous complete recovery.

Syncope shares many clinical features with other disorders; it therefore presents in many differential diagnoses. This group of disorders is labelled TLOC.

- *TLOC* is defined as a state of real or apparent LOC with loss of awareness, characterized by amnesia for the period of unconsciousness, abnormal motor control, loss of responsiveness, and a short duration.

The two main groups of TLOC are 'TLOC due to head trauma' and 'non-traumatic TLOC' (*Figure 2*). Traumatic TLOC will not be considered further in this document, so TLOC will be used to mean non-traumatic TLOC.

The clinical features characterizing TLOC are usually derived from history taking from patients and eyewitnesses. Specific characteristics that aid diagnosis are outlined in section 3 of the *Web Practical Instructions*.

TLOC groups are defined using pathophysiology: the qualifying criterion for syncope is cerebral hypoperfusion; for epileptic seizures, it is abnormal excessive brain activity; and for psychogenic TLOC it is the psychological process of conversion. The syncope definition rests on pathophysiology because no set of clinical features encompasses all forms of syncope while also excluding all epileptic seizures and psychogenic TLOC events.

- The adjective *presyncope* is used to indicate symptoms and signs that occur before unconsciousness in syncope. Note that the noun *presyncope* is often used to describe a state that resembles the prodrome of syncope, but which is not followed by LOC.

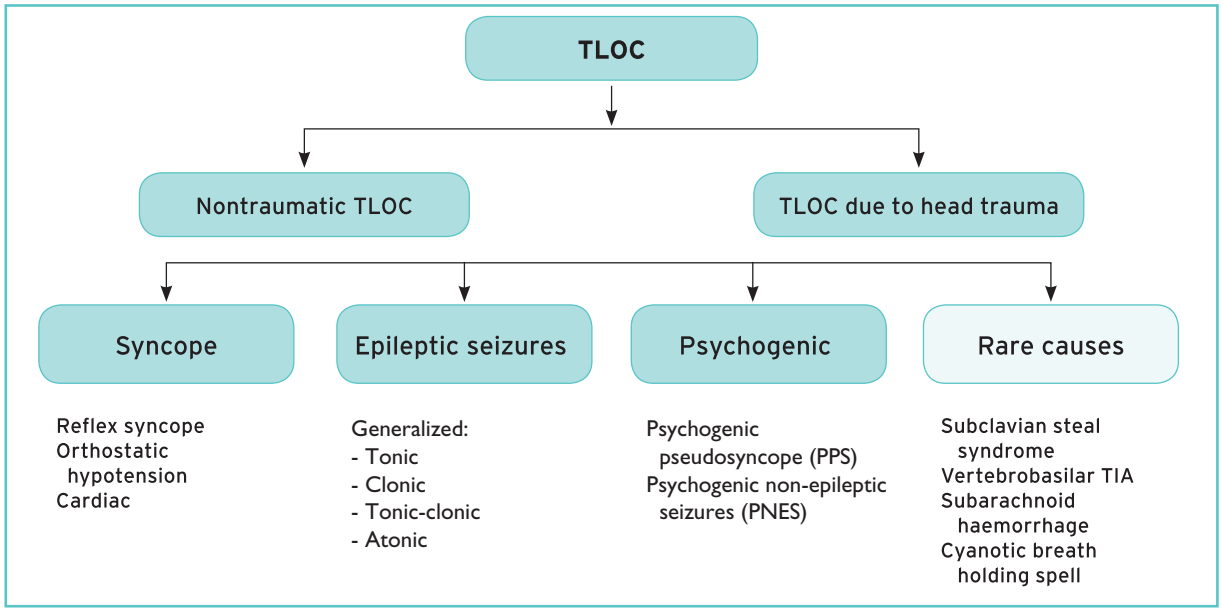


Figure 2 Syncope in the context of transient loss of consciousness. Non-traumatic transient loss of consciousness is classified into one of four groupings: syncope, epileptic seizures, psychogenic transient loss of consciousness, and a miscellaneous group of rare causes. This order represents their rate of occurrence. Combinations occur; e.g. non-traumatic transient loss of consciousness causes can cause falls with concussion, in which case transient loss of consciousness is both traumatic and non-traumatic. TIA = transient ischaemic attack; TLOC = transient loss of consciousness.

A variety of terms are used that generally do not match the definitions in this document closely enough to be used as synonyms of the defined terms. For example, a 'faint' approximately conforms to syncope but emphasizes vasovagal syncope (VVS) over other forms. A glossary of uncertain terms is shown in section 1 of the *Web Practical Instructions*.

3.2 Classification and pathophysiology of syncope and transient loss of consciousness

3.2.1 Syncope

Table 3 provides a classification of the principal causes of syncope, emphasizing groups of disorders with common pathophysiology, presentation, and risk. Clinical features, epidemiology, prognosis, impact on quality of life, and economic issues are shown in section 2 of the *Web Practical Instructions*.

The pathophysiological classification centres on a fall in systemic blood pressure (BP) with a decrease in global cerebral blood flow as the defining characteristic of syncope. *Figure 3* shows low BP and global cerebral hypoperfusion as the central final common pathway of syncope. A sudden cessation of cerebral blood flow for as short as 6–8 s can cause complete LOC. A systolic BP of 50–60 mmHg at heart level, i.e. 30–45 mmHg at brain level in the upright position, will cause LOC.[8,9]

Systemic BP is the product of cardiac output and total peripheral resistance; a fall in either can cause syncope. However, in syncope, both mechanisms often act together to a varying degree.

There are three primary causes of a low total peripheral resistance. The first is decreased reflex activity causing vasodilatation through withdrawal of sympathetic vasoconstriction: this is the 'vasodepressive type' of reflex syncope, seen in the outer ring in *Figure 3*. The second is a functional impairment, and the third a structural impairment of the autonomic nervous system, with drug-induced, primary, and secondary autonomic failure in the outer ring. In autonomic failure, there is insufficient sympathetic vasoconstriction in response to the upright position.

There are four primary causes of low cardiac output. The first is a reflex bradycardia, known as cardioinhibitory reflex syncope. The second concerns cardiovascular causes: arrhythmia, structural disease including pulmonary embolism, and pulmonary hypertension. The third is inadequate venous return due to volume depletion or venous pooling. Finally, chronotropic and inotropic incompetence through autonomic failure may impair cardiac output.

Note that these primary mechanisms may interact in different ways: firstly, venous pooling and inadequate venous return is also a factor that can trigger an inappropriate reflex in orthostatic reflex syncope; secondly, a low total peripheral resistance may cause venous pooling of blood below the diaphragm, in turn decreasing venous return and consequently cardiac output.

The three main groups of syncope, i.e. reflex, cardiovascular, and secondary to orthostatic hypotension (OH), are shown outside the rings in *Figure 3*. Both reflex syncope and OH span the two main pathophysiological mechanisms.

3.2.2 Non-syncopal forms of (real or apparent) transient loss of consciousness

Only those forms of epilepsy in which normal motor control is lost, so patients may fall, are included in *Figure 2*. These are tonic, clonic,

Table 3 Classification of syncope

Reflex (neurally mediated) syncope
Vasovagal: - orthostatic VVS: standing, less common sitting - emotional: fear, pain (somatic or visceral), instrumentation, blood phobia Situational: - micturition - gastrointestinal stimulation (swallow, defaecation) - cough, sneeze - post-exercise - others (e.g. laughing, brass instrument playing) Carotid sinus syndrome Non-classical forms (without prodromes and/or without apparent triggers and/or atypical presentation)
Syncope due to OH
Note that hypotension may be exacerbated by venous pooling during exercise (exercise-induced), after meals (postprandial hypotension), and after prolonged bed rest (deconditioning). Drug-induced OH (most common cause of OH): - e.g. vasodilators, diuretics, phenothiazine, antidepressants Volume depletion: - haemorrhage, diarrhoea, vomiting, etc. Primary autonomic failure (neurogenic OH): - pure autonomic failure, multiple system atrophy, Parkinson's disease, dementia with Lewy bodies Secondary autonomic failure (neurogenic OH): - diabetes, amyloidosis, spinal cord injuries, auto-immune autonomic neuropathy, paraneoplastic autonomic neuropathy, kidney failure
Cardiac syncope
Arrhythmia as primary cause: Bradycardia: - sinus node dysfunction (including bradycardia/tachycardia syndrome) - atrioventricular conduction system disease Tachycardia: - supraventricular - ventricular Structural cardiac: aortic stenosis, acute myocardial infarction/ischaemia, hypertrophic cardiomyopathy, cardiac masses (atrial myxoma, tumours, etc.), pericardial disease/tamponade, congenital anomalies of coronary arteries, prosthetic valve dysfunction Cardiopulmonary and great vessels: pulmonary embolus, acute aortic dissection, pulmonary hypertension
Remarks
• All forms of syncope, but mostly reflex syncope and OH, are more likely to occur or are more severe when various factors are present: medication causing low BP (due to vasodilatation or hypovolaemia), alcohol use, volume depletion (haemorrhage, low fluid intake, diarrhoea, vomiting), pulmonary diseases causing reduction in brain oxygen supply, environmental factors (thermal stress). • There are two main pathophysiological mechanisms in reflex syncope. "Vasodepression" refers to conditions in which insufficient sympathetic vasoconstriction results in hypotension.[1,2] "Cardioinhibition" is used when bradycardia or asystole predominates, reflecting a shift towards parasympathetic predominance. The haemodynamic pattern, i.e. cardioinhibitory, vasodepressive, or both, is independent of the trigger evoking reflex syncope. For example, micturition syncope and orthostatic VVS may equally well present as cardioinhibitory or as vasodepressor syncope • The non-classical form of reflex syncope involves a heterogeneous group of patients. The term is used to describe reflex syncope that occurs with uncertain or apparently absent triggers and/or atypical presentation. The diagnosis of reflex syncope is probable when other causes of syncope are excluded (absence of structural heart disease) and/or symptoms are reproduced in the tilt test.[3] At present, this group also contains syncope associated with low adenosine plasma levels[4,5] • The cardiovascular causes of orthostatic intolerance include classical OH, initial OH, delayed OH, POTS, and VVS, which in this context can be called orthostatic VVS.[6,7] Syndromes of orthostatic intolerance that may cause syncope are presented in *Web Practical Instruction section 2*.

BP = blood pressure; OH = orthostatic hypotension; POTS = postural orthostatic tachycardia syndrome; VVS = vasovagal syncope.

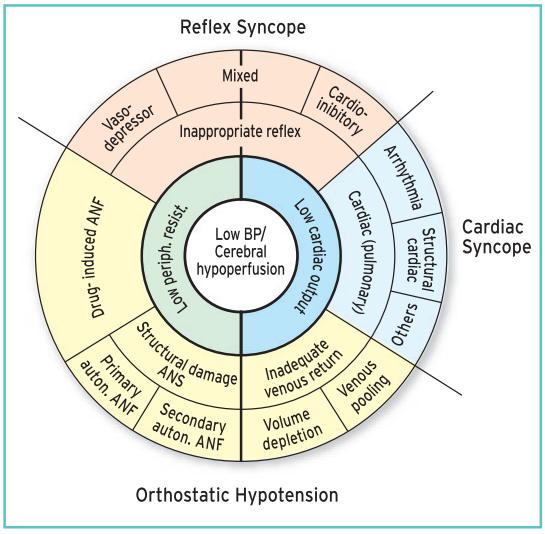


Figure 3 Pathophysiological basis of the classification of syncope. ANS = autonomic nervous system; auton. = autonomic; BP = blood pressure; OH = orthostatic hypotension; periph. = peripheral; resist. = resistance.

tonic-clonic, and atonic generalized seizures, and can be classified as primary or secondary. The forms of epilepsy in which people remain actively upright, i.e. sitting or standing (e.g. complex partial seizures or absence epilepsy) are not regarded as TLOC, but sometimes they are incorrectly diagnosed as syncope.

Psychogenic TLOC consists of two forms: one resembles epileptic seizures (psychogenic non-epileptic seizures [PNES]) and one, without gross movements, resembles syncope (psychogenic pseudosyncope [PPS]).

The rare causes of TLOC only seldomly cause confusion with the main TLOC forms, probably because in most cases they differ enough clinically to be clearly not syncope. Both vertebrobasilar transient ischaemic attacks (TIAs) and subclavian steal syndrome are associated with focal neurological signs. A subarachnoid haemorrhage may present with a short LOC, but the associated abrupt extreme headache suggests the cause. In cyanotic breath-holding spells, expiratory apnoea with hypoxia is the primary mechanism.[10] So-called 'pallid breath-holding spells' in children do not constitute a primary respiratory problem, but are cardioinhibitory reflex syncope.[11]

Table 4 lists the main features that distinguish syncope from disorders that may be mistaken for syncope.

Table 4 Conditions that may be incorrectly diagnosed as syncope

Condition	Characteristic features that distinguish from syncope
Generalized seizures	See section 8, *Table 10*.
Complex partial seizures, absence epilepsy	No falls, yet unresponsive and later amnesia
PPS or "pseudocoma"	Duration of apparent LOC lasting many minutes to hours; high frequency, up to several times a day
Falls without TLOC	No unresponsiveness or amnesia
Cataplexy	Falls with flaccid paralysis and non-responsive, yet no later amnesia
Intracerebral or subarachnoid haemorrhage	Consciousness may be progressively reduced rather than immediately lost. Accompanying severe headache, other neurological signs
Vertebrobasilar TIA	Always focal neurological signs and symptoms, usually without LOC; if consciousness is lost this usually lasts longer than in TLOC.
Carotid TIA	Consciousness is for all practical purposes not lost in carotid TIAs, but there are pronounced focal neurological signs and symptoms
Subclavian steal syndrome	Associated with focal neurological signs
Metabolic disorders including hypoglycaemia, hypoxia, hyperventilation with hypocapnia	Duration much longer than in TLOC; consciousness may be impaired instead of lost
Intoxication	Duration much longer than in TLOC; consciousness may be impaired instead of lost
Cardiac arrest	LOC yet no spontaneous recovery
Coma	Duration much longer than TLOC

LOC = loss of consciousness; PPS = psychogenic pseudosyncope; TIA = transient ischaemic attack; TLOC = transient loss of consciousness.

4. Diagnostic evaluation and management according to risk stratification

4.1 Initial evaluation

The clinical features characterizing TLOC are usually derived from history taking from patients and eyewitnesses. When a patient first presents with possible TLOC, history taking should first establish whether there was indeed a TLOC. Often, this allows a distinction between the major TLOC groups. The flow diagram for the evaluation of TLOC is shown in *Figure 4*. The initial evaluation should answer key questions:

(1) Was the event TLOC?

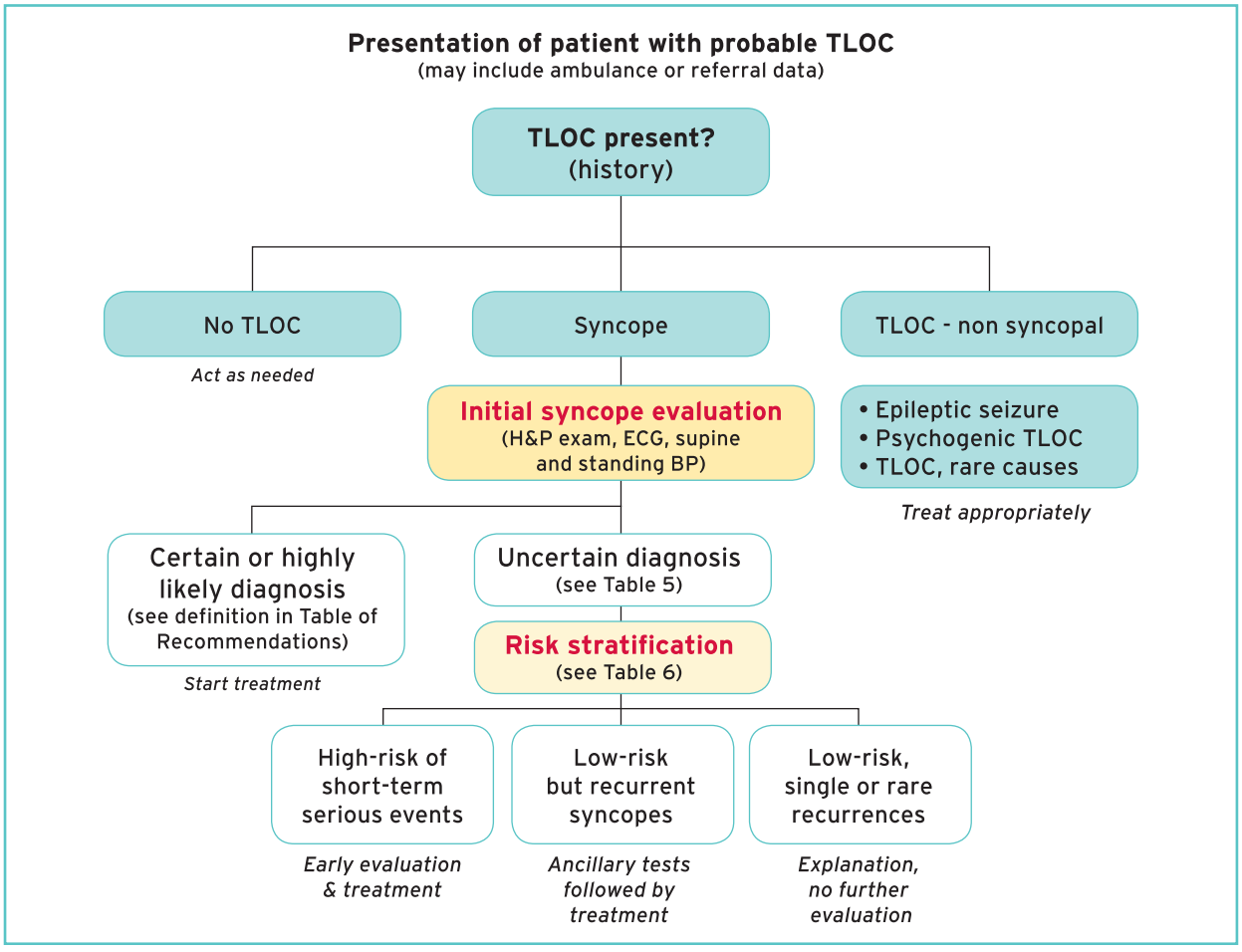


Figure 4 Flow diagram for the initial evaluation and risk stratification of patients with syncope. BP = blood pressure; ECG = electrocardiogram; H&P exam = history and physical examination; TLOC = transient loss of consciousness.

(2) In case of TLOC, is it of syncopal or non-syncopal origin?
(3) In case of suspected syncope, is there a clear aetiological diagnosis (see section 4.1.1)?
(4) Is there evidence to suggest a high risk of cardiovascular events or death (see section 4.1.2)?

TLOC has four specific characteristics: short duration, abnormal motor control, loss of responsiveness, and amnesia for the period of LOC (for an explanation of the clinical features of TLOC see *Web Table 4* in section 4.1 of the *Web Practical Instructions*).

TLOC is probably syncope when: (i) there are signs and symptoms specific for reflex syncope, syncope due to OH, or cardiac syncope, and (ii) signs and symptoms specific for other forms of TLOC (head trauma, epileptic seizures, psychogenic TLOC, and/or rare causes) are absent. Practical instructions for history taking are given in sections 3 and 4 of the *Web Practical Instructions*.

When epileptic seizures or psychogenic attacks are likely, appropriate steps should be taken. By using a detailed clinical history, physicians can differentiate syncope from other forms of TLOC in approximately 60% of cases.[12] For non-syncopal TLOC, refer to sections 7 and 8.

4.1.1 Diagnosis of syncope

The starting point of the diagnostic evaluation of TLOC of suspected syncopal nature is the initial syncope evaluation, which consists of:

- Careful history taking concerning present and previous attacks, as well as eyewitness accounts, in person or through a telephone interview.
- Physical examination, including supine and standing BP measurements.
- Electrocardiogram (ECG).

Based on these findings, additional examinations may be performed when needed (see section 4.2):

- Immediate ECG monitoring when there is a suspicion of arrhythmic syncope.
- Echocardiogram when there is previous known heart disease, data suggestive of structural heart disease, or syncope secondary to cardiovascular cause.

- Carotid sinus massage (CSM) in patients aged >40 years.
- Head-up tilt testing when there is suspicion of syncope due to OH or reflex syncope.
- Blood tests when clinically indicated, e.g. haematocrit or haemoglobin when haemorrhage is suspected, oxygen saturation and blood gas analysis when hypoxia is suspected, troponin when cardiac ischaemia-related syncope is suspected, or D-dimer when pulmonary embolism is suspected, etc.

Even if there is no independent gold/reference standard to diagnose syncope, there is strong consensus that the initial evaluation may lead to certain or highly likely diagnosis when the diagnostic criteria listed in the table of recommendations are met.

Diagnostic criteria with initial evaluation

Recommendations	Class[a]	Level[b]
Reflex syncope and OH		
VVS is highly probable if syncope is precipitated by pain, fear, or standing, and is associated with typical progressive prodrome (pallor, sweating, and/or nausea).[8,13–17]	I	C
Situational reflex syncope is highly probable if syncope occurs during or immediately after specific triggers, listed in *Table 3*.[8,13–17]	I	C
Syncope due to OH is confirmed when syncope occurs while standing and there is concomitant significant OH.[18–24]	I	C
In the absence of the above criteria, reflex syncope and OH should be considered likely when the features that suggest reflex syncope or OH are present and the features that suggest cardiac syncope are absent (see *Table 5*).	IIa	C
Cardiac syncope		
Arrhythmic syncope is highly probable when the ECG shows[25–39]: • Persistent sinus bradycardia <40 b.p.m. or sinus pauses >3 s in awake state and in absence of physical training; • Mobitz II second- and third-degree AV block; • Alternating left and right BBB; • VT or rapid paroxysmal SVT; • Non-sustained episodes of polymorphic VT and long or short QT interval; or • Pacemaker or ICD malfunction with cardiac pauses.	I	C
Cardiac ischaemia-related syncope is confirmed when syncope presents with evidence of acute myocardial ischaemia with or without myocardial infarction.[25–39]	I	C
Syncope due to structural cardiopulmonary disorders is highly probable when syncope presents in patients with prolapsing atrial myxoma, left atrial ball thrombus, severe aortic stenosis, pulmonary embolus, or acute aortic dissection.	I	C
Additional advice and clinical perspectives The initial syncope evaluation, as described in this document, can define the cause of syncope in most patients. Strict adherence to the above definitions of VVS and situational reflex syncope, and of syncope due to OH, can be considered certain or highly likely irrespective of the presence of any other abnormal finding. In young subjects with unexplained syncope and no history of cardiac disease, no family history of sudden death, no supine syncope or syncope during sleep or exercise, no unusual triggers, and a normal ECG, the chance of cardiac syncope is very low. SCD rates in subjects <35 years amount to 1 – 3/100 000.		

AV = atrioventricular; BBB = bundle branch block; b.p.m. = beats per minute; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; OH = orthostatic hypotension; SCD = sudden cardiac death; SVT = supraventricular tachycardia; VT = ventricular tachycardia; VVS = vasovagal syncope.
[a]Class of recommendation.
[b]Level of evidence.

When a diagnosis is nearly certain or highly likely, no further evaluation is needed, and treatment—if any—can be planned. In other cases, the initial evaluation may suggest a diagnosis when the features listed in *Table 5* are present, or otherwise is unable to suggest any diagnosis.

Table 5 Clinical features that can suggest a diagnosis on initial evaluation

Reflex syncope
- Long history of recurrent syncope, in particular occurring before the age of 40 years
- After unpleasant sight, sound, smell, or pain
- Prolonged standing
- During meal
- Being in crowded and/or hot places
- Autonomic activation before syncope: pallor, sweating, and/or nausea/vomiting
- With head rotation or pressure on carotid sinus (as in tumours, shaving, tight collars)
- Absence of heart disease

Syncope due to OH
- While or after standing
- Prolonged standing
- Standing after exertion
- Post-prandial hypotension
- Temporal relationship with start or changes of dosage of vasodepressive drugs or diuretics leading to hypotension
- Presence of autonomic neuropathy or parkinsonism

Cardiac syncope
- During exertion or when supine
- Sudden onset palpitation immediately followed by syncope
- Family history of unexplained sudden death at young age
- Presence of structural heart disease or coronary artery disease
- ECG findings suggesting arrhythmic syncope:
  - Bifascicular block (defined as either left or right BBB combined with left anterior or left posterior fascicular block)
  - Other intraventricular conduction abnormalities (QRS duration ≥0.12 s)
  - Mobitz I second-degree AV block and 1° degree AV block with markedly prolonged PR interval
  - Asymptomatic mild inappropriate sinus bradycardia (40–50 b.p.m.) or slow atrial fibrillation (40–50 b.p.m.) in the absence of negatively chronotropic medications
  - Non-sustained VT
  - Pre-excited QRS complexes
  - Long or short QT intervals
  - Early repolarization
  - ST-segment elevation with type 1 morphology in leads V1-V3 (Brugada pattern)
  - Negative T waves in right precordial leads, epsilon waves suggestive of ARVC
  - Left ventricular hypertrophy suggesting hypertrophic cardiomyopathy

ARVC = arrhythmogenic right ventricular cardiomyopathy; AV = atrioventricular; BBB = bundle branch block; b.p.m. = beats per minute; ECG = electrocardiogram; OH = orthostatic hypotension; VT = ventricular tachycardia.

4.1.2 Management of syncope in the emergency department based on risk stratification

The management of TLOC of suspected syncopal nature in the ED should answer the following three key questions:

(1) Is there a serious underlying cause that can be identified?
(2) What is the risk of a serious outcome?
(3) Should the patient be admitted to hospital?

Figure 5 shows a flow chart for the management and risk stratification of patients referred to the ED for TLOC suspected to be syncope (modified from Casagranda *et al.*[40]).

Question 1: Is there a serious underlying cause that can be identified in the ED?

Normally the presenting complaint of syncope can be established. The primary aim for an ED clinician is then to establish an underlying diagnosis, especially those associated with the potential for rapid clinical deterioration.[41,42] It is the acute underlying disease that most frequently determines short-term adverse events rather than the syncope itself.[43] Subsequent management will focus on treating this underlying cause (*Figure 5*). Many (40–45%) non-cardiovascular and some cardiovascular life-threatening underlying conditions are obvious in the ED.[44] *Table 6* lists high-risk features that suggest the presence of a serious underlying cause and low-risk features that suggest a benign underlying cause.

Question 2: What is the risk of a serious outcome?

High-risk features are shown in *Table 6*, and how to use this risk profile to guide subsequent management and disposition is shown in *Figure 6*.

Risk stratification is important, for two reasons:

(1) To recognize patients with a likely *low*-risk condition able to be discharged with adequate patient education.
(2) To recognize patients with a likely *high*-risk cardiovascular condition requiring urgent investigation. This may require admission.

High-risk patients are more likely to have cardiac syncope. Structural heart disease[25–27,31,35,36,45] and primary electrical disease[46] are major risk factors for sudden cardiac death (SCD) and overall mortality in patients with syncope. Low-risk patients are more likely to have reflex syncope and have an excellent prognosis.[47] OH is associated with a two-fold higher risk of death owing to the severity of comorbidities compared with the general population.[48]

Question 3: Should the patient be admitted to hospital?

Approximately 50% of patients who present to the ED with syncope are admitted (although the rate varies between 12–86%) (see *Supplementary Data Table 4*). The use of clinical decision rules and standardized protocols has not changed this rate significantly. The composite estimate of outcomes is that in the next 7–30 days, only 0.8% die and 6.9% have a non-fatal severe outcome whilst in the ED, while another 3.6% have a post-ED serious outcome (see *Supplementary Data Table 4*). Unnecessary admission in low-risk patients can be harmful.[87] Whereas it is crucial to identify these high-risk patients to ensure early, rapid, and intensive investigation, not all patients at high risk need hospitalization.[80]

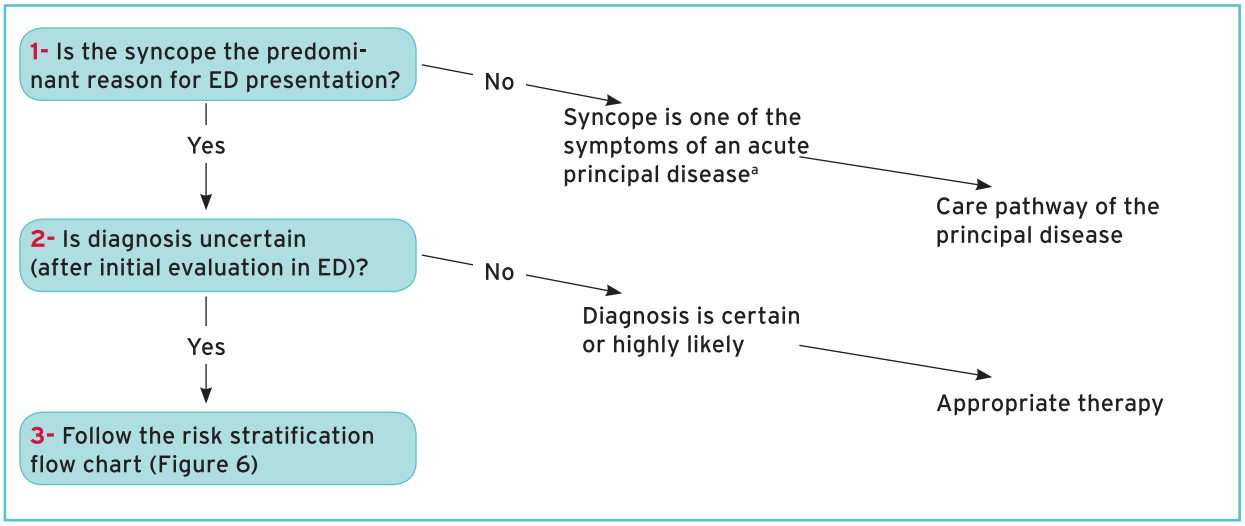


Figure 5 The management of patients presenting to the emergency department for transient loss of consciousness suspected to be syncope (modified from Casagranda *et al.*[40]). ED = emergency department; TLOC = transient loss of consciousness.
[a]For example, this includes pulmonary embolism presenting with shortness of breath, pleuritic chest pain, and syncope, but not trauma secondary to syncope.

Management of syncope in the emergency department

Recommendations	Class[a]	Level[b]
It is recommended that patients with low-risk features, likely to have reflex or situational syncope, or syncope due to OH, are discharged from the ED.[27,35,36,49–54,58,62,69]	I	B
It is recommended that patients with high-risk features receive an early intensive and prompt evaluation in a syncope unit or in an ED observation unit (if available), or are hospitalized.[26,27,35,36,44–46,50,55–57,59,60,70–76]	I	B
It is recommended that patients who have neither high- nor low-risk features are observed in the ED or in a syncope unit instead of being hospitalized.[40,63–65,77]	I	B
Risk stratification scores may be considered for risk stratification in the ED.[78–86]	IIb	B

Additional advice and clinical perspectives

- In the ED, presyncope should be managed with the same accuracy as syncope as it carries the same prognosis.[66–68]
- Diagnostic radiology and laboratory tests such as chest X-ray, brain computed tomography, routine blood haematology, biochemistry, and D-dimer and cardiac markers have a low diagnostic yield, impact on risk stratification of patients with syncope, and should not routinely be used unless specifically suggested by clinical evaluation.
- Around 10% of patients with syncope in the ED will suffer from a serious outcome within 7–30 days of their visit, with just under half occurring after their stay in the ED (see *Supplementary Data Table 4*). It is crucial to identify these high-risk patients to ensure early, rapid, and intensive investigation.
- As syncope units are both effective and efficient, this early, rapid, and intensive investigation can be performed on an outpatient basis (either in a syncope unit or an ED observation unit) in most cases. Only patients with a risk of a short-term serious outcome should be considered for hospital admission.
- To reduce inappropriate admissions, patients who have a cardiac device and syncope should undergo prompt device interrogation.
- Risk stratification scores perform no better than good clinical judgement and should not be used alone to perform risk stratification in the ED.

ED = emergency department; OH = orthostatic hypotension.
[a]Class of recommendation.
[b]Level of evidence.

Table 6 **High-risk features (that suggest a serious condition) and low-risk features (that suggest a benign condition) in patients with syncope at initial evaluation in the emergency department**

SYNCOPAL EVENT
Low-risk
• Associated with prodrome typical of reflex syncope (e.g. light-headedness, feeling of warmth, sweating, nausea, vomiting)[36,49] • After sudden unexpected unpleasant sight, sound, smell, or pain[36,49,50] • After prolonged standing or crowded, hot places[36] • During a meal or postprandial[51] • Triggered by cough, defaecation, or micturition[52] • With head rotation or pressure on carotid sinus (e.g. tumour, shaving, tight collars)[53] • Standing from supine/sitting position[54]
High-risk
Major
• New onset of chest discomfort, breathlessness, abdominal pain, or headache[26, 44, 55] • Syncope during exertion or when supine[36] • Sudden onset palpitation immediately followed by syncope[36]
Minor (high-risk only if associated with structural heart disease or abnormal ECG):
• No warning symptoms or short (<10 s) prodrome[36, 38, 49, 56] • Family history of SCD at young age[57] • Syncope in the sitting position[54]
PAST MEDICAL HISTORY
Low-risk
• Long history (years) of recurrent syncope with low-risk features with the same characteristics of the current episode[58] • Absence of structural heart disease[27, 58]
High-risk
Major
• Severe structural or coronary artery disease (heart failure, low LVEF or previous myocardial infarction)[26, 27, 35, 55, 59]
PHYSICAL EXAMINATION
Low-risk
• Normal examination

PHYSICAL EXAMINATION	
High-risk	
Major	
• Unexplained systolic BP in the ED <90 mmHg[26, 55] • Suggestion of gastrointestinal bleed on rectal examination[44] • Persistent bradycardia (<40 b.p.m.) in awake state and in absence of physical training • Undiagnosed systolic murmur[60]	
ECG[a]	
Low-risk	
• Normal ECG[26, 35, 36, 55]	
High-risk	
Major	**Minor** (high-risk only if history consistent with arrhythmic syncope)
• ECG changes consistent with acute ischaemia • Mobitz II second- and third-degree AV block • Slow AF (<40 b.p.m.) • Persistent sinus bradycardia (<40 b.p.m.), or repetitive sinoatrial block or sinus pauses >3 seconds in awake state and in absence of physical training • Bundle branch block, intraventricular conduction disturbance, ventricular hypertrophy, or Q waves consistent with ischaemic heart disease or cardiomyopathy[44, 56] • Sustained and non-sustained VT • Dysfunction of an implantable cardiac device (pacemaker or ICD) • Type 1 Brugada pattern • ST-segment elevation with type 1 morphology in leads V1-V3 (Brugada pattern) • QTc >460 ms in repeated 12-lead ECGs indicating LQTS[46]	• Mobitz I second-degree AV block and 1°degree AV block with markedly prolonged PR interval • Asymptomatic inappropriate mild sinus bradycardia (40–50 b.p.m.), or slow AF (40–50 b.p.m.)[56] • Paroxysmal SVT or atrial fibrillation[50] • Pre-excited QRS complex • Short QTc interval (≤340 ms)[46] • Atypical Brugada patterns[46] • Negative T waves in right precordial leads, epsilon waves suggestive of ARVC[46]

AF = atrial fibrillation; ARVC = arrhythmogenic right ventricular cardiomyopathy; AV = atrioventricular; BP = blood pressure; b.p.m. = beats per minute; ECG = electrocardiogram; ED = emergency department; ICD = implantable cardioverter defibrillator; LQTS = long QT syndrome; LVEF = left ventricular ejection fraction; SCD = sudden cardiac death; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

[a]Some ECG criteria are *per se* diagnostic of the cause of the syncope (see recommendations: Diagnostic criteria); in such circumstances appropriate therapy is indicated without further investigations. We strongly suggest the use of standardized criteria to identify ECG abnormalities with the aim of precise diagnosis of ECG-defined cardiac syndromes in ED practice.[61]

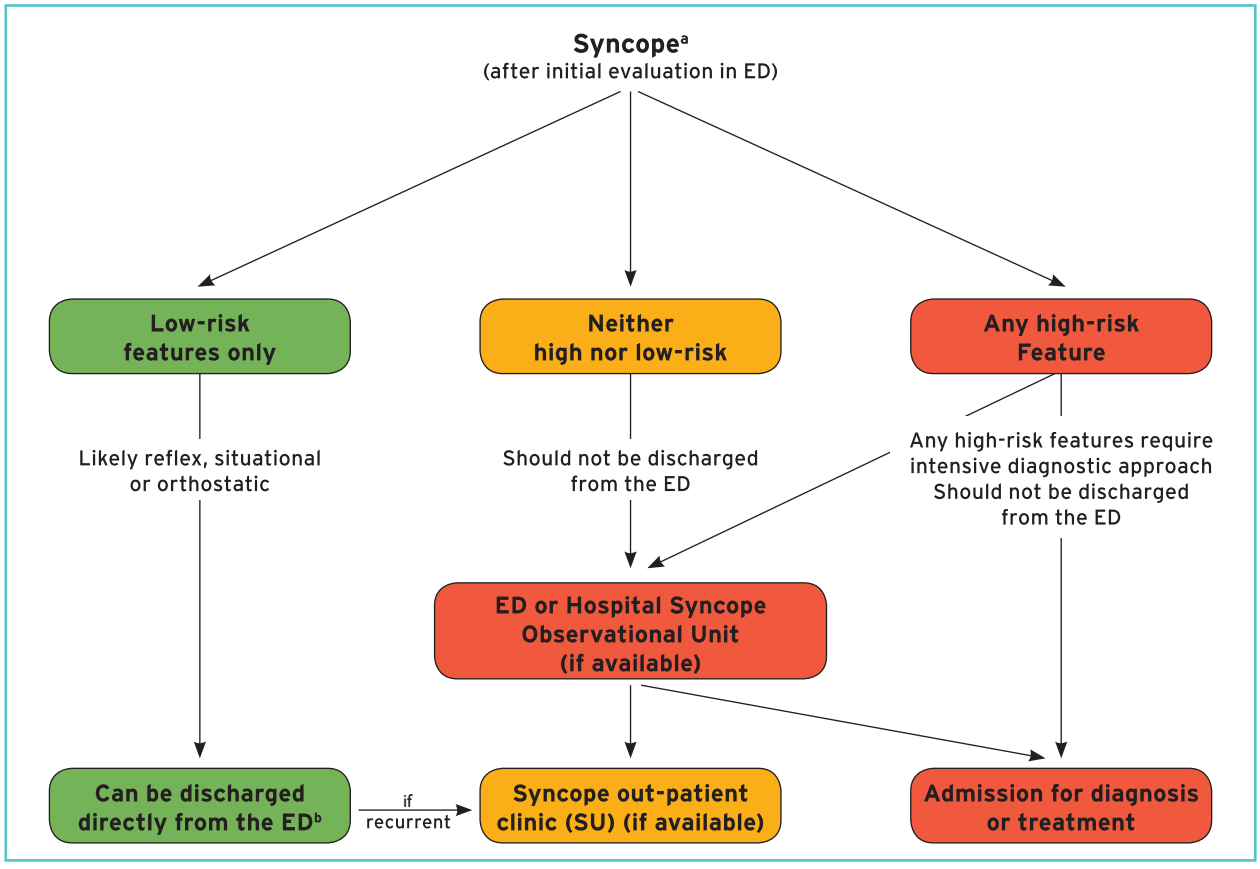


Figure 6 Emergency department risk stratification flow chart. Low- and high-risk features are listed in *Table 6*. ED = emergency department; SU = syncope unit.

Patients with low-risk features. These patients do not need further diagnostic tests in the ED as they are likely to have reflex, situational, or orthostatic syncope. They may benefit from reassurance, or counselling (see *Web Practical Instructions section 9.1: ESC information sheet for patients affected by reflex syncope*).

Patients with high-risk features. These patients should be classified as HIGH RISK; they require an intensive diagnostic approach and may need urgent treatment and admission. These patients should be monitored (although it is unclear for how long this should be, most studies suggesting up to 6 hours in the ED and up to 24 hours in hospital) in a setting where resuscitation can be performed in case of deterioration.[40,62]

Patients that have neither high- nor low-risk features. These patients will require expert syncope opinion, which can probably be safely managed in an outpatient setting.[63] There is no direct evidence that admitting patients to hospital changes their outcome, whilst there is evidence that management in an ED observation unit and/or fast-track to a syncope outpatient unit is beneficial.[64,65]

[a]Recent studies have suggested that outcomes in patients presenting with presyncope are similar to those presenting with syncope.[66–68]

[b]These patients may still require admission to hospital for associated illness, injury or welfare reasons. Low-risk patients can be referred to the outpatient syncope clinic for therapy purposes, if needed.

The diagnostic tests, procedures, and interventions that may require admission in patients with high-risk features are listed in *Table 7*. Furthermore, this Task Force believes that the implementation of novel care pathways and organizational approaches, such as ED observation units and syncope in- and outpatient units (*Figure 6*), offer safe and effective alternatives to admission in the cases listed in *Table 7*. Based on a consensus document,[40] a single-centre experience consisting of a short stay in the ED under observation of ≤48 h coupled with fast-tracking to a syncope unit reduced the admission rate to 29%.[77] Among patients not admitted, 20% were discharged after a short observation in the ED, 20% were fast-tracked to the syncope unit, and 31% were discharged directly from the ED.[77]

Risk stratification scores: There are several ED syncope clinical decision rules that aim to stratify patients with syncope based on medical history, examination, and ECG findings (see *Supplementary*

Table 7 High-risk syncope patients: criteria favouring a stay in an emergency department observation unit and/or fast-tracking to a syncope unit vs. requiring admission to hospital

Favour initial management in ED observation unit and/or fast-track to syncope unit	Favour admission to hospital
High-risk features AND: • Stable, known structural heart disease • Severe chronic disease • Syncope during exertion • Syncope while supine or sitting • Syncope without prodrome • Palpitations at the time of syncope • Inadequate sinus bradycardia or sinoatrial block • Suspected device malfunction or inappropriate intervention • Pre-excited QRS complex • SVT or paroxysmal atrial fibrillation • ECG suggesting an inheritable arrhythmogenic disorders • ECG suggesting ARVC	**High-risk features AND:** • Any potentially severe coexisting disease that requires admission • Injury caused by syncope • Need of further urgent evaluation and treatment if it cannot be achieved in another way (i.e. observation unit), e.g. ECG monitoring, echocardiography, stress test, electrophysiological study, angiography, device malfunction, etc. • Need for treatment of syncope

ARVC = arrhythmogenic right ventricular cardiomyopathy; ECG = electrocardiogram; ED = emergency department; SVT = supraventricular tachycardia.

Data Table 3).[26,34–36,44,88] None of these rules are used widely in EDs due to poor sensitivity and specificity reported from external validation, or due to a lack of external validation.[70,78–85] Syncope clinical decision rules perform no better than clinician judgment at predicting short-term serious outcomes.[86] Clinical decision rules can predict poor outcomes, but most syncope deaths and many poor outcomes are associated with underlying illness rather than syncope *per se*,[58] particularly in the long term.[56]

Even if the quality of evidence is moderate, there is strong consensus from several studies that currently available risk stratification scores have not shown better sensitivity, specificity, or prognostic yield compared with clinical judgment in predicting short-term serious outcomes after syncope. Therefore, they should not be used alone to perform risk stratification in the ED.

4.2 Diagnostic tests

4.2.1 Carotid sinus massage

A ventricular pause lasting >3 s and/or a fall in systolic BP of >50 mmHg is known as carotid sinus hypersensitivity. Carotid sinus hypersensitivity is a common finding in older men without syncope; abnormal responses are frequently observed (≤40%) in patients without syncope, especially if they are older and affected by cardiovascular disease.[89] Carotid sinus hypersensitivity is exceptional in patients <40 years of age.[90] The specificity of the test increases if spontaneous syncope is reproduced during CSM. Syncope was induced in only 5% of asymptomatic persons aged >65 years.[89] For the above reasons, the diagnosis of carotid sinus syndrome (CSS) requires the reproduction of spontaneous symptoms and, in addition, that patients have syncope of unknown origin compatible with a reflex mechanism. In such circumstances, CSM usually shows a period of asystole >6 s.[91] The prevalence of CSS, as defined here, was 8.8% when CSM was performed after the initial evaluation in 1855 consecutive patients >40 years of age with syncope compatible with a reflex mechanism.[92,93] In a multicentre study[94] aimed at validation of the 2009 ESC Guidelines, CSM was indicated after initial evaluation in 73% of 700 patients and was diagnostic in 12%. The precise methodology and results of CSM are shown in section 5 of the *Web Practical Instructions*.

The main complications of CSM are neurological. When pooling the data from four studies[90,95–97] in which 8720 patients were analysed, TIAs or strokes were observed in 21 (0.24%).

The relationship between abnormal response to CSM and spontaneous syncope is a crucial point that has been studied using two methods. The first was a pre-post comparison of the recurrence rate of syncope after pacing. Non-randomized studies demonstrated fewer recurrences at follow-up in paced patients than in those without pacing. These results were confirmed in two randomized trials.[98,99] The second method was to analyse the occurrence of asystolic episodes registered in patients with a cardioinhibitory response to CSM using an implanted device. Recordings of long pauses were very common in the two trials that employed this method.[100,101] These results suggest that a positive response to CSM, reproducing symptoms, in patients with syncope is highly predictive of the occurrence of spontaneous asystolic episodes.

There is strong consensus that the diagnosis of CSS requires both the reproduction of spontaneous symptoms during CSM and clinical features of spontaneous syncope compatible with a reflex mechanism. The quality of evidence is moderate and is given by studies of ECG correlation between CSM and spontaneous events, and indirectly by studies of efficacy of cardiac pacing. Further research is likely to have an important impact on our confidence in the estimation of effect and may change the estimate.

Cardiac sinus massage

Recommendations	Class[a]	Level[b]
Indications		
CSM is indicated in patients >40 years of age with syncope of unknown origin compatible with a reflex mechanism.[92–94]	I	B
Diagnostic criteria		
CSS is confirmed if CSM causes bradycardia (asystole) and/or hypotension that reproduce spontaneous symptoms, and patients have clinical features compatible with a reflex mechanism of syncope.[89,90,92,93,98–102]	I	B
Additional advice and clinical perspectives • History of syncope and its reproduction by CSM defines CSS; positive CSM without a history of syncope defines carotid sinus hypersensitivity.[89,90,92,93] Carotid sinus hypersensitivity in patients with unexplained syncope may be a non-specific finding because it is present in ≤40% of older populations and should be used with caution for diagnosis of the mechanism of syncope. • CSM should be performed with the patient in the supine and upright positions, and with continuous beat-to-beat BP monitoring. This may be more readily performed in the tilt laboratory.[90] • Although neurological complications are very rare,[90,95–97] the risk of provocation of TIA with the massage suggests that CSM should be undertaken with caution in patients with previous TIA, stroke, or known carotid stenosis >70%.		

BP = blood pressure; CSM = carotid sinus massage; CSS = carotid sinus syndrome; TIA = transient ischaemic attack.
[a]Class of recommendation.
[b]Level of evidence.

4.2.2 Orthostatic challenge

Changing from the supine to the upright position produces a displacement of blood from the thorax to the lower limbs and abdominal cavity that leads to a decrease in venous return and cardiac output. In the absence of compensatory mechanisms, a fall in BP may lead to syncope.[20,103,104] The diagnostic criteria for OH have been defined by consensus.[6]

Currently, there are three methods for assessing the response to change in posture from supine to erect[20,103,104]: active standing (see section 4.2.2.1), head-up tilt (see section 4.2.2.2), and 24-h ambulatory BP monitoring (ABPM) (see section 4.2.3.4).

4.2.2.1 Active standing

Indications: This test is used to diagnose different types of orthostatic intolerance (see *Web Practical Instructions Web Table 1*). A sphygmomanometer is adequate for routine clinical testing for classical OH and delayed OH because of its ubiquity and simplicity. Automatic arm-cuff devices, which are programmed to repeat and confirm measurements when discrepant values are recorded, are at a disadvantage due to the rapidly falling BP during OH. With a sphygmomanometer, more than four measurements per minute cannot be obtained without venous obstruction in the arm. When more frequent readings are required, as for initial OH, continuous beat-to-beat non-invasive BP measurement is needed.[20,103,104]

Diagnostic criteria: Abnormal BP fall is defined as a progressive and sustained fall in systolic BP from baseline value ≥20 mmHg or diastolic BP ≥10 mmHg, or a decrease in systolic BP to <90 mmHg. This definition of OH differs from the 2011 consensus[6] in adding the 90 mmHg threshold. This Task Force believes that an absolute threshold of 90 mmHg of systolic BP is useful, especially in patients with a supine BP <110 mmHg. An isolated diastolic BP drop is very rare and its clinical relevance for OH diagnosis is limited. Orthostatic heart rate (HR) increase is blunted or absent [usually not >10 beats per minute (b.p.m.)] in patients with neurogenic OH, but increases or even exaggerates with anaemia or hypovolaemia. The probability that syncope and orthostatic complaints are due to OH can be assessed using the information given in *Table 8*.

Table 8 Association of orthostatic intolerance and orthostatic hypotension

		History of syncope and orthostatic complaints	
		Highly suggestive of OH: *syncope and pre-syncope are present during standing, absent while lying, and less severe or absent while sitting; a predilection for the morning; sitting or lying down must help; complaints may get worse immediately after exercise, after meals or in high temperatures; no "autonomic activation"*	Possibly due to OH: *not all of the features highly suggestive of OH are present*
Supine and standing BP measurement	Symptomatic abnormal BP fall	**Syncope is due to OH** (Class I)	**Syncope is likely due to OH** (Class IIa)
	Asymptomatic abnormal BP fall	**Syncope is likely due to OH** (Class IIa)	**Syncope may be due to OH** (Class IIb)
	No abnormal BP drop	**Unproven**	**Unproven**

BP = blood pressure; OH = orthostatic hypotension.

Active standing

Recommendations	Class[a]	Level[b]
Indications		
Intermittent determination by sphygmomanometer of BP and HR while supine and during active standing for 3 min are indicated at initial syncope evaluation.[20,103,104]	I	C
Continuous beat-to-beat non-invasive BP and HR measurement may be preferred when short-lived BP variations are suspected, such as in initial OH.[20,103,104]	IIb	C
Diagnostic criteria		
Syncope due to OH is confirmed when there is a fall in systolic BP from baseline value ≥20 mmHg or diastolic BP ≥10 mmHg, or a decrease in systolic BP to <90 mmHg that reproduces spontaneous symptoms.[6,20,103,104]	I	C
Syncope due to OH should be considered likely when there is an asymptomatic fall in systolic BP from baseline value ≥20 mmHg or diastolic BP ≥10 mmHg, or a decrease in systolic BP to <90 mmHg, and symptoms (from history) are consistent with OH.[6,20,103,104]	IIa	C
Syncope due to OH should be considered likely when there is a symptomatic fall in systolic BP from baseline value ≥20 mmHg or diastolic BP ≥10 mmHg, or a decrease in systolic BP to <90 mmHg, and not all of the features (from history) are suggestive of OH.[6,20,103,104]	IIa	C
POTS should be considered likely when there is an orthostatic HR increase (>30 b.p.m. or to >120 b.p.m. within 10 min of active standing) in the absence of OH that reproduces spontaneous symptoms.[6,20,103,104]	IIa	C
Syncope due to OH may be considered possible when there is an asymptomatic fall in systolic BP from baseline value ≥20 mmHg or diastolic BP ≥10 mmHg, or a decrease in systolic BP to <90 mmHg, and symptoms (from history) are less consistent with OH.[6,20,103,104]	IIb	C

BP = blood pressure; b.p.m. = beats per min; OH = orthostatic hypotension; HR = heart rate; POTS = postural orthostatic tachycardia syndrome.
[a]Class of recommendation.
[b]Level of evidence.

4.2.2.2 Tilt testing

Since its introduction in 1986,[105] many protocols have been reported with variations in the initial stabilization phase, duration, tilt angle, type of support, and pharmacological provocation. The most commonly used are the trinitroglycerin (TNG) test using 300–400 μg of sublingual TNG after a 20-min unmedicated phase,[106,107] and the low-dose intravenous isoproterenol test, which uses incremental doses to increase average HR by about 20–25% over baseline (usually ≤3 μg/min).[108,109] In a recent systematic literature review,[110] the overall positivity rate in patients with syncope was 66% for the TNG protocol and 61% for the isoproterenol protocol; the respective positivity rate in subjects without syncope (controls) ranged from 11–14%; and the test differentiated patients with syncope from controls with an odds ratio of 12. The methodology and classification of responses are described in section 6 of the *Web Practical Instructions*. Adding video recording to a tilt table permits objective and repeated review of clinical signs in relation to BP and HR, and helps to assess the relative contribution of bradycardia and hypotension to syncope (see section 5.2.6.3 and the explanatory video in *Web Practical Instructions* section 6.3.15), and to distinguish between VVS and PPS (see section 4.2.5).

The clinical situation corresponding to tilt-induced syncope is that which is triggered by prolonged standing. The test should be considered: (i) to confirm a diagnosis of reflex syncope in patients in whom this diagnosis was suspected but not confirmed by initial evaluation[105–109,111], and (ii) for the assessment of autonomic failure, especially for the reproduction of delayed OH (which could not be detected by active standing because of its delayed onset)[23,24,112,113] and postural orthostatic tachycardia syndrome (POTS).[114] Tilt testing may be helpful in separating syncope from PPS.[115–117]

Tilt testing has limited value in assessing treatment efficacy.[118] However, tilt testing is widely accepted as a useful tool to demonstrate susceptibility of the patient to reflex syncope, especially a hypotensive (vasodepressive) tendency, and thereby to initiate treatment (e.g. physical manoeuvres, see section 5).[119–121]

The endpoint of tilt testing is the reproduction of symptoms along with the characteristic circulatory pattern of the indication mentioned above, namely the induction of reflex hypotension/bradycardia, OH, POTS, or PPS. The typical tilt test result patterns are shown in the Web Practical Instructions section 6.

Interpretation of tilt testing results in patients with reflex syncope: Some studies[122,123] compared the response to tilt testing with spontaneous syncope recorded by an implantable loop recorder (ILR). While a positive cardioinhibitory response to tilt testing predicts, with a high probability, an asystolic spontaneous syncope, the presence of a

Tilt testing

Recommendations	Class[a]	Level[b]
Indications		
Tilt testing should be considered in patients with suspected reflex syncope, OH, POTS, or PPS.[23,24,105–109,111–117]	IIa	B
Tilt testing may be considered to educate patients to recognize symptoms and learn physical manoeuvres.[119–121]	IIb	B
Diagnostic criteria		
Reflex syncope, OH, POTS, or PPS should be considered likely if tilt testing reproduces symptoms along with the characteristic circulatory pattern of these conditions.[23,24,105–109,111–117]	IIa	B

Additional advice and clinical perspectives

- A negative tilt table response does not exclude a diagnosis of reflex syncope.
- While sensitivity and specificity are at acceptable levels when measured in patients with VVS and healthy controls, in usual clinical settings of syncope of uncertain origin tilt testing suggests the presence of a *hypotensive susceptibility*, which may exist not only in reflex syncope but also with other causes of syncope including some forms of cardiac syncope. The concept of hypotensive susceptibility rather than diagnosis has important practical utility, because the presence or absence of hypotensive susceptibility plays a major role in guiding pacemaker therapy in patients affected by reflex syncope and in the management of hypotensive therapies, which are frequently present in the elderly with syncope (see sections 5.1 and 5.2).
- A positive cardioinhibitory response to tilt testing predicts, with high probability, asystolic spontaneous syncope; this finding is relevant for therapeutic implications when cardiac pacing is considered (see section 5.2.6). Conversely, the presence of a positive vasodepressor, a mixed response, or even a negative response does not exclude the presence of asystole during spontaneous syncope.[122,123]
- Tilt testing may be helpful in separating syncope with abnormal movements from epilepsy.[137]
- Tilt testing may have value in distinguishing syncope from falls.[23]
- Tilt testing may be helpful in separating syncope from PPS. In suspected PPS, the tilt test should preferably be performed together with EEG monitoring; a normal EEG helps to confirm the diagnosis.[116,117] In the absence of an EEG, a video recording will be helpful in confirming the diagnosis.
- Tilt testing should not be used to assess the efficacy of a drug treatment.[118]

EEG = electroencephalogram; OH = orthostatic hypotension; POTS = postural orthostatic tachycardia syndrome; PPS = psychogenic pseudosyncope; VVS = vasovagal syncope.
[a]Class of recommendation.
[b]Level of evidence.

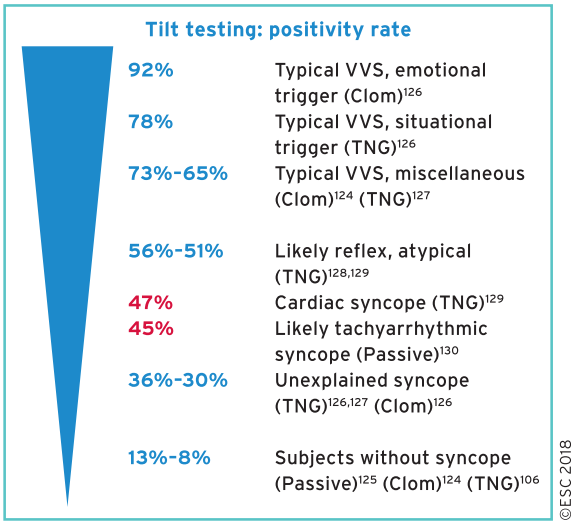


Figure 7 Rates of tilt testing positivity in different clinical conditions. These studies used the Westminster protocol for passive tilt,[125] the Italian protocol for trinitroglycerin tilt,[106] and the clomipramine protocol,[124] for a total of 1453 syncope patients and 407 controls without syncope. Studies using other tilt protocols, e.g. isoproterenol challenge, were not included. Clom = clomipramine; TNG = trinitroglycerin; VVS = vasovagal syncope.

positive vasodepressor, mixed response, or even a negative response, does not exclude the presence of asystole during spontaneous syncope.[122,123]

Tilt testing has an acceptable sensitivity[124] and specificity[106,124,125] when these are calculated in patients with true VVS or without a history of syncope. However, there is an inability to apply the test to populations with syncope of uncertain cause where it is hoped that tilt testing might prove decisive. In these clinical settings, tilt testing fails to deliver (*Figure 7*). Indeed, tilt testing was positive in 51–56% of patients with atypical clinical features suggesting a reflex mechanism,[106,124–128] in 30–36% with unexplained syncope after full investigation,[124,129] and in 45–47% with true cardiac arrhythmic syncope.[130,131] In other words, tilt testing offers little diagnostic value in patients for whom it is most needed. In these patients, a positive tilt test reveals a susceptibility to orthostatic stress.[132] This *hypotensive susceptibility* plays a role in causing syncope irrespective of the aetiology and mechanism of syncope. For example, in arrhythmic syncope caused by paroxysmal atrial tachyarrhythmias, the mechanism is a combination of onset of the arrhythmia itself and hypotensive susceptibility, corroborated by positive tilt testing.[130,131] Similarly, multifactorial mechanisms are likely in other types of cardiac syncope, e.g. aortic stenosis,[133] hypertrophic cardiomyopathy (HCM),[134] and sick sinus syndrome.[135,136] The presence or absence of susceptibility explains the occurrence of syncope in some and not in others affected by the same severity of arrhythmia or structural defect. Tilt testing should now be considered a means of exposing a hypotensive tendency rather than being diagnostic of VVS. This concept has practical implications for therapy (see sections 5.1 and 5.2).

4.2.3 Basic autonomic function tests

Autonomic function assessment helps to identify autonomic failure as the underlying cause of syncope.

4.2.3.1 Valsalva manoeuvre

The methodology of the Valsalva manoeuvre is described in section 7.1.1 of the *Web Practical Instructions* and in *Web Video 2*. There is strong evidence that the absence of a BP overshoot and an absence of a HR increase during the Valsalva is pathognomonic for neurogenic OH, occurring in primary and secondary autonomic failure, and the degree of hypotension and/or lack of compensation during forced expiration usually correlate with the degree of autonomic dysfunction and related symptoms.[138–143] In contrast, a pronounced BP fall beyond what is normally expected during forced expiration, but a normal chronotropic response during the manoeuvre, may occur in patients with suspected situational syncope, i.e. syncope occurring during some forms of situational syncope, e.g. coughing, brass instrument playing, singing, and weightlifting.[144]

4.2.3.2 Deep breathing

The methodology of the deep-breathing test is described in section 7.1.2 of the *Web Practical Instructions*. Under physiological conditions, HR rises during inspiration and falls during expiration. HR variability during deep breathing (also called the expiratory/inspiratory index or E/I index) is ≥15 b.p.m. in healthy individuals aged >50 years.[145] There is strong consensus that blunted or abolished variation is suggestive of parasympathetic dysfunction.[142,143,146,147]

4.2.3.3 Other autonomic function tests

Further tests to evaluate cardiovascular sympathetic function include calculation of the 30:15 ratio, the cold pressure test, the sustained hand grip test, and mental arithmetic. There is weak evidence that these tests may be useful.[13,142,143,147]

4.2.3.4 Twenty-four-hour ambulatory and home blood pressure monitoring

Twenty-four-hour ABPM and home BP monitoring (HBPM) are increasingly used to diagnose and monitor the treatment of hypertension.[148] There is strong evidence that OH is frequently associated with a nocturnal 'non-dipping' or even 'reverse-dipping' BP pattern in patients with autonomic failure, with relevant therapeutic and prognostic implications[140,148–151] (see *Web Practical Instructions* section 7.1.3). In these patients, ABPM allows the assessment of nocturnal hypertension, postprandial hypotension, and exercise- and drug-induced hypotension, as well as monitoring for side effects of antihypotensive regimens and pointing to additional disorders such as sleep apnoea.[152] There is weak evidence that ABPM may also detect the degree of OH in daily life better than single office BP measurements.[153]

HBPM may be used to investigate the cause of orthostatic intolerance, i.e. to clarify whether symptoms are due to OH or to other causes, such as vertigo or motor imbalance in Parkinson's disease or multiple system atrophy. The evidence is weak. Finally, HBPM can be used to clarify that BP is not low during episodes of PPS.[154]

Basic autonomic function tests

Recommendations	Class[a]	Level[b]
Valsalva manoeuvre		
Valsalva manoeuvre should be considered for the assessment of autonomic function in patients with suspected neurogenic OH.[138–143]	IIa	B
Valsalva manoeuvre may be considered for confirming the hypotensive tendency induced by some forms of situational syncope, e.g. coughing, brass instrument playing, singing, and weightlifting.[144]	IIb	C
Deep-breathing test		
Deep-breathing tests should be considered for the assessment of autonomic function in patients with suspected neurogenic OH.[142,143,146,147]	IIa	B
Other autonomic function tests		
Other autonomic function tests (30:15 ratio, cold pressure test, sustained hand grip test, and mental arithmetic test) may be considered for the assessment of autonomic function in patients with suspected neurogenic OH.[13,142,143,147]	IIb	C
ABPM		
ABPM is recommended to detect nocturnal hypertension in patients with autonomic failure.[140,148–151]	I	B
ABPM should be considered to detect and monitor the degree of OH and supine hypertension in daily life in patients with autonomic failure.[152,153]	IIa	C
ABPM and HBPM may be considered to detect whether BP is abnormally low during episodes suggestive of orthostatic intolerance.	IIb	C
Additional advice and clinical perspectives • Whenever possible, reproduction of the trigger situation (e.g. coughing, swallowing, laughing, bass instrument playing, weightlifting) under beat-to-beat non-invasive HR and BP measurement should be performed in patients with suspected situational syncope. • The effects of age and sex should be considered when interpreting autonomic function tests.[145,155–157] • Compliance with autonomic function tests may be limited in patients with dementia. Patients with tremor or Parkinsonism may not succeed in performing the sustained hand grip test. The cold pressure test may be uncomfortable in patients with Raynaud's phenomena.[147]		

ABPM = ambulatory blood pressure monitoring; BP = blood pressure; HBPM = home blood pressure monitoring; HR = heart rate; OH = orthostatic hypotension.
[a]Class of recommendation.
[b]Level of evidence.

4.2.4 Electrocardiographic monitoring (non-invasive and invasive)

The role of ECG monitoring cannot be defined in isolation. As a rule, ECG monitoring is indicated only when there is a high pre-test probability of identifying an arrhythmia associated with syncope, such as those listed in *Table 5*.

4.2.4.1 In-hospital monitoring

In-hospital monitoring (in bed or by telemetry) is warranted in patients with high-risk clinical features (defined in *Table 6*) suggesting arrhythmic syncope, especially if the monitoring is applied immediately after syncope. Although the diagnostic yield of ECG monitoring varies from 1.9–17.6%,[158–160] it is justified by the need to avoid immediate risk to the patient.

4.2.4.2 Holter monitoring

Since, in most patients, symptoms do not recur during monitoring, the true yield of Holter monitoring in syncope may be as low as 1–2% in an unselected population. In 15% of patients, symptoms were not associated with arrhythmia.[161] Thus, in these patients, a rhythm disturbance could potentially be excluded as a cause of syncope. Holter monitoring in syncope is inexpensive in terms of set-up costs, but expensive in terms of cost per diagnosis.[162] Holter monitoring in syncope may be of more value if symptoms are frequent. Daily single or multiple episodes of LOC might increase the potential for symptom–ECG correlation.

4.2.4.3 Prospective external event recorders

Event recorders are external devices that are applied by the patient when symptoms occur. Whereas these recorders can be useful in

the investigation of palpitations,[163] they have a marginal role in the evaluation of syncope.

4.2.4.4 Smartphone applications

Because up to now smartphone applications have recorded real-time ECG, their current role in syncope is limited for the same reason as for prospective event recorders.[164,165] However, home video records are very useful in all forms of TLOC (see section 4.2.5.2).

4.2.4.5 External loop recorders

In general, external loop recorders have a higher diagnostic yield than Holter monitoring.[162] External loop recorders can be useful in patients with relatively frequent syncope episodes.[166–168] In a recent multicentre international registry, the diagnostic yield in syncope was 24.5%, with the most common finding being bradyarrhythmias; the stronger predictor for diagnostic findings was early monitoring after the index event.[166]

4.2.4.6 Remote (at home) telemetry

Most recently, external and implantable device systems have been developed that provide continuous ECG recording or 24-h loop memory with wireless transmission (real time) to a service centre. Some recent studies have shown that implementing remote monitoring increases the diagnostic yield and achieves diagnosis earlier than without remote monitoring.[169–171]

4.2.4.7 Implantable loop recorders

In a meta-analysis of five randomized controlled trials (RCTs),[172–176] 660 patients with unexplained syncope were randomized to a conventional strategy consisting of an external loop recorder, tilt testing, and an electrophysiological study (EPS), or to prolonged monitoring with an ILR. The results showed that initial implantation of an ILR in the workup provided a 3.7 [95% confidence interval (CI) 2.7–5.0] increased relative probability of a diagnosis compared with the conventional strategy (see *Supplementary Data Table 5*). ILR was more cost-effective than a conventional strategy.[172,173,177,178]

In pooled data from nine studies[179] performed in 506 patients with unexplained syncope at the end of complete negative work-up, a correlation between syncope and ECG was found in 176 patients (35%); of these, 56% had asystole (or bradycardia in a few cases) at the time of the recorded event, 11% had tachycardia, and 33% had no arrhythmia. Presyncope was much less likely to be associated with an arrhythmia than syncope. Similar findings were subsequently observed with ILR use expanded in an early phase of evaluation in patients with recurrent syncope of uncertain origin, in the absence of high-risk criteria and structural heart disease,[176,180–183] and in suspected reflex syncope.[184–186] In particular, an asystolic pause was present during syncope in about 50% of these patients.

There are several areas of interest other than unexplained syncope in which ILRs have been investigated:

- Patients with bundle branch block (BBB) in whom paroxysmal atrioventricular (AV) block is likely despite negative complete EPS: an arrhythmia was observed in 41% of these patients (being paroxysmal AV block in 70%) under ILR observation, based on pooled data from three studies[174,187,188] (see *Supplementary Data Table 6*).
- Patients in whom epilepsy was suspected but the treatment has proven ineffective: in pooled data, an attack could have been documented by ILR in 62% of patients, with an arrhythmic cause being responsible in 26%[137,189–191] (see *Supplementary Data Table 7*).
- Patients with unexplained falls: in pooled data, an attack could have been documented by ILR in 70% of patients, with an arrhythmic cause being responsible in 14%[191–194] (see *Supplementary Data Table 8*).
- Patients with HCM, arrhythmogenic right ventricular cardiomyopathy (ARVC), or primary electrical diseases (see section 5.4).

4.2.4.8 Diagnostic criteria

The gold standard for the diagnosis of arrhythmic syncope is when there is a correlation between the symptoms and an ECG recording.[195,196] The presence of asymptomatic significant arrhythmias—defined as prolonged asystole (≥3 s), rapid supraventricular tachycardias (SVTs) (i.e. >160 b.p.m. for >32 beats), or ventricular tachycardias (VTs)—has been considered by several authors to be a diagnostic finding.[185,188,197–199] On the other hand, although the absence of documentation of an arrhythmia during a syncopal episode cannot be considered to be a specific diagnosis, it allows the exclusion of an arrhythmia as the mechanism of the syncope. Most evidence in support of the above diagnostic criteria is indirectly based on the benefit of specific therapies guided by ECG monitoring in preventing syncopal recurrences.[172,184–186,188,200]

Even if the quality of evidence is moderate, there is strong consensus based on evidence from several controlled trials that a correlation between symptoms and a documented arrhythmia, or the presence of some asymptomatic significant arrhythmias (defined above), is diagnostic of the cause of syncope and specific treatment must be prescribed.

The principal limitation of any ECG monitoring device is the inability to record BP together with ECG. In reflex syncope, the documentation of bradycardia/asystole during a syncopal episode does not rule out the possibility that a hidden hypotensive reflex is the principal cause for syncope, and that bradycardia/asystole is a secondary late event. This issue has important implications for therapy (see section 5). A classification of ECG recordings with their probable related pathophysiology is available in *Web Table 6 and Web Practical Instructions* section 8.

Electrocardiographic monitoring

Recommendations	Class[a]	Level[b]
Indications		
Immediate in-hospital monitoring (in bed or by telemetry) is indicated in high-risk patients (defined in *Table 6*).	I	C
Holter monitoring should be considered in patients who have frequent syncope or presyncope (≥1 episode per week).[161]	IIa	B
External loop recorders should be considered, early after the index event, in patients who have an inter-symptom interval ≤4 weeks.[162,166,168,201]	IIa	B
ILR is indicated in an early phase of evaluation in patients with recurrent syncope of uncertain origin, absence of high-risk criteria (listed in *Table 6*), and a high likelihood of recurrence within the battery life of the device.[175,176,181–184,202], *Supplementary Data Table 5*	I	A
ILR is indicated in patients with high-risk criteria (listed in *Table 6*) in whom a comprehensive evaluation did not demonstrate a cause of syncope or lead to a specific treatment, and who do not have conventional indications for primary prevention ICD or pacemaker indication.[174,180,187,188,195], *Supplementary Data Tables 5 and 6*	I	A
ILR should be considered in patients with suspected or certain reflex syncope presenting with frequent or severe syncopal episodes.[184–186]	IIa	B
ILR may be considered in patients in whom epilepsy was suspected but the treatment has proven ineffective.[137,189–191], *Supplementary Data Table 7*	IIb	B
ILR may be considered in patients with unexplained falls.[191–194], *Supplementary Data Table 8*	IIb	B
Diagnostic criteria		
Arrhythmic syncope is confirmed when a correlation between syncope and an arrhythmia (bradyarrhythmia or tachyarrhythmia) is detected.[172,184–186,188,200]	I	B
In the absence of syncope, arrhythmic syncope should be considered likely when periods of Mobitz II second- or third-degree AV block or a ventricular pause >3 s (with the possible exception of young trained persons, during sleep or rate-controlled atrial fibrillation), or rapid prolonged paroxysmal SVT or VT are detected.[185,188,197–199]	IIa	C
Additional advice and clinical perspectives • Be aware that the pre-test selection of the patients influences the subsequent findings. Include patients with a high likelihood of arrhythmic events. The duration (and technology) of monitoring should be selected according to the risk and the predicted recurrence rate of syncope.[158–160,183] • Exclude patients with a clear indication for ICD, pacemaker, or other treatments independent of a definite diagnosis of the cause of syncope. • Include patients with a high probability of recurrence of syncope in a reasonable time. Owing to the unpredictability of syncope recurrence, be prepared to wait up to 4 years or more before obtaining such a correlation.[203] • In the absence of a documented arrhythmia, presyncope cannot be considered a surrogate for syncope, whereas the documentation of a significant arrhythmia at the time of presyncope can be considered a diagnostic finding.[199] • The absence of arrhythmia during syncope excludes arrhythmic syncope.		

AV = atrioventricular; ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; SVT = supraventricular tachycardia; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.

4.2.5 Video recording in suspected syncope

4.2.5.1 In-hospital video recording

For PNES, a video-electroencephalogram (EEG) forms the highest level of diagnostic probability.[204] For syncope and PPS, video can play a similar, probably underused, role (see section 7). Adding video recording to a tilt table test adds the ability to review clinical signs in relation to BP and HR objectively and repeatedly, thus helping to distinguish VVS from PPS. This approach has revealed new pathophysiological insights in syncope.[9] Attaching the camera to the tilt table allows detailed study of the face and head, which is useful when assessing the start and end of LOC.[9,205] Video recording of tilt-induced PPS[116] ensures that apparent TLOC occurs while BP and HR

are not low; adding an EEG increases the diagnostic probability of PPS even further. The method has been proven to show the combined presence of VVS and PPS.[117]

4.2.5.2 Home video recording

Home video records (by means of smartphone technology) are very useful in all forms of TLOC to allow signs of an attack to be studied. Patients and their relatives should be urged to record attacks, if possible, in cases of diagnostic uncertainty. In epilepsy, advances are made towards prolonged video and EEG recording in patients' homes.[206,207] For syncope or PPS, experience suggests that the chances of obtaining a video record are higher for PPS than for syncope, which is probably the effect of a high frequency and long duration of attacks in PPS. It is rare for the beginning of events to be recorded.[206] Home video records allow complex events such as syncope-induced epileptic seizures to be diagnosed.[208]

Video recording in suspected syncope

Recommendations	Class[a]	Level[b]
Home video recordings of spontaneous events should be considered. Physicians should encourage patients and their relatives to obtain home video recordings of spontaneous events.[206,208]	IIa	C
Adding video recording to tilt testing may be considered in order to increase the reliability of clinical observation of induced events.[9,116,117,205]	IIb	C

[a]Class of recommendation.
[b]Level of evidence.

4.2.6 Electrophysiological study

Indications: In an overview of eight studies, including 625 patients with syncope undergoing EPS,[209] positive results occurred predominantly in patients with structural heart disease. In recent years, the development of powerful non-invasive methods, i.e. prolonged ECG monitoring, showing a higher diagnostic value, has decreased the importance of EPS as a diagnostic test. In clinical practice, registry data show that approximately 3% of patients with unexplained syncope evaluated by cardiologists undergo EPS and even fewer if they are evaluated by other specialists.[71] Nevertheless, EPS remains useful for diagnosis in the following specific clinical situations: asymptomatic sinus bradycardia (suspected sinus arrest causing syncope), bifascicular BBB (impending high-degree AV block), and suspected tachycardia.

Diagnostic criteria: *4.2.6.1 Asymptomatic sinus bradycardia: suspected sinus arrest causing syncope*

The pre-test probability of bradycardia-related syncope is relatively high when there is asymptomatic sinus bradycardia (<50 b.p.m.) or sinoatrial block, usually documented by 12-lead ECG or ECG monitoring. The prognostic value of a prolonged sinus node recovery time (SNRT) is not well defined. An abnormal response is defined as ≥1.6 or 2 s for SNRT, or ≥525 ms for corrected SNRT.[210] One observational study showed a relationship between the presence of prolonged SNRT at EPS and the effect of pacing on symptoms.[211] Another small prospective study showed that a corrected SNRT ≥800 ms had an eight-fold higher risk of syncope than a SNRT below this value.[212]

4.2.6.2 Syncope in bifascicular bundle branch block (impending high-degree atrioventricular block)

Patients with bifascicular block and syncope are at higher risk of developing high-degree AV block.[213] A prolonged HV interval ≥70 ms, or induction of second- or third-degree AV block by pacing or by pharmacological stress (ajmaline, procainamide, or disopyramide), identifies a group at higher risk of developing AV block. By combining the above-mentioned parts of the electrophysiological protocol, a positive EPS yielded a positive predictive value as high as ≥80% for the identification of patients who will develop AV block in old studies.[214–216] This finding has been indirectly confirmed by recent studies that showed a significant reduction in syncopal recurrences in patients with prolonged HV implanted with a pacemaker compared with a control group of untreated patients with a negative EPS[188], or with a control group who received an empiric pacemaker.[217] These results justify an upgrade of the recommendation for EPS-guided therapy (i.e. cardiac pacing) in patients with a positive EPS from class IIa to class I.

Even if the quality of evidence is moderate, there is strong consensus that a positive EPS indicates that the likely mechanism of syncope is paroxysmal AV block.

Conversely, approximately one-third of patients with a negative EPS in whom an ILR was implanted developed intermittent or permanent AV block on follow-up.[187] Thus, EPS has a low negative predictive value.

Mortality is high in patients with syncope and BBB. However, neither syncope nor prolonged H-V interval were associated with a higher risk of death, and pacemaker therapy did not decrease this risk.[213]

4.2.6.3 Suspected tachycardia

In patients with syncope preceded by a sudden onset of brief palpitations suggesting SVT or VT, an EPS may be indicated to assess the exact mechanism, especially when a curative catheter ablation procedure is considered to be beneficial.

In patients with a previous myocardial infarction and preserved left ventricular ejection fraction (LVEF), induction of sustained monomorphic VT is strongly predictive of the cause of syncope,[218] whereas the induction of ventricular fibrillation (VF) is considered a non-specific finding.[37] The absence of induction of ventricular arrhythmias identifies a group at lower risk of arrhythmic syncope.[219]

The role of EPS and the use of pharmacological challenge by class I antiarrhythmic drugs in patients with syncope and suspected Brugada syndrome is controversial. In a recent meta-analysis,[220] the risk of arrhythmic events was slightly increased in patients with a history of unexplained syncope or a spontaneous type 1 pattern, and who had induction of VT or VF with one or two extra stimuli. However, the absence of induction in such individuals does not necessarily preclude arrhythmia risk, particularly in patients with high-risk features.

Electrophysiological study

Recommendations	Class[a]	Level[b]
Indications		
In patients with syncope and previous myocardial infarction, or other scar-related conditions, EPS is indicated when syncope remains unexplained after non-invasive evaluation.[218]	I	B
In patients with syncope and bifascicular BBB, EPS should be considered when syncope remains unexplained after non-invasive evaluation.[188,214–217,221]	IIa	B
In patients with syncope and asymptomatic sinus bradycardia, EPS may be considered in a few instances when non-invasive tests (e.g. ECG monitoring) have failed to show a correlation between syncope and bradycardia.[210–212]	IIb	B
In patients with syncope preceded by sudden and brief palpitations, EPS may be considered when syncope remains unexplained after non-invasive evaluation.	IIb	C
EPS-guided therapy		
In patients with unexplained syncope and bifascicular BBB, a pacemaker is indicated in the presence of either a baseline H-V interval of ≥70 ms, second- or third-degree His-Purkinje block during incremental atrial pacing, or with pharmacological challenge.[188,214–217,221]	I	B
In patients with unexplained syncope and previous myocardial infarction, or other scar-related conditions, it is recommended that induction of sustained monomorphic VT is managed according to the current ESC Guidelines for VA.[46]	I	B
In patients without structural heart disease with syncope preceded by sudden and brief palpitations, it is recommended that the induction of rapid SVT or VT, which reproduce hypotensive or spontaneous symptoms, is managed with appropriate therapy according to the current ESC Guidelines.[46,222]	I	C
In patients with syncope and asymptomatic sinus bradycardia, a pacemaker should be considered if a prolonged corrected SNRT is present.[210–212]	IIa	B
Additional advice and clinical perspectives • In general, whereas a positive EPS predicts the cause of syncope, a negative study is unable to exclude an arrhythmic syncope and further evaluation is warranted. • The induction of polymorphic VT or VF in patients with ischaemic cardiomyopathy or DCM cannot be considered a diagnostic finding of the cause of syncope. • EPS is generally not useful in patients with syncope, normal ECG, no heart disease, and no palpitations.		

BBB = bundle branch block; DCM = dilated cardiomyopathy; ECG = electrocardiogram; EPS = electrophysiological study; ESC = European Society of Cardiology; SNRT = sinus node recovery time; SVT = supraventricular tachycardia; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.

4.2.7 Endogenous adenosine and other biomarkers

Established cardiac biomarkers such as troponin and B-type natriuretic peptide have been used to distinguish cardiac from non-cardiac syncope and identify structural heart disease.[223–225]

4.2.7.1 Adenosine (triphosphate) test and plasma concentration

The purinergic signalling system, including adenosine and its receptors, has been proposed to be involved in unexplained syncope without prodrome.[4,226] A low plasma adenosine level is associated with paroxysmal AV block or CSS, whereas a high level is seen in those with a hypotensive/vasodepressive tendency and VVS. In parallel, the adenosine/adenosine triphosphate (ATP) provocation test has been performed to demonstrate the utility of adenosine sensitivity and paroxysmal cardioinhibitory propensity for the selection of appropriate pacemaker candidates.[4,227,228] The test requires rapid (<2 s) injection of a 20 mg bolus of ATP/adenosine during ECG monitoring. The induction of AV block with ventricular asystole lasting >6 s, or the induction of AV block lasting >10 s, is considered abnormal. ATP testing was positive in most patients with syncope of unknown origin (especially syncope without prodrome and without structural heart disease[4]) but not in controls, suggesting that paroxysmal AV

block could be the cause of unexplained syncope. Although cardiac pacing may lead to substantial reduction of syncopal attacks in elderly patients with unexplained syncope and a positive ATP test,[229] previous studies showed no correlation between AV block induced by ATP and ECG findings (documented by ILR) during spontaneous syncope.[122,123,227] Thus, the low predictive value of the test does not support its routine use in selecting patients for cardiac pacing, but rather its positivity suggests that it can be used to confirm the suspicion of asystolic syncope by means of prolonged ECG monitoring. The role of endogenous adenosine release in triggering a special form of asystolic syncope (so-called adenosine-sensitive syncope) remains under investigation.

4.2.7.2 Cardiovascular biomarkers

Some cardiovascular biomarkers are increased in autonomic dysfunction underlying syncope, such as elevated copeptin (vasopressin), endothelin-1, and N-terminal pro-B-type natriuretic peptide in OH,[113,230,231] whereas atrial natriuretic peptide may be reduced in POTS.[113] At present, the use of cardiovascular biomarkers in the diagnosis of syncope awaits more evidence and verification in independent cohorts.

4.2.7.3 Immunological biomarkers

Autoantibodies against adrenergic receptors in OH and POTS have been reported, but further studies are needed.[232–234]

4.2.8 Echocardiography

For patients with suspected heart disease, echocardiography serves to confirm or refute the suspicions in equal proportions and plays an important role in risk stratification.[235,236] Echocardiography identifies the cause of syncope in very few patients when no more tests are needed (i.e. severe aortic stenosis, obstructive cardiac tumours or thrombi, pericardial tamponade, or aortic dissection).[237–239] In a literature review, right and left atrial myxoma presented with syncope in <20% of cases.[240–244]

4.2.8.1 Exercise stress echocardiography

Upright or semi-supine exercise stress echocardiography to detect provocable left ventricular outflow tract obstruction should be considered in patients with HCM that complain of exertional or postural syncope, particularly when it recurs during similar circumstances (e.g. when rushing upstairs or straining). A gradient of ≥50 mmHg is usually considered to be the threshold at which left ventricular outflow tract obstruction becomes haemodynamically important.[245–249]

Echocardiography

Recommendations	Class[a]	Level[b]
Indications		
Echocardiography is indicated for diagnosis and risk stratification in patients with suspected structural heart disease.[235,236]	I	B
Two-dimensional and Doppler echocardiography *during exercise* in the standing, sitting, or semi-supine position to detect provocable left ventricular outflow tract obstruction is indicated in patients with HCM, a history of syncope, and a resting or provoked peak instantaneous left ventricular outflow tract gradient <50 mmHg.[245–249]	I	B
Diagnostic criteria		
Aortic stenosis, obstructive cardiac tumours or thrombi, pericardial tamponade, and aortic dissection are the most probable causes of syncope when the electrocardiogram shows the typical features of these conditions.[237–244]	I	C
Additional advice and clinical perspectives • For patients without suspected cardiac disease after history taking, physical examination, and electrocardiography, the electrocardiogram does not provide additional useful information, suggesting that syncope alone is not an indication for echocardiography. • Computed tomography or MRI should be considered in selected patients presenting with syncope of suspected cardiac structural origin when echocardiography is not diagnostic.		

HCM = hypertrophic cardiomyopathy; MRI = magnetic resonance imaging.
[a]Class of recommendation.
[b]Level of evidence.

4.2.9 Exercise stress testing

Exercise-induced syncope is infrequent, and the literature is limited to case reports. Exercise testing should be performed in patients who have experienced episodes of syncope during or shortly after exertion. Syncope can occur during or immediately after exercise. These two situations should be considered separately. Indeed, syncope occurring during exercise is likely due to cardiac causes (even though some case reports have shown that it might be a manifestation of an exaggerated reflex vasodilatation), whereas syncope occurring after exercise is almost invariably due to a reflex mechanism.[250–252] Tachycardia-related exercise-induced second- and third-degree AV block has been shown to be located distal to the AV node[253] and predicts progression to permanent AV block.[254,255] A resting ECG frequently shows intraventricular conduction abnormalities,[253,254] but cases with a normal resting ECG have also been described.[256,257] There are no data supporting an indication for exercise testing in a general population with syncope.

Exercise testing

Recommendations	Class[a]	Level[b]
Indications		
Exercise testing is indicated in patients who experience syncope during or shortly after exertion.	I	C
Diagnostic criteria		
Syncope due to second- or third-degree AV block is confirmed when the AV block develops during exercise, even without syncope.[253–257]	I	C
Reflex syncope is confirmed when syncope is reproduced immediately after exercise in the presence of severe hypotension.[250–252]	I	C
Additional advice and clinical perspectives There are no data supporting routine exercise testing in patients with syncope.		

AV = atrioventricular.
[a]Class of recommendation.
[b]Level of evidence.

4.2.10 Coronary angiography

In patients presenting with syncope and obstructive coronary artery disease, percutaneous coronary intervention is not associated with a significant reduction in readmission for syncope.[258] Angiography alone is not diagnostic of the cause of syncope. Therefore, cardiac catheterization techniques should be carried out in suspected myocardial ischaemia or infarction with the same indications as for patients without syncope.

Coronary angiography

Recommendations	Class[a]	Level[b]
Indications		
In patients with syncope, the same indications for coronary angiography should be considered as in patients without syncope.[258]	IIa	C
Additional advice and clinical perspectives Angiography alone is not diagnostic of the cause of syncope.		

[a]Class of recommendation.
[b]Level of evidence.

5. Treatment

5.1 General principles of treatment of syncope

The general framework of treatment is based on risk stratification and the identification of specific mechanisms when possible (*Figure 8*).

The following three general principles should be considered:

- The efficacy of therapy aimed at preventing syncope recurrence is largely determined by the mechanism of syncope rather than its aetiology. Bradycardia is a frequent mechanism of syncope. Cardiac pacing is the most powerful therapy for bradycardia but its efficacy is less if hypotension coexists (see *Table 9* and *Supplementary Data Table 9*). The treatment of syncope due to a hypotensive reflex or to OH is more challenging because specific therapies are less effective.
- Often, therapy to prevent recurrence differs from that for the underlying disease. The management of patients at high risk of SCD requires careful assessment of the individual patient's risk (see section 5.5).
- Syncopal recurrences often decrease spontaneously after medical assessment, even in the absence of a specific therapy; in general, syncope recurs in <50% of patients within 1–2 years (see *Supplementary Data Table 10*). The decrease seems to be more evident when there is a lack of a clear anatomical substrate for syncope, such as in the case of reflex syncope and unexplained syncope. The reason for this decrease is not known. Several potential clinical, statistical, and psychological explanations have been provided and all probably play a role (see *Supplementary Data Table 10*). Whatever the reason, the possibility of spontaneous improvement has major practical importance for treatment that can be postponed in low-risk conditions. The consequence of the spontaneous decrease is that any therapy for syncope prevention appears to be more effective than it actually is, which makes the results of observational data on therapy questionable in the absence of a control group.

5.2 Treatment of reflex syncope

Despite its benign course, recurrent and unpredictable reflex syncope may be disabling. The cornerstone of management of these

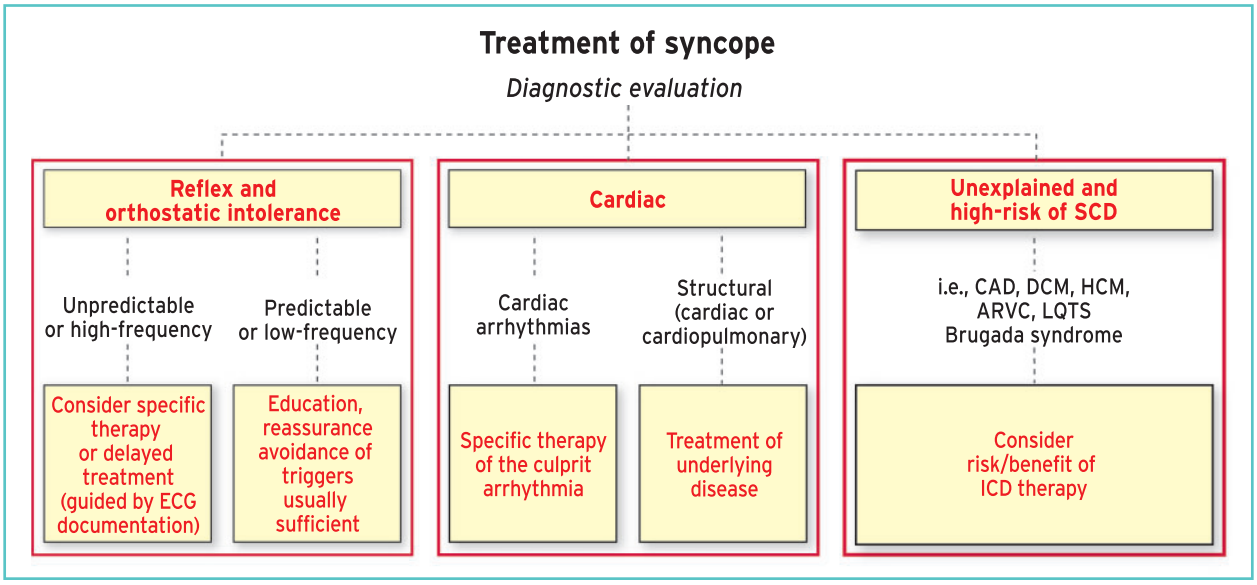


Figure 8 General framework of treatment is based on risk stratification and the identification of specific mechanisms when possible. ARVC = arrhythmogenic right ventricular cardiomyopathy; CAD = coronary artery disease; DCM = dilated cardiomyopathy; ECG = electrocardiographic; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter defibrillator; LQTS = long QT syndrome; SCD = sudden cardiac death.

Table 9 Expected syncope recurrence rates with a permanent pacemaker in different clinical settings (for more details see *Supplementary Data Table 9*).

Clinical setting	Expected 2-year syncope recurrence rate with cardiac pacing
Syncope due to established bradycardia and absence of hypotensive mechanism	High efficacy (≤5% recurrence rate)
Syncope due to established bradycardia and associated hypotensive mechanism	Moderate efficacy (5–25% recurrence rate)
Syncope due to suspected bradycardia and associated hypotensive mechanism	Low efficacy (>25% recurrence rate)

patients is non-pharmacological treatment, including education, lifestyle modification, and reassurance regarding the benign nature of the condition.

Additional treatment may be necessary in patients with *severe forms*, as defined in *Web Practical Instructions* section 2.3, in particular: when very frequent syncope alters quality of life; when recurrent syncope without, or with a very short, prodrome exposes the patient to a risk of trauma; and when syncope occurs during a high-risk activity (e.g. driving, machine operation, flying, or competitive athletics, etc.). Only 14% of the highly selected population with reflex syncope who are referred to specialized syncope units may need such additional treatment.[186] In general, no therapy is appropriate for every form of reflex syncope. The most important discriminant for the choice of therapy is age. A decision pathway for the selection of a specific therapy according to age, severity of syncope, and clinical forms is summarized in *Figure 9*.

5.2.1 Education and lifestyle modifications

Education and lifestyle modifications have not been evaluated in randomized studies, but there is a consensus for implementing them as first-line therapy in all cases. These comprise reassurance about the benign nature of the disease, education regarding awareness and the possible avoidance of triggers and situations (e.g. dehydration and/or hot crowded environments), and the early recognition of prodromal symptoms in order to sit or lie down and activate counter-pressure manoeuvres without delay. If possible, triggers should be addressed directly, such as cough suppression in cough syncope, micturition in the sitting position, etc. Increased intake of oral fluids is also advised. Salt supplementation at a dose of 120 mmol/day of sodium chloride has been proposed.[259] In general, >50% of patients with recurrent syncopal episodes in the 1 or 2 years before evaluation do not have syncopal recurrences in the following 1 or 2 years and, in those with recurrences,

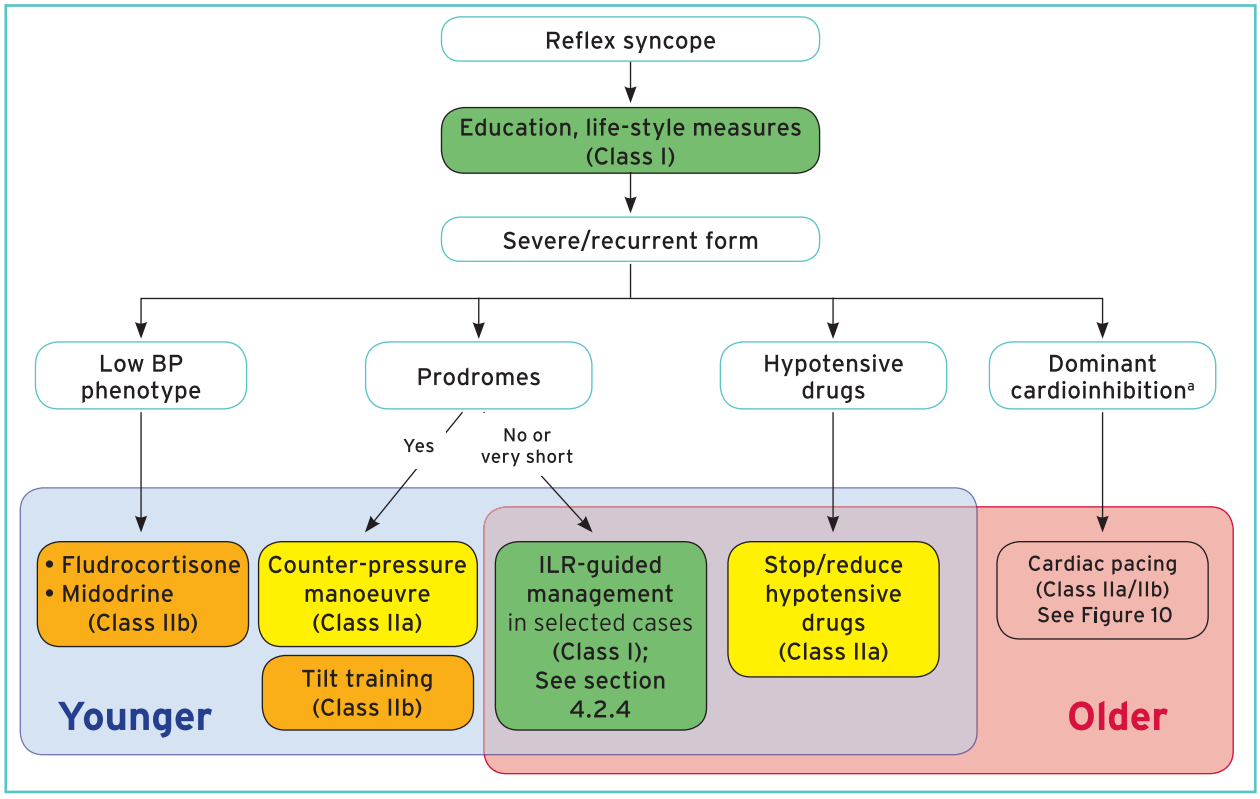


Figure 9 Schematic practical decision pathway for the first-line management of reflex syncope (based on patient's history and tests) according to age, severity of syncope, and clinical forms. *Younger patients* are those aged <40 years while *older patients* are >60 years, with an overlap between 40 and 60 years. *Severity* of reflex syncope is defined in the text. The *duration* of prodrome is largely subjective and imprecise. A value of ≤5 s distinguishes arrhythmic from reflex syncope[49]; in patients without structural heart disease, a duration >10 s can distinguish reflex syncope from cardiac syncope.[38] In practice, the prodrome is 'absent or very short' if it does not allow patients enough time to act, such as to sit or lie down. The heading' *low BP phenotype*' identifies patients with chronic low BP values (in general, systolic around 110 mmHg, who have a clear history of orthostatic intolerance and orthostatic VVS). The group '*dominant cardioinhibition*' identifies patients in whom clinical features and results of tests suggest that sudden cardioinhibition is mainly responsible for syncope. One such clue is lack of prodrome, so patients without prodromes may, after analysis, fall into this category.
Remark:

- Overlap between subgroups is expected.
- In selected cases, pacing may be used in patients aged <40 years. This Task Force cannot give recommendations due to the lack of sufficient evidence from studies.
- In selected cases, fludrocortisone may be used in patients aged >60 years. This Task Force cannot give recommendations due to the lack of sufficient evidence from studies.
- Midodrine can be used at any age even if existing studies were performed in young patients.
- Patients with short or no prodrome should continue investigations to identify the underlying mechanism and guide subsequent therapy.
- Sometimes an ILR strategy should also be considered in patients aged <40 years.

BP = blood pressure; ILR = implantable loop recorder; VVS = vasovagal syncope.
[a]Spontaneous or provoked by, sequentially, carotid sinus massage, tilt testing, or ILR.

the burden of syncope decreases by >70% compared with the preceding period. The effect of education and reassurance is probably the most likely reason for the decrease in syncope (see *Supplementary Data Table 10*). An example of a patient instruction sheet can be found in the *Web Practical Instructions* section 9.1: European Society of Cardiology information sheet for patients affected by reflex syncope.

Despite the lack of controlled studies, there is strong consensus that education and lifestyle modifications have a high impact in reducing recurrence of syncope.

5.2.2 Discontinuation/reduction of hypotensive therapy

Careful avoidance of agents that lower BP, i.e. any antihypertensive agents, nitrates, diuretics, neuroleptic antidepressants, or

dopaminergic drugs, is key in the prevention of recurrence of syncope. In a small randomized trial[260] performed in 58 patients (mean age 74 ± 11 years) affected by vasodepressor reflex syncope diagnosed by tilt testing or CSM, who were taking on average 2.5 hypotensive drugs, discontinuation or reduction of the vasoactive therapy caused a reduction of the rate of the primary combined endpoint of syncope, presyncope, and adverse events from 50 to 19% (hazard ratio 0.37) compared with a control group who continued hypotensive therapy during a follow-up of 9 months. In the Systolic Blood Pressure Intervention Trial,[261] patients at high cardiovascular risk who were already using antihypertensive drugs targeting a systolic BP of 120 mmHg had an approximately two-fold risk of syncope vs. the control group targeting a systolic BP of 140 mmHg. In a short-term randomized trial[262] conducted in 32 patients affected by CSS, withdrawal of vasodilator therapy reduced the magnitude of the vasodepressor reflex induced by CSM.

There is moderate evidence that discontinuation/reduction of hypotensive therapy targeting a systolic BP of 140 mmHg should be effective in reducing syncopal recurrences in patients with hypotensive susceptibility. Further research is likely to have an important impact on our confidence in the estimate.

5.2.3 Physical counter-pressure manoeuvres

Isometric muscle contractions increase cardiac output and arterial BP during the phase of impending reflex syncope. Three clinical studies[119,120,263] and one prospective multicentre randomized trial[121] assessed the effectiveness of physical counter-pressure manoeuvres (PCM) of the legs or arms and showed that they allowed the patient to avoid or delay losing consciousness in most cases. In the Physical Counterpressure Manoeuvres Trial (PC-Trial),[121] 223 patients aged 38 ± 15 years with recurrent reflex syncope and recognizable prodromal symptoms were randomized to receive standardized conventional therapy alone or conventional therapy plus training in PCM. Actuarial recurrence-free survival was better in the PCM group (log-rank P=0.018), resulting in a relative risk reduction of 39% (95% CI 11–53). No adverse events were reported. A limitation of this treatment is that it cannot be used in patients with short or absent prodrome and that PCM are less effective in patients older than 60 years.[264] An instruction sheet on how to perform PCM can be found in the *Web Practical Instructions* section 9.2.

There is moderate evidence that PCM is effective in reducing syncopal recurrences in patients <60 years old with long-lasting recognizable prodromal symptoms.

5.2.4 Tilt training

In highly motivated young patients with recurrent vasovagal symptoms triggered by orthostatic stress, the prescription of progressively prolonged periods of enforced upright posture (so-called tilt training) has been proposed to reduce syncope recurrence.[265] While some studies suggested modest benefit with outpatient tilt training,[266,267] most controlled trials reported no significant effect.[268–272] Moreover, this treatment is hampered by the low compliance of patients in continuing the training programme for a long period.

There is sufficient evidence from multiple trials that tilt training has little efficacy in reducing recurrence of syncope in young patients with long-lasting recognizable prodromal symptoms. Further research is unlikely to have an important impact on our confidence in the estimate.

5.2.5 Pharmacological therapy

Pharmacological therapy may be considered in patients who have recurrent syncope despite education and lifestyle modifications including training in PCM. Many drugs have been tested in the treatment of reflex syncope, for the most part with disappointing results. While results have been satisfactory in uncontrolled trials or short-term controlled trials, several long-term placebo-controlled prospective trials have not shown a benefit of the active drug over placebo, with some exceptions.

5.2.5.1 Fludrocortisone

Fludrocortisone, by increasing renal sodium reabsorption and expanding plasma volume, may counteract the physiological cascade leading to the orthostatic vasovagal reflex.[273] The mechanism of action can be compared with that of saline infusion, which has also proved effective in acute tilt test studies.[274] The Prevention of Syncope Trial (POST) 2[275] enrolled 210 young (median age 30 years) patients with low–normal values of arterial BP and without comorbidities, and randomized them to receive fludrocortisone (titrated at a dosage of 0.05–0.2 mg once per day) or placebo. The primary endpoint showed only a marginal non-significant reduction in syncope in the fludrocortisone group compared with the placebo group (hazard ratio 0.69, 95% CI 0.46–1.03; P=0.069), which became more significant when the analysis was restricted to patients who achieved 0.2 mg/day dose stabilization at 2 weeks. The clinical benefit of fludrocortisone therapy was modest: at 12 months, 44% of patients in the fludrocortisone arm continued to suffer syncope, a rate only slightly lower than the 60.5% rate observed in the placebo arm. In the meantime, a similar number of patients discontinued fludrocortisone therapy owing to side effects, thus equating the benefit/risk ratio. Fludrocortisone should not be used in patients with hypertension or heart failure. Fludrocortisone was ineffective in a small randomized double-blind trial in children.[276]

There is moderate evidence that fludrocortisone may be effective in reducing syncopal recurrences in young patients with low normal values of arterial BP and without comorbidities. Further research is likely to have an important impact on our confidence in the estimate of effect.

5.2.5.2 Alpha-agonists

As failure to achieve proper vasoconstriction of the peripheral vessels is common in reflex syncope, alpha-agonist vasoconstrictors (etilefrine and midodrine) have been used. Etilefrine has been studied in a large randomized placebo-controlled double-blind trial.[277] During follow-up, patients treated twice daily with etilefrine 25 mg or placebo showed no difference in the frequency of syncope or the time to recurrence. Midodrine [usually 2.5–10 mg, three times daily (t.i.d)] has proved effective in small studies but none satisfied the criteria of a pivotal clinical trial. A recent systematic review of these trials[278]

showed that the confidence in estimates was moderate because of imprecision and publication bias. The most frequent side effects that led to discontinuation of midodrine were supine hypertension, pilomotor reactions, and urinary problems (urinary retention, hesitancy, or urgency). The major limitation of midodrine is frequent dosing, which limits long-term compliance. Overall, these data suggest that chronic pharmacological treatment with alpha-agonists alone may be of little use in reflex syncope and that long-term treatment cannot be advised for occasional symptoms.

There are contrasting results from multiple trials that alpha-agonists may be effective in reducing syncopal recurrences in patients with the orthostatic form of VVS. Further research is likely to have an important impact on our confidence in the estimate.

5.2.5.3 Beta-blockers

Beta-blockers have been presumed to lessen the degree of ventricular mechanoreceptor activation owing to their negative inotropic effect in reflex syncope. This theory has not been supported by the outcome of clinical trials. Beta-blockers failed to be effective in VVS in two randomized double-blind controlled trials.[279,280] A rationale for the use of beta-blockers in other forms of neutrally-mediated syncope is lacking. It should be emphasized that beta-blockers may enhance bradycardia in CSS.

There is sufficient evidence from multiple trials that beta-blockers are not appropriate in reducing syncopal recurrences. Desirable and undesirable effects are closely balanced.

5.2.5.4 Other drugs

Paroxetine, a selective serotonin reuptake inhibitor, was effective in one placebo-controlled trial, which included highly symptomatic patients from one institution.[281] This finding has not been confirmed in other studies and has no experimental support. Conversely, human studies with different subtypes of serotonin-receptor antagonists demonstrated a decreased tolerance to tilt.[1,282] In a small randomized trial, benzodiazepine was as effective as metoprolol.[283] A somatostatin analogue (octreotide)[284] was used in a few patients affected by orthostatic intolerance and its effect cannot be properly evaluated.

5.2.5.5 Emerging new therapies in specific subgroups

Low-adenosine phenotype. In a series of case reports, theophylline appeared effective in patients with recurrent sudden onset (pre)syncope who presented with the common biological characteristic of low circulating adenosine levels.[285,286] Theophylline is a non-selective adenosine receptor antagonist that is potentially effective when adenosine is suspected to be involved in the mechanism of syncope. An intra-patient comparison between a period with and a period without theophylline therapy, with the support of prolonged ECG monitoring, showed that symptoms disappeared and the number of prolonged asystolic pauses was impressively reduced from a median of 1.11 per month during 13 months of no treatment to 0 per month during 20 months of theophylline treatment.

Low-norepinephrine phenotype. A mismatch between sympathetic nerve activity and norepinephrine spillover is present in patients with orthostatic VVS.[287] Norepinephrine transport inhibitors (reboxetine and sibutramine) lead to a selective increase in sympathetic tone during stress by inhibiting the reuptake of norepinephrine in sympathetic neuronal synapses. In double-blind, randomized, crossover fashion, reboxetine and sibutramine block or attenuate the vasovagal reflex during tilt testing.[288] In an open-label prospective clinical study in seven very symptomatic patients who had not responded to any previous treatment, sibutramine achieved 94% suppression of syncopal episodes at 6 months.[289]

Ganglionic plexus ablation. Radiofrequency ablation of vagal ganglia located close to the sinus node and AV node was reported to abolish the vagal efferent output during VVS in some observational studies and case reports.[290,291] However, owing to a weak rationale, small populations, weak documentation of follow-up results, procedural risks, and lack of control groups, the current evidence is insufficient to confirm the efficacy of vagal ganglia ablation.

5.2.6 Cardiac pacing

Permanent pacemaker therapy may be effective if asystole is a dominant feature of reflex syncope. Establishing a relationship between symptoms and bradycardia should be the goal of the clinical evaluation of patients with syncope and a normal baseline ECG. The efficacy of pacing depends on the clinical setting. A comparative table of results in different settings is reported in the *Supplementary Data Table 9*. *Figure 10* summarizes the recommended indication for pacing.

5.2.6.1 Evidence from trials in suspected or certain reflex syncope and electrocardiogram-documented asystole

In two observational studies, cardiac pacing reduced syncope burden in patients with documented asystolic syncope by 92[184] and 83%,[200] but did not prevent all syncopal events. In the randomized double-blind Third International Study on Syncope of Uncertain Etiology (ISSUE)-3 trial,[185] 77 patients who had documentation, by means of ILR, of syncope with ≥3-s asystole or ≥6-s asystole without syncope were randomly assigned to receive either dual-chamber pacing with rate drop response or sensing only. During follow-up, the 2-year estimated rate of syncope recurrence was 57% with pacemaker off and 25% with pacemaker on (log-rank $P=0.039$). The risk of recurrence was reduced by 57%. In the ILR subgroup of the multicentre Syncope Unit Project (SUP) 2 study,[292] the estimated rates of syncope recurrence with pacing were 11% at 1 year, 24% at 2 years, and 24% at 3 years, and were significantly lower than the corresponding rates observed in untreated control patients. The above evidence supports a class IIa recommendation

There is sufficient evidence that dual-chamber cardiac pacing should be considered to reduce recurrence of syncope when the correlation between symptoms and ECG is established in patients ≥40 years of age with the clinical features of those in the ISSUE studies.

5.2.6.2 Evidence from trials in patients with carotid sinus syndrome

The evidence supporting the benefit of cardiac pacing in patients affected by cardioinhibitory CSS is limited to a few small controlled trials and retrospective observational studies. In a review[293] including

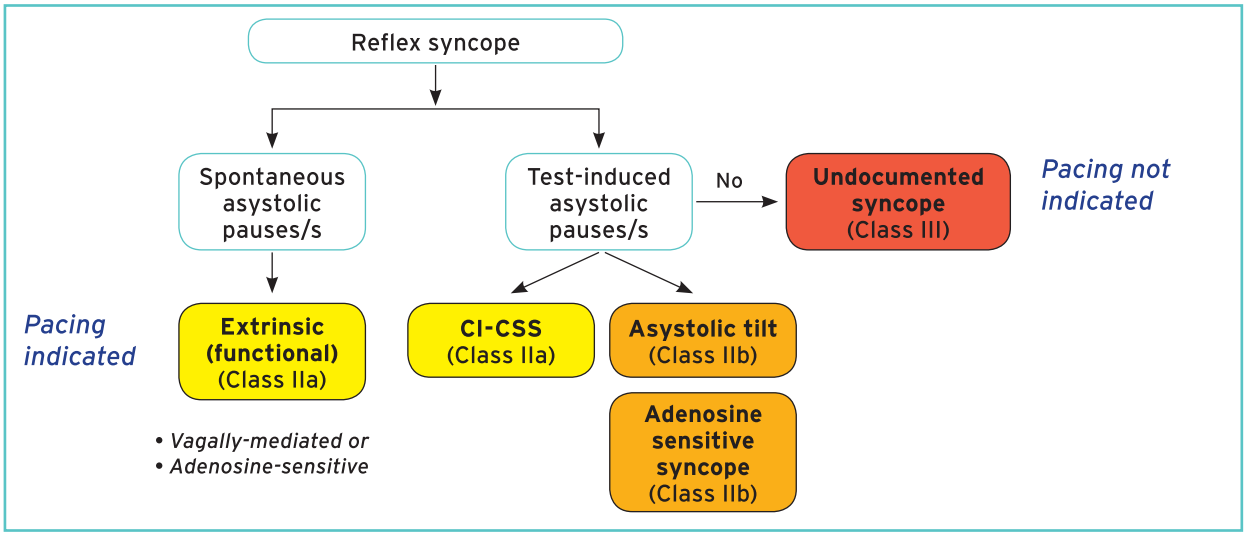


Figure 10 Summary of indications for pacing in patients with reflex syncope. CI-CSS = cardioinhibitory carotid sinus syndrome.

12 studies for a total of 601 paced and 305 unpaced patients, the syncopal recurrence rate during follow-up ranged from 0–20% with pacing, whereas the recurrence of syncope was always higher in untreated patients, who showed a rate between 20–60%. In a meta-analysis of the three studies[293] with a control group of untreated patients, syncope recurred in 9% of 85 paced patients and in 38% of 91 controls (relative risk 0.24, 95% CI 0.12–0.48). In a single-centre registry of 169 consecutive patients treated with pacemakers, the actuarial estimate of syncopal recurrence was 7% at 1 year, 16% at 3 years, and 20% at 5 years.[90] In the CSS subgroup of the multicentre SUP 2 study,[292] the estimated syncope recurrence rates with pacing were 9% at 1 year, 18% at 2 years, and 20% at 3 years, and were significantly lower than the corresponding rates observed in untreated controls, which were 21%, 33%, and 43%, respectively. Given the similar outcome of patients with reflex spontaneous asystolic pauses and those with CSS, this Task Force voted to downgrade the recommendation for pacing in patients with CSS from class I (as in the 2013 ESC Pacing Guidelines[294]) to class IIa.

Despite the lack of large RCTs, there is sufficient evidence that dual-chamber cardiac pacing should be considered to reduce syncopal recurrences in patients affected by dominant cardioinhibitory CSS.

Two variables are well known to hamper the efficacy of pacing therapy in CSS: the mixed forms[93,98] (see also *Web Practical Instructions* section 5) and the association with positivity of tilt testing. Patients who have positive tilt tests have a three-fold greater probability of syncope recurrence after dual chamber pacing than those with negative tilt tests[293,295]; thus, when tilt testing is positive, caution must be recommended over pacemaker implantation.

5.2.6.3 Evidence from trials in patients with tilt-induced vasovagal syncope

Effectiveness of pacing in patients with tilt-induced VVS has been studied in five multicentre RCTs.[296–300] When combining the results of these trials, 318 patients were evaluated; syncope recurred in 21% of the paced patients and in 44% of unpaced patients ($P < 0.001$). A meta-analysis of all studies suggested a non-significant 17% reduction in syncope from the double-blind studies, and an 84% reduction in the studies where the control group did not receive a pacemaker.[301] In general, pacing was ineffective in trials that enrolled patients without an asystolic tilt response.[299,300] All of these studies have limitations, and a direct comparison is somewhat difficult because of important differences in study design, largely focused on patient selection. Overall, in typical vasovagal populations, pacing seems to have marginal efficacy.

The rationale for the efficacy of cardiac pacing is that the cardioinhibitory reflex is dominant in some patients, as there is no role for pacing in the preventing vasodilatation and hypotension. In a substudy of the ISSUE-3 trial,[302] an asystolic response during tilt testing predicted a similar asystolic form during spontaneous ILR-documented syncope, with a positive predictive value of 86%. In the tilt subgroup of the SUP 2 study,[292] among 38 patients with dominant cardioinhibitory reflex (with a mean asystolic pause of 22 ± 16 s) the estimated rates of syncope recurrence with pacing were 3% at 1 year, 17% at 2 years, and 23% at 3 years; these figures were significantly lower than the corresponding rates observed in untreated controls, and were similar to those observed in patients with CSS or with ECG-documented asystole. In a recent multicentre crossover RCT performed in 46 patients aged >40 years, affected by severely recurrent (>5 episodes during life) cardioinhibitory VVS,[303] during 24-month follow-up, syncope recurred in 4 (9%) patients treated with a dual-

chamber pacemaker with closed-loop stimulation compared with 21 (46%) patients who had received a sham pacemaker programmed off (P=0.0001).

Adding video recording to tilt testing, Saal *et al.*[205] recently showed, in patients with asystole, that asystole occurred 3 s before syncope or later in one-third of patients, in whom cardioinhibition was too late to have primarily caused syncope; in the other two-thirds of asystolic tilt responses, the cause must have been mainly cardioinhibition or a combination of cardioinhibition and vasodepression.

The clinical presentation is probably as important as tilt test positivity when selecting patients who can benefit from cardiac pacing. The SUP 2 study population was characterized by higher mean age, history of recurrent syncope beginning in middle or older age, and frequent injuries, probably due to presentation without warning.[292]

Owing to the contrasting results of the randomized trials, the estimated benefit of dual-chamber pacing in cardioinhibitory tilt-positive patients is weak. Divergence of opinion exists among experts. Further research is very likely to have an important impact on recommendations. Conversely, there is strong consensus that pacing cannot be offered to patients with non-cardioinhibitory tilt-positive response, and further tests (e.g. ILR) are warranted to document the mechanism of the spontaneous reflex.

5.2.6.4 Evidence from trials in patients with adenosine-sensitive syncope

Under this term, classified as a non-classical form of reflex syncope in *Table 3*, different clinical conditions are included, which have a supposed role of adenosine in the genesis of syncope in common.

A new clinical entity, called idiopathic AV block, has recently been described in patients with a long history of syncope and in whom paroxysmal AV block could be recorded at the time of syncope recurrence.[5] These patients had an otherwise normal heart and no sign of conduction disease on ECG and EPS; they had very low plasma adenosine levels and a high induction rate of transient complete heart block during exogenous injections of adenosine. No syncope recurrence was observed after permanent cardiac pacing over very long periods of follow-up and there was no permanent AV block.

Similarly, the entity of '*low-adenosine syncope*' has recently been described in patients who have an otherwise unexplained syncope with sudden onset without prodrome, a normal heart, and normal ECG.[4] The clinical, laboratory, and biological features of these patients are similar to those observed in patients affected by idiopathic paroxysmal AV block. Unlike in VVS, tilt testing is usually negative.[4,226] No syncope recurrence was observed after permanent cardiac pacing in 10 patients who had ECG documentation of asystolic pause due to sinus arrest or AV block.[286]

In a small multicentre trial[227] performed in 80 highly selected elderly patients with unexplained unpredictable syncope who had a positive response to intravenous injection of a bolus of 20 mg of ATP, dual-chamber cardiac pacing significantly reduced the 2-year syncope recurrence rate from 69% in the control group to 23% in the active group.

There is weak evidence that dual-chamber cardiac pacing may be useful in reducing recurrences of syncope in patients with the clinical features of adenosine-sensitive syncope. The documentation of possible bradyarrhythmia in spontaneous syncope remains the preferred eligibility criterion for pacing.

5.2.6.5 Choice of pacing mode

In CSS, a few small controlled studies[304,305] and one registry[306] showed that dual-chamber pacing is better than the single chamber ventricular mode in counteracting BP fall during CSM and in preventing symptom recurrences. Even if the quality of evidence is weak, dual-chamber pacing is widely preferred in clinical practice.

In patients with VVS, dual-chamber pacing was used mostly with a rate drop response feature that instituted rapid dual-chamber pacing if the device detected a rapid decrease in HR. A comparison between dual-chamber closed-loop stimulation and conventional dual-chamber pacing has been performed by means of a crossover design in two small studies; these studies showed fewer syncope recurrences with closed-loop stimulation, both in the acute setting during repeated tilt testing[307] and during 18-month clinical follow-up.[308]

5.2.6.6 Selection of patients for pacing and proposed algorithm

The fact that pacing is effective does not mean that it is always necessary. In patients with reflex syncope, cardiac pacing should be the last choice and should only be considered in highly selected patients, i.e. those ≥40 years of age (mostly >60 years), affected by severe forms of reflex syncope with frequent recurrences associated with a high risk of injury, often due to the lack of prodrome.[186] While there is growing scepticism over the diagnostic accuracy of tilt testing for syncope diagnosis, emerging evidence supports the use of tilt testing for the assessment of reflex *hypotensive susceptibility*[132], which may be considered to identify patients with an associated hypotensive response who would be less likely to respond to permanent cardiac pacing (see section 4.2.2.2). In a meta-analysis[309] of individual patient data from four studies performed in patients with asystolic reflex syncope documented by an ILR, the estimated 3-year recurrence rate of syncope was 2% (95% CI ± 4%) in tilt-negative patients and 33% (95% CI ± 20%) in tilt-positive patients; a positive tilt test response was the only significant predictor of syncope recurrence with a hazard ratio of 4.3. Patients with hypotensive susceptibility should need measures directed to counteract hypotensive susceptibility in addition to cardiac pacing, e.g. the discontinuation/reduction of hypotensive drugs and the administration of fludrocortisone or midodrine.

The algorithm shown in *Figure 11* has recently been prospectively validated in a multicentre pragmatic study, which showed a low recurrence rate of syncope with pacing of 9% at 1 year and 15% at 2 years, significantly lower than the 22% and 37%, respectively, observed in unpaced controls.[186]

Treatment of reflex syncope

Recommendations	Class[a]	Level[b]
Education and lifestyle modifications		
Explanation of the diagnosis, the provision of reassurance, and explanation of the risk of recurrence and the avoidance of triggers and situations are indicated in all patients. *Supplementary Data Table 10*	I	B
Discontinuation/reduction of hypotensive therapy		
Modification or discontinuation of hypotensive drug regimen should be considered in patients with vasodepressor syncope, if possible.[260–262]	IIa	B
Physical manoeuvres		
Isometric PCM should be considered in patients with prodromes who are <60 years of age.[119–121,263,264]	IIa	B
Tilt training may be considered for the education of young patients.[265–272]	IIb	B
Pharmacological therapy		
Fludrocortisone may be considered in young patients with the orthostatic form of VVS, low–normal values of arterial BP, and the absence of contraindication to the drug.[275]	IIb	B
Midodrine may be considered in patients with the orthostatic form of VVS.[278]	IIb	B
Beta-adrenergic blocking drugs are not indicated.[279,280]	III	A
Cardiac pacing		
Cardiac pacing should be considered to reduce syncopal recurrences in patients aged >40 years, with spontaneous documented symptomatic asystolic pause(s) >3 s or asymptomatic pause(s) >6 s due to sinus arrest, AV block, or the combination of the two.[184,185,200,292]	IIa	B
Cardiac pacing should be considered to reduce syncope recurrence in patients with cardioinhibitory carotid sinus syndrome who are >40 years with recurrent frequent unpredictable syncope.[90,292,293]	IIa	B
Cardiac pacing may be considered to reduce syncope recurrences in patients with tilt-induced asystolic response who are >40 years with recurrent frequent unpredictable syncope.[292,297,298,303]	IIb	B
Cardiac pacing may be considered to reduce syncope recurrences in patients with the clinical features of adenosine-sensitive syncope.[5,227,286]	IIb	B
Cardiac pacing is not indicated in the absence of a documented cardioinhibitory reflex.[299,300]	III	B

Additional advice and clinical perspectives

- In general, no therapy can completely prevent syncope recurrence during long-term follow-up. A decrease of the syncope burden is a reasonable goal of therapy.
- The fact that pacing may be effective does not mean that it is also always necessary. It must be emphasized that the decision to implant a pacemaker needs to be made in the clinical context of a benign condition that frequently affects young patients. Thus, cardiac pacing should be limited to a highly selected small proportion of patients affected by severe reflex syncope. Patients suitable for cardiac pacing are older with a history of recurrent syncope beginning in middle or older age and with frequent injuries, probably due to presentation without warning. Syncope recurrence is still expected to occur despite cardiac pacing in a minority of patients.
- Tilt test response is the strongest predictor of pacemaker efficacy.[309] Patients with a negative tilt test response will have a risk of syncope recurrence of as low as that observed in patients paced for intrinsic AV block. Further research is very unlikely to change the confidence in the estimate of effect. On the contrary, patients with a positive tilt test response will have a higher risk of recurrence of syncope with a large confidence range, which makes any estimate of the benefit of pacing uncertain. Further research is warranted.

AV = atrioventricular; BP = blood pressure; PCM = physical counter-pressure manoeuvres; VVS = vasovagal syncope.
[a]Class of recommendation.
[b]Level of evidence.

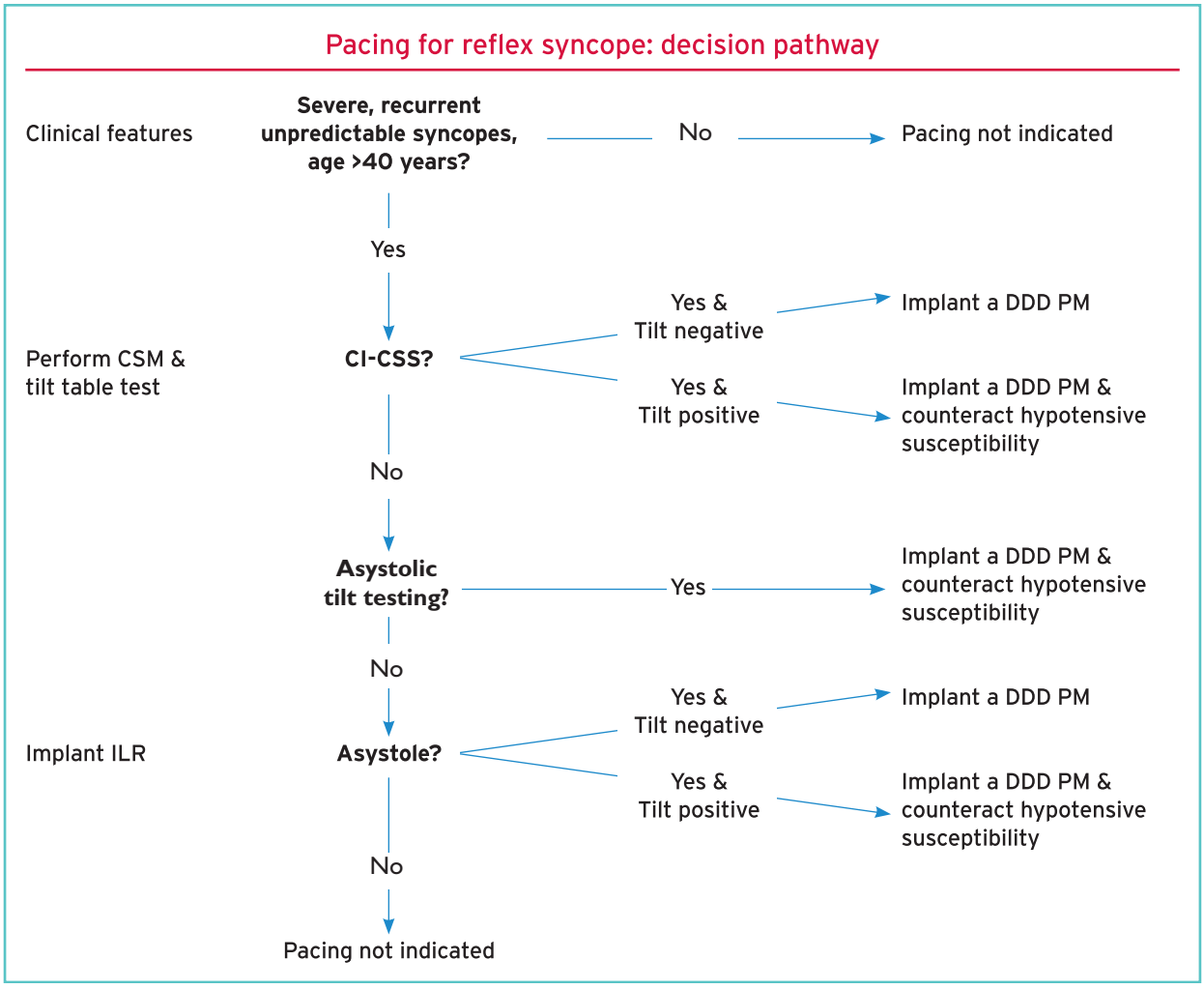


Figure 11 Decision pathway for cardiac pacing in patients with reflex syncope. CI-CSS = cardioinhibitory carotid sinus syndrome; CSM = carotid sinus massage; DDD PM = dual-chamber pacemaker; ILR = implantable loop recorder.

5.3 Treatment of orthostatic hypotension and orthostatic intolerance syndromes

Current management strategies for OH are summarized in *Figure 12*.

5.3.1 Education and lifestyle measures

Education regarding the nature of the condition in conjunction with the lifestyle advice outlined in section 5.2.1 can markedly improve orthostatic symptoms, even though the rise in BP is relatively small (10–15 mmHg); raising standing BP to just within the autoregulatory zone can make a substantial functional difference. Ambulatory BP recordings may be helpful in identifying abnormal diurnal patterns. These recordings may also help identify supine or nocturnal hypertension in treated patients.

5.3.2 Adequate hydration and salt intake

The expansion of extracellular volume is an important goal. In the absence of hypertension, patients should be instructed to have a sufficient salt and water intake, targeting 2–3 L of fluids per day and 10 g of sodium chloride.[310] Rapid ingestion of cool water is reported to be effective in combating orthostatic intolerance and postprandial hypotension.[311]

5.3.3 Discontinuation/reduction of vasoactive drugs

Several studies that have evaluated the association of vasoactive drugs (i.e. any antihypertensive agents, nitrates, diuretics, neuroleptic antidepressants, or dopaminergic drugs) with OH and falls have yielded contrasting results.[312] However, intensely prescribed antihypertensive therapy can increase the risk of OH. Intensive antihypertensive treatment can be defined as higher doses of antihypertensive medications, an increased number of antihypertensive drugs, or lowering BP to a target <140/90 mmHg. The total number of BP-lowering medications[313] or the use of three or more antihypertensive drugs may be a significant predictor of OH.[314] Angiotensin-converting enzyme inhibitors, angiotensin receptors blockers, and calcium channel blockers are less likely to be associated with OH compared with beta-blockers and thiazide diuretics.[315–318]

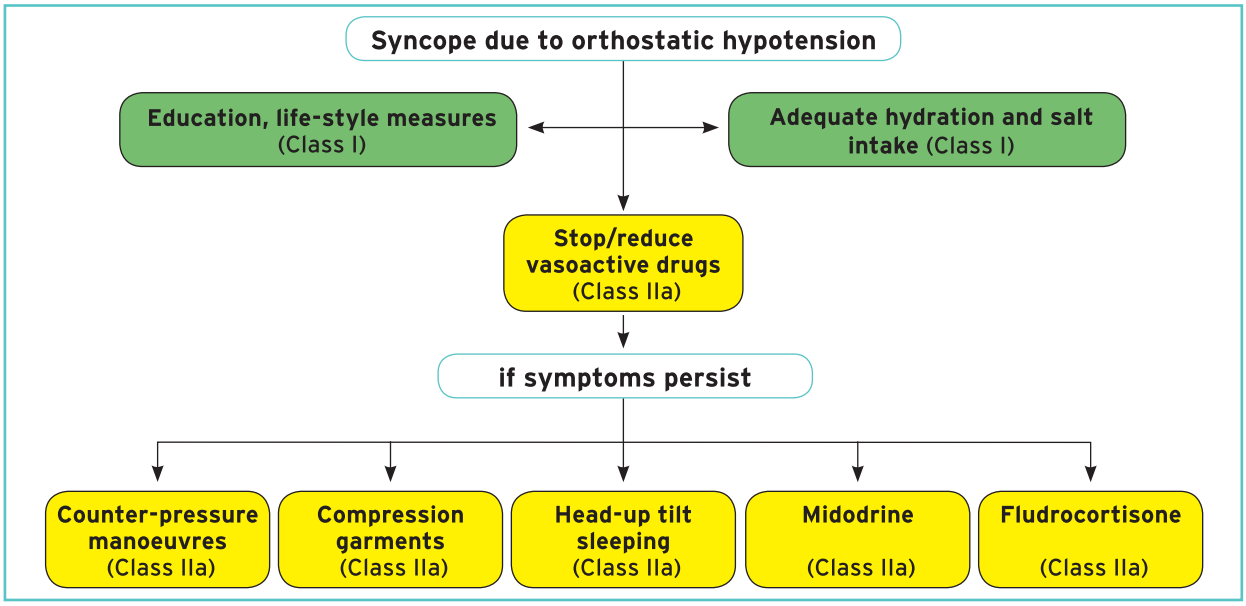


Figure 12 Schematic practical guide for the treatment of orthostatic hypotension.

The principal treatment strategy in drug-induced autonomic failure is eliminating the offending agent. The quality of evidence is moderate. Longer-term future RCTs are likely to have an important impact on determining the net risk—benefit ratio of the withdrawal of culprit medications.

5.3.4 Counter-pressure manoeuvres

PCM such as leg crossing and squatting should be encouraged in patients with warning symptoms who are able to perform them.[319]

5.3.5 Abdominal binders and/or support stockings

Gravitational venous pooling in older patients can be treated with abdominal binders or compression stockings.[23,320,321]

5.3.6 Head-up tilt sleeping

Sleeping with the head of the bed elevated (>10 degrees) prevents nocturnal polyuria, maintains a more favourable distribution of body fluids, and ameliorates nocturnal hypertension.[104,322,323]

5.3.7 Midodrine

The alpha-agonist midodrine is a useful addition to first-line treatment in patients with chronic autonomic failure. It cannot be regarded as a cure, nor is it helpful in all affected patients, but it is very useful in some. There is no doubt that midodrine increases BP both in the supine and upright posture, and ameliorates the symptoms of OH. Midodrine (2.5–10 mg t.i.d) was shown to be effective in three randomized placebo-controlled trials.[324–326]

The desirable effects of midodrine outweigh the undesirable effects. The quality of evidence is moderate and further research is likely to have an important impact on the estimate of benefit.

5.3.8 Fludrocortisone

Fludrocortisone (0.1–0.3 mg once daily) is a mineralocorticoid that stimulates renal sodium retention and expands fluid volume.[327] The evidence in favour of fludrocortisone is from two small observational studies (in combination with head-up sleeping) and one double-blind trial in 60 patients; the observational studies showed haemodynamic benefit and, in the trial, treated patients were less symptomatic with higher BP.[322,327,328]

The desirable effects of fludrocortisone outweigh the undesirable effects. The quality of evidence is moderate and further research is likely to have an important impact on the estimate of benefit.

5.3.9 Additional therapies

Additional and less frequently used treatments, alone or in combination, include desmopressin in patients with nocturnal polyuria, octreotide in postprandial hypotension, erythropoietin in anaemia, pyridostigmine, the use of walking sticks, frequent small meals, and the judicious exercise of leg and abdominal muscles, especially swimming. Their efficacy is less established.[104]

5.3.10 Emerging new pharmacological therapy in specific subgroups

Droxidopa, a precursor of norepinephrine, is a centrally and peripherally acting alpha/beta-agonist approved by the US Food and Drug Administration for the treatment of symptomatic neurogenic OH. Droxidopa has recently been investigated for the treatment of neurogenic OH in four short-term RCTs[329–332] with a total of 485 patients. They showed a modest increase in standing systolic BP and the symptom benefit of droxidopa over placebo regarding some items of quality of life after 2 weeks of treatment, but its benefit was

Treatment of orthostatic hypotension

Recommendations	Class[a]	Level[b]
Explanation of the diagnosis, the provision of reassurance, and explanation of the risk of recurrence and the avoidance of triggers and situations are indicated in all patients.	I	C
Adequate hydration and salt intake are indicated.[310,311]	I	C
Modification or discontinuation of hypotensive drug regimens should be considered.[312–318]	IIa	B
Isometric PCM should be considered.[319]	IIa	C
Abdominal binders and/or support stockings to reduce venous pooling should be considered.[23,320,321]	IIa	B
Head-up tilt sleeping (>10 degrees) to increase fluid volume should be considered.[104,322,323]	IIa	C
Midodrine should be considered if symptoms persist.[324–326]	IIa	B
Fludrocortisone should be considered if symptoms persist.[322,327,328]	IIa	C

Additional advice and clinical perspectives

- In individuals with established OH and risk factors for falls, aggressive BP-lowering treatment should be avoided; their treatment targets should be revised to a systolic BP value of 140–150 mmHg and medication withdrawal should be considered.
- The BP-lowering agents (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers) should be used preferentially, especially among patients at high risk of falls, as diuretics and beta-blockers are associated with OH and falls and should be avoided in at-risk individuals.

BP = blood pressure; OH = orthostatic hypotension; PCM = physical counter-pressure manoeuvres.
[a]Class of recommendation.
[b]Level of evidence.

lost after 8 weeks.[333] Thus, current evidence is insufficient to confirm the efficacy of droxidopa for long-term use.

5.4 Cardiac arrhythmias as the primary cause

5.4.1 Syncope due to intrinsic sinoatrial or atrioventricular conduction system disease

Current management strategies in patients with syncope due to intrinsic cardiac bradycardia are summarized in *Figure 13*.

5.4.1.1 Sinus node disease

In general, cardiac pacemaker therapy is indicated and has proved effective in intrinsic sinus node disease when intermittent sinus arrest or sinoatrial block has been demonstrated to account for syncope by means of ECG documentation during spontaneous syncope.[334–338] A frequent situation is that of patients who have prolonged sinus pause following the termination of tachycardia in bradycardia-tachycardia syndrome due to the abnormally prolonged time needed for the recovery of automaticity by a diseased sinus node. Permanent pacing does not affect survival.

When the correlation between symptoms and ECG is established, there is general consensus that cardiac pacing is effective and useful for symptom relief.

In the absence of the above situations, despite adequate pacing, syncope recurs in approximately 15–28% of patients at 5 years[339–341] (see *Supplementary Data Table 9*). This is due to the frequent association of a vasodepressor reflex mechanism with sinus node disease. In patients with sinus node disease and syncope, carotid sinus hypersensitivity and a positive response to tilt are present in ≤50% of patients. Thus, an increased susceptibility to neurally mediated bradycardia/hypotension is often the cause of syncope.[135,136] A reflex mechanism of syncope fits well with the unpredictable natural history of syncope recurrence. Physicians should be aware that effectiveness of therapy is not well documented in such cases. From a practical perspective, cardiac pacing may be a reasonable solution in patients affected by sinus node disease, who have had documentation of an asymptomatic ventricular pause >3 s (with exceptions for young trained persons, during sleep, and medicated patients), when a competitive diagnosis, i.e. hypotension, can be ruled out.[294] An abnormal SNRT enhances the probability of efficacy of cardiac pacing (see section 4.2.6.1).[210–212]

When the correlation between symptoms and ECG is not established, cardiac pacing may be reasonable in patients with intrinsic sinus node disease, syncope, and documentation of asymptomatic pause(s).

The elimination of drugs that may exacerbate or unmask an underlying susceptibility to bradycardia is an important element in preventing syncope recurrence. Percutaneous cardiac ablative techniques for the control of atrial tachyarrhythmia have become of increasing importance in selected patients with the bradycardia-tachycardia form of sick sinus syndrome, but are infrequently used for the prevention of syncope.

5.4.1.2 Atrioventricular conduction system disease

Cardiac pacing is the treatment of syncope associated with symptomatic AV block (*Figure 13*). Although formal RCTs of pacing in third- or second-degree type 2 AV block have not been performed, some observational studies suggest that pacing is highly effective in preventing syncope recurrences when AV block is documented. Langenfeld *et al.*[341] observed a decline in the rate of syncope from 44 to 3.4% over 5-year follow-up in 115 patients paced for AV block; the recurrence rate was 7% in the subgroup with syncope before pacemaker implantation. More recently, Sud *et al.*[200] reported no syncope recurrence, and Aste *et al.*[255] reported a recurrence of 1% at 5 years after pacemaker implantation among 73 patients with documented

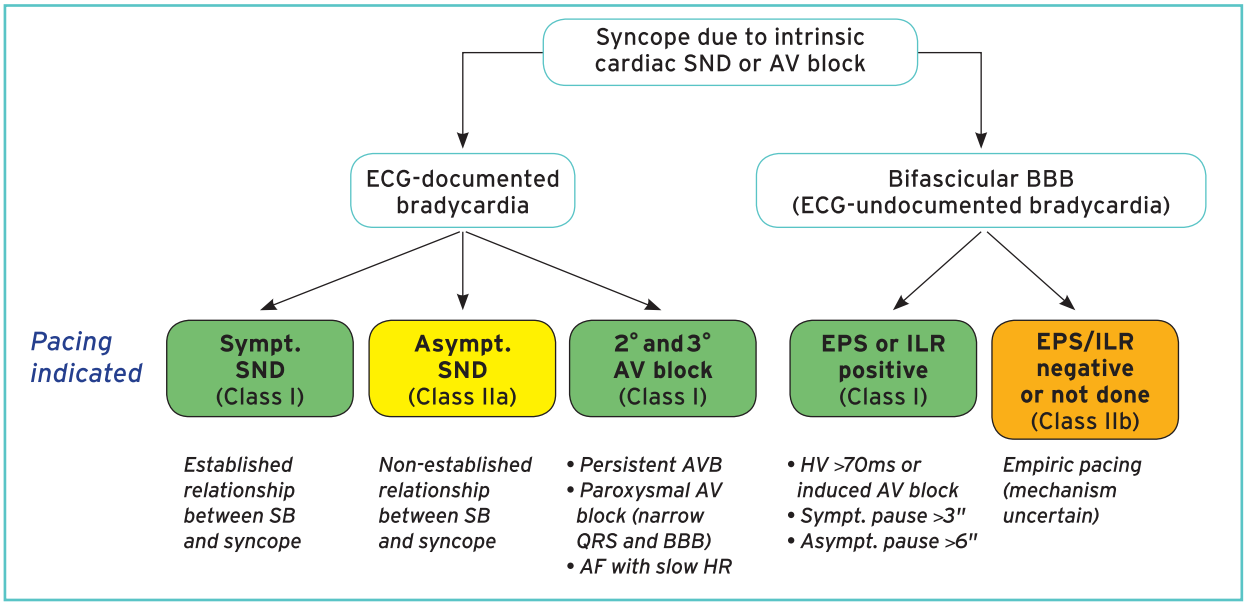


Figure 13 Summary of indications for pacing in patients with syncope due to intrinsic cardiac bradycardia. AF = atrial fibrillation; asympt. = asymptomatic; AV = atrioventricular; BBB = bundle branch block; ECG = electrocardiogram; EPS = electrophysiological study; HR = heart rate; ILR = implantable loop recorder; SB = sinus bradycardia; SND = sinus node dysfunction; sympt. = symptomatic.

persistent or intermittent documented AV block (see *Supplementary Data Table 9*).

5.4.1.3 Bundle branch block and unexplained syncope

The presence of bifascicular BBB suggests that the cause of syncope may be complete heart block. Nevertheless, less than half of the patients with bifascicular BBB and syncope will have a final diagnosis of AV block, a similar percentage will have a final diagnosis of reflex syncope, and, in approximately 15%, the cause will remain unexplained at the end of a complete workup.[342] In addition, among patients receiving an ILR, approximately half remained free of syncope for >2 years after the implantation.[187,188,342,343] Conversely, implantation of a pacemaker without documentation of AV block (empirical pacing) exposed patients to the risk of recurrence of syncope in about one-quarter of cases during long-term follow-up and was unnecessary in another half.[217,344] Thus, only one in four pacemakers will finally be appropriate. Finally, pacemaker treatment has not been proven to have a survival benefit. The above considerations justify a class IIb indication in the ESC Guidelines on pacing.[294]

To overcome the above problems, ESC Guidelines on pacing[294]—in patients with LVEF >35%—recommend a strategy of EPS followed by ILR if the EPS findings are unremarkable. With this strategy, a pacemaker was implanted in approximately half of the patients and these patients had syncope recurrence after pacemaker implantation in 0–7% of cases[188,217]. This strategy was safe; however, this Task Force recognizes that in the 'real world', an empirical pacemaker may be acceptable in selected patients at high risk of traumatic recurrence (e.g. elderly patients with unpredictable syncopes) and that an individual risk–benefit evaluation is warranted (*Figure 14*).

Even if the quality of evidence is moderate, there is strong consensus that in patients with bifascicular BBB with a positive EPS or documentation of paroxysmal AV block during prolonged ECG monitoring, cardiac pacing is highly effective in preventing syncope recurrence. The evidence of efficacy of empirical pacing strategy is weak and the estimate of benefit is uncertain.

Although syncope is not associated with an increased incidence of sudden death in patients with preserved cardiac function, a high incidence of total deaths (about one-third sudden) was observed in patients with BBB and heart failure, previous myocardial infarction, or low ejection fraction.[345–347] Indeed, the high total and sudden mortality seems to be mainly related to underlying structural heart disease and ventricular tachyarrhythmias. In this latter situation, syncope is a risk factor, rather than the cause, of death.[218] Unfortunately, ventricular programmed stimulation does not seem to identify these patients correctly, and the finding of inducible ventricular arrhythmia (VA) should therefore be interpreted with caution.[345,346] Therefore, an implantable cardioverter defibrillator (ICD) or a cardiac resynchronization therapy defibrillator is indicated in patients with BBB, congestive heart failure, or previous myocardial infarction and depressed systolic function for the prevention of SCD, but may be unable to prevent the recurrence of syncope, which is often due to non-arrhythmic causes such as OH or vasodepressor reflex. The strategy for the management of patients with unexplained syncope and BBB is summarized in *Figure 14*.

5.4.2 Syncope due to intrinsic cardiac tachyarrhythmias

Current management strategies in patients with syncope due to intrinsic cardiac tachyarrhythmia are summarized in *Figure 15*.

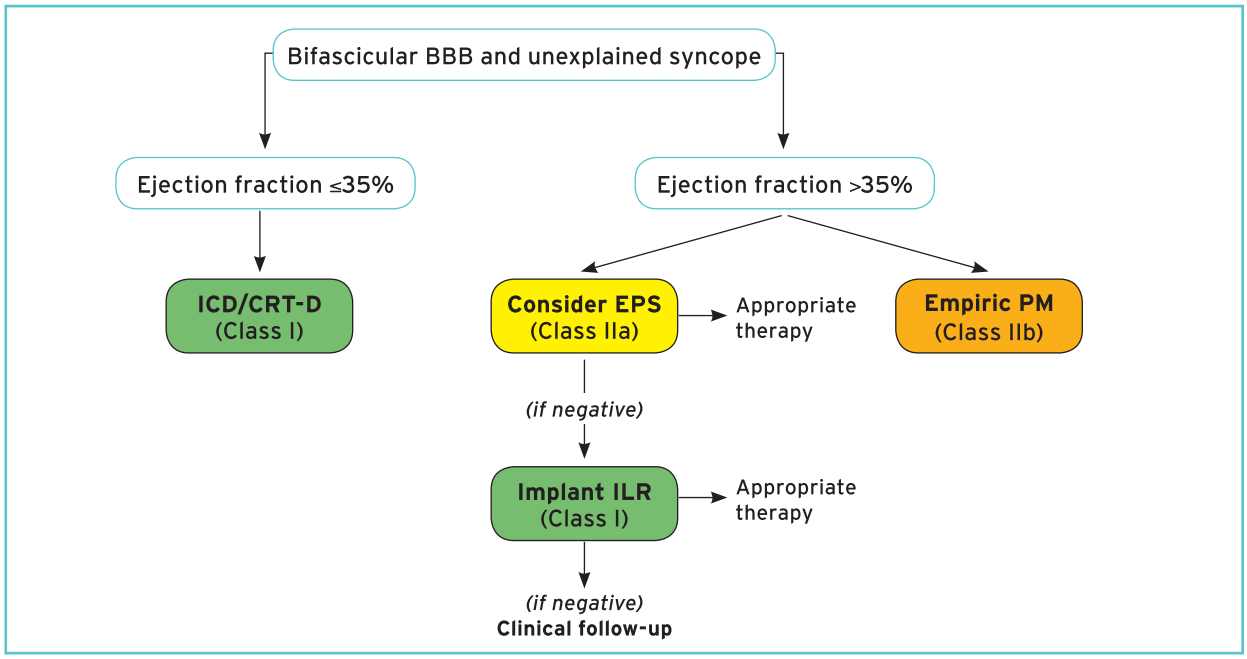


Figure 14 Therapeutic algorithm for patients presenting with unexplained syncope and bundle branch block. BBB = bundle branch block; CRT-D = cardiac resynchronization therapy defibrillator; EPS = electrophysiological study; ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; PM = pacemaker.

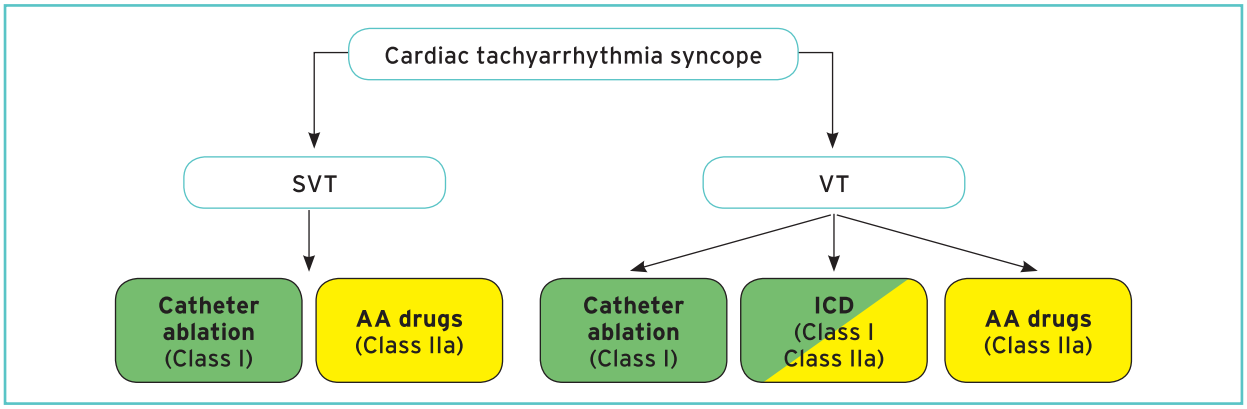


Figure 15 Choice of therapy for patients presenting with syncope due to cardiac tachyarrhythmias as the primary cause. AA = antiarrhythmic; ICD = implantable cardioverter defibrillator; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

5.4.2.1 Paroxysmal supraventricular tachycardia

In patients with paroxysmal AV nodal re-entrant tachycardia, AV re-entrant tachycardia, typical atrial flutter, and ectopic tachycardia associated with syncope, catheter ablation is the first-choice treatment. In these patients, the role of drug therapy is limited to being a bridge to ablation or being used when ablation has failed. In patients with syncope associated with atrial fibrillation or atypical left atrial flutter, the decision should be individualized.

5.4.2.2 Paroxysmal ventricular tachycardia

Syncope due to torsade de pointes is not uncommon and is, in its acquired form, the result of drugs that prolong the QT interval. Treatment is the immediate discontinuation of the suspected drug.

Catheter ablation or drug therapy is recommended in patients with syncope due to VT in the presence or absence of structural heart disease in order to prevent syncope recurrence (*Figure 15*). Detailed guidelines regarding antiarrhythmic drug usage in patients

with VT can be found in the 2015 ESC Guidelines for VA and the prevention of SCD.[46]

An ICD is indicated in patients with syncope and depressed cardiac function, and VT or VF without correctable cause. Although ICD may not prevent syncope recurrence in these patients,[31,348] it is indicated to reduce the risk of SCD (refer to the 2015 ESC Guidelines for VA and the prevention of SCD[46]). An ICD is also indicated in patients with syncope and previous myocardial infarction who have VT induced during EPS[346] (see section 4.2.6).

In patients with preserved systolic function, the indication for ICD is weaker because trials have not addressed this specific issue. However, when VT causes syncope, this Task Force believes that an ICD is warranted if catheter ablation and pharmacological therapy have failed or could not be performed (*Figure 15*).

Treatment of syncope due to cardiac arrhythmias

Recommendations	Class[a]	Level[b]
Bradycardia (intrinsic)		
Cardiac pacing is indicated when there is an established relationship between syncope and symptomatic bradycardia due to:		
• Sick sinus syndrome.[210–212,334–338]	I	B
• Intrinsic AV block.[200,255,341]	I	B
Cardiac pacing is indicated in patients with intermittent/paroxysmal intrinsic third- or second-degree AV block (including AF with slow ventricular conduction), although there is no documentation of a correlation between symptoms and ECGs.	I	C
Cardiac pacing should be considered when the relationship between syncope and asymptomatic sinus node dysfunction is less established.[135,136,210–212,339,340]	IIa	C
Cardiac pacing is not indicated in patients when there are reversible causes for bradycardia.	III	C
Bifascicular BBB		
Cardiac pacing is indicated in patients with syncope, BBB, and a positive EPS or ILR-documented AV block.[188,217]	I	B
Cardiac pacing may be considered in patients with unexplained syncope and bifascicular BBB.[217,255,344]	IIb	B
Tachycardia		
Catheter ablation is indicated in patients with syncope due to SVT or VT in order to prevent syncope recurrence.[46]	I	B
An ICD is indicated in patients with syncope due to VT and an ejection fraction ≤35%.[46]	I	A
An ICD is indicated in patients with syncope and previous myocardial infarction who have VT induced during EPS.[218]	I	C
An ICD should be considered in patients with an ejection fraction >35% with recurrent syncope due to VT when catheter ablation and pharmacological therapy have failed or could not be performed.[46]	IIa	C
Antiarrhythmic drug therapy, including rate-control drugs, should be considered in patients with syncope due to SVT or VT.	IIa	C

Additional advice and clinical perspectives

- The major factors predicting the efficacy of pacing in preventing syncope recurrence are an established relationship between symptoms and bradycardia and the absence of associated hypotensive susceptibility (*Table 8* and *Supplementary Data Table 9*). When this relationship is less established, or some hypotensive mechanism is present, syncope can recur in a minority of patients.
- Pacing is not indicated in unexplained syncope without evidence of any conduction disturbance.
- Less than half of the patients with bifascicular BBB and syncope have a final diagnosis of cardiac syncope, albeit the probability is different among the types of BBB. We recommend conducting any useful investigation (e.g. CSM, EPS, or ILR) to provoke/document the mechanism of syncope before deciding to implant a pacemaker or selecting the correct therapy.
- Elderly patients with bifascicular BBB and unexplained syncope after a reasonable workup might benefit from empirical pacemaker implantation, especially if syncope is unpredictable (with no or short prodromes) or has occurred in the supine position or during effort.
- When indicated, ICD prevents SCD but it may be unable to prevent syncope due to VT recurrence.[31,348] Thus, when syncope is due to VT (including when the diagnosis is established by the induction of VT during EPS), catheter ablation should be always attempted when feasible in addition to ICD implantation.

AF = atrial fibrillation; AV = atrioventricular; BBB = bundle branch block; CSM = carotid sinus massage; ECG = electrocardiogram; EPS = electrophysiological study; ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; SCD = sudden cardiac death; SVT = supraventricular tachycardia; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.

5.5 Treatment of syncope secondary to structural cardiac, cardiopulmonary, and great vessel disease

Cardiac syncope is diagnosed when syncope presents in patients with severe aortic stenosis, acute myocardial infarction/ischaemia, HCM, cardiac masses (atrial myxoma, ball thrombus, etc.), pericardial disease/tamponade, congenital anomalies of the coronary arteries, prosthetic valve dysfunction, pulmonary embolus, acute aortic dissection, and pulmonary hypertension (see section 4.1.1). Structural cardiac or cardiopulmonary disease can be present in some patients with syncope, and its incidence increases in older patients. The mere presence of heart disease does not imply that syncope is related to the underlying cardiac disorder. Some of these patients have typical reflex syncope; in others, such as those with inferior myocardial infarction or aortic stenosis, the underlying cardiac disease may play a role in triggering or potentiating a reflex mechanism, and—finally—the underlying cardiac disease may be the substrate for conduction disturbances, supraventricular arrhythmia, or VA that causes syncope.

Even in the absence of specific trials, there is strong consensus that with syncope secondary to structural cardiac disease, the goal of treatment is not only to prevent syncopal recurrence, but to treat the underlying disease and decrease the risk of death.

5.6 Treatment of unexplained syncope in patients at high risk of sudden cardiac death

The underlying clinical situation is that of a patient being evaluated for ICD implantation because they are affected by syncope(s) supposedly due to transient self-terminating ventricular tachyarrhythmias (fast VT or VF), which have not yet been documented because of their short duration.[349] Syncope due to documented VT/VF is outside the scope of this section; please refer to section 5.4.2. General guidance may be sought in the 2015 ESC Guidelines for VA and the prevention of SCD.[46]

5.6.1 Definition

In general, a history of syncope in patients with structural heart disease or inheritable arrhythmia syndromes is associated with a two- to four-fold increased risk of death,[348,350–353] but varies between specific conditions.[354–356] Moreover, there have been very few studies on ICDs in patients with syncope associated with left ventricular dysfunction,[31,348] cardiomyopathy, or inheritable arrhythmia syndromes.[357] In these Guidelines, we complement previous ESC Guidelines for VA and the prevention of SCD[46] by providing a precise definition of unexplained syncope, and making recommendations for its investigation and management in different clinical settings.

- For this section, '*unexplained syncope*' is defined as syncope that does not meet any class I diagnostic criterion defined in the tables of recommendations in section 4. In the presence of clinical features described in this section, unexplained syncope is considered a '*suspected arrhythmic syncope*'.

When the mechanism of syncope is non-arrhythmic, the management of patients at high risk of SCD is the same as for patients without syncope.

5.6.2 Left ventricular systolic dysfunction

The benefit of an ICD to reduce the risk of death is established. Thus, patients with unexplained syncope who have an established ICD indication per current Guidelines[46] must receive an ICD before, and independently of, the evaluation of the mechanism of syncope, even if the mechanism of syncope is unknown or uncertain at the end of a complete workup. While this strategy may help to prolong life, patients often remain at risk of recurrent syncope, implying a need for precise identification of the mechanism of syncope and specific treatment when possible.

Few data exist concerning the prevalence and the prognostic implications of unexplained syncope in unselected patients with left ventricular dysfunction or non-ischaemic dilated cardiomyopathy with

Implantable cardioverter defibrillator indications in patients with unexplained syncope[a] and left ventricular systolic dysfunction

Recommendations	Class[b]	Level[c]
ICD therapy is recommended to reduce SCD in patients with symptomatic heart failure (NYHA class II–III) and LVEF ≤35% after ≥3 months of optimal medical therapy, who are expected to survive ≥1 year with good functional status.[46]	I	A
An ICD should be considered in patients with unexplained syncope[a] with systolic impairment, but without a current indication for ICD, to reduce the risk of sudden death.[27,28,359,360]	IIa	C
Instead of an ICD, an ILR may be considered in patients with recurrent episodes of unexplained syncope[a] with systolic impairment, but without a current indication for ICD.	IIb	C

Additional advice and clinical perspectives

- The presence of syncope increases mortality regardless of its cause.[348] Thus, syncope is a risk factor for life-threatening events.
- The decision to implant an ICD or to complete the investigation (e.g. ILR implantation) in patients with unexplained syncope depends on a global clinical evaluation of the patient's conditions, the potential benefit and harm of such therapy, and the presence of other risk factors for SCD.

ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SCD = sudden cardiac death.

[a]Unexplained syncope is defined as syncope that does not meet a class I diagnostic criterion defined in the tables of recommendations in section 4. In the presence of clinical features described in this section, unexplained syncope is considered a risk factor for ventricular tachyarrhythmias.

[b]Class of recommendation.

[c]Level of evidence.

less severe systolic impairment who do not meet the current indication for ICD.[358] Data from observational studies in selected cohorts show a high rate of occurrence of ventricular arrhythmias, ICD discharge, and death in patients with a history of unexplained syncope but, owing to a lack of control groups, are unable to show the benefit of an ICD.[27,28,359,360] This Task Force believes that an ICD should be considered in patients with unexplained syncope with systolic impairment but without a current indication for ICD to reduce the risk of sudden death.

5.6.3 Hypertrophic cardiomyopathy

Unexplained syncope is an independent predictor for SCD and appropriate ICD discharge. In a systematic review, the average hazard ratio of unexplained syncope (irrespective of definition) was 2.68 (95% CI 0.97–4.38).[361] In the largest multicentre study to date (>3600 patients with HCM), syncope was an independent predictor of the composite of SCD and ICD discharge (hazard ratio 2.05, 95% CI 1.48–2.82).[350] A prophylactic ICD is appropriate in individuals with other features indicative of a high risk of SCD that are used to estimate the 5-year risk of SCD using the HCM Risk-SCD model[245]; they include: age, family history of SCD, maximum left ventricular wall thickness, left atrial diameter, and non-sustained VT.

Implantable cardioverter defibrillator indications in patients with unexplained syncope[a] and hypertrophic cardiomyopathy

Recommendations	Class[b]	Level[c]
It is recommended that decisions for ICD implantation in patients with unexplained syncope[a] are made according to the ESC HCM Risk-SCD score.[d,245]	I	B
Instead of an ICD, an ILR should be considered in patients with recurrent episodes of unexplained syncope[a] who are at low risk of SCD, according to the HCM Risk-SCD score.[d,245]	IIa	C
Additional advice and clinical perspectives The decision to implant an ICD or to complete the investigation (e.g. ILR implantation) in patients with unexplained syncope depends on a global clinical evaluation of the patient's condition, the potential benefit and harm of such therapy, and the presence of other risk factors for SCD.		

ESC = European Society of Cardiology; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; SCD = sudden cardiac death.
[a]Unexplained syncope is defined as syncope that does not meet the class I diagnostic criterion defined in the tables of recommendations in section 4. In the presence of clinical features described in this section, unexplained syncope is considered a risk factor for ventricular tachyarrhythmias.
[b]Class of recommendation.
[c]Level of evidence.
[d]A web-based calculator of the HCM risk score can be found at: http://www.doc2do.com/hcm/webHCM.html. It can also be found in the ESC Pocket Guidelines App found in all app stores.

5.6.4 Arrhythmogenic right ventricular cardiomyopathy

Although limited and diverse, current data suggest that unexplained syncope is a marker of arrhythmic risk in patients with ARVC.[46,351,362,363] The decision to implant an ICD should take into account the other known risk factors for arrhythmic events[46]: frequent non-sustained VT, family history of premature sudden death, extensive right ventricular disease, marked QRS prolongation, late gadolinium enhancement on magnetic resonance imaging (MRI) (including left ventricular involvement), left ventricular dysfunction, and VT induction during EPS.[46]

Implantable cardioverter defibrillator indications in patients with unexplained syncope[a] and arrhythmogenic right ventricular cardiomyopathy

Recommendations	Class[b]	Level[c]
ICD implantation may be considered in patients with ARVC and a history of unexplained syncope.[a,46]	IIb	C
Instead of an ICD, an ILR should be considered in patients with recurrent episodes of unexplained syncope who are at low risk of SCD, based on a multiparametric analysis that takes into account the other known risk factors for SCD.	IIa	C

ARVC = arrhythmogenic right ventricular cardiomyopathy; ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; SCD = sudden cardiac death.
[a]Unexplained (or uncertain) syncope is defined any syncope that does not meet class I diagnostic criteria defined in the tables of recommendations in section 4. In the presence of clinical features described in this section, unexplained syncope is considered a risk factor for ventricular tachyarrhythmias.
[b]Class of recommendation.
[c]Level of evidence.

5.6.5 Patients with inheritable arrhythmogenic disorders

5.6.5.1 Long QT syndrome

Syncopal events in long QT syndrome (LQTS) are associated with an increased risk of subsequent cardiac arrest. The annual rate of SCD in patients with untreated LQTS is around 0.9% overall and 5% for those with syncope.[352,364] Beta-blocker therapy substantially reduces the risk of syncope and SCD, but presentation with cardiac arrest and recurrent syncope during beta-blocker therapy is associated with the same risk of fatal events as in untreated patients.[46] For this reason, ICD treatment should be considered in patients with LQTS and recurrent unexplained syncope despite beta-blocker therapy, especially in cases of good treatment compliance, in the absence of precipitating factors, and in LQT2 and LQT3 syndromes. Left cardiac sympathetic denervation should also be considered in this situation, particularly in LQT1.[46]

5.6.5.2 Brugada syndrome

A history of syncope may increase the risk of arrhythmic events up to two- to three-fold compared with that in asymptomatic patients. In the largest registry (1029 patients), the incidence of arrhythmic events

(sustained VT or VF, appropriate ICD therapy, or sudden death) in patients with Brugada syndrome was 7.7% per year in those with a history of sudden cardiac arrest, 1.9% per year with syncope, and 0.5% per year in asymptomatic patients.[353] However, in a second study, the rate of appropriate ICD shocks was similar in asymptomatic patients and in those with syncope, a difference possibly explained by patient selection and a high rate of non-arrhythmic syncope.[355]

Implantable cardioverter defibrillator indications in patients with unexplained syncope[a] and long QT syndrome

Recommendations	Class[b]	Level[c]
ICD implantation in addition to beta-blockers should be considered in LQTS patients who experience unexplained syncope[a] while receiving an adequate dose of beta-blockers.[46]	IIa	B
Left cardiac sympathetic denervation should be considered in patients with symptomatic LQTS when: (1) beta-blockers are not effective, not tolerated, or are contraindicated; (2) ICD therapy is contraindicated or refused; or (3) when patients on beta-blockers with an ICD experience multiple shocks.[46]	IIa	C
Instead of an ICD, an ILR should be considered in patients with recurrent episodes of unexplained syncope[a] who are at low risk of SCD based on a multiparametric analysis that takes into account the other known risk factors for SCD.	IIa	C
Additional advice Beta-blockers are recommended in all patients with a clinical diagnosis of LQTS, with the possible exception of those with LQTS3 form.		

ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; LQTS = long QT syndrome; SCD = sudden cardiac death.
[a]Unexplained (or uncertain) syncope is defined as any syncope that does not meet class I diagnostic criteria defined in the tables of recommendations in section 4. In the presence of clinical features described in this section, unexplained syncope is considered a risk factor for ventricular tachyarrhythmias.
[b]Class of recommendation.
[c]Level of evidence.

On balance, this Task Force believes that it is reasonable to consider an ICD in the case of unexplained syncope. New studies[356,365] published after the 2015 ESC Guidelines for VA and the prevention of SCD[46] showed that non-arrhythmic syncope is frequent in Brugada syndrome and appears to be more benign; thus, ICD should be avoided in patients with non-arrhythmic syncope that is established according to the definition reported in this section. ILR is increasingly used in doubtful cases to exclude a VA as the cause of syncope.[365,366]

The final decision to implant an ICD in patients with Brugada syndrome and unexplained syncope should also take into account other risk factors for arrhythmic events, including spontaneous type 1 Brugada ECG pattern, family history of sudden death, VF inducibility with one or two ventricular premature beats during EPS, fractionated QRS, early repolarization in the peripheral leads, increased $T_{peak-}T_{end}$ interval, and long PR interval.[220,367–371] A drug-induced type 1 ECG pattern has a lower risk of sudden death than a spontaneous type 1 response.

Implantable cardioverter defibrillator indications in patients with unexplained syncope[a] and Brugada syndrome

Recommendations	Class[b]	Level[c]
ICD implantation should be considered in patients with a spontaneous diagnostic type 1 ECG pattern and a history of unexplained syncope.[a],[46,353,355,365,366]	IIa	C
Instead of an ICD, an ILR should be considered in patients with recurrent episodes of unexplained syncope[a] who are at low risk of SCD, based on a multiparametric analysis that takes into account the other known risk factors for SCD.	IIa	C

ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; SCD = sudden cardiac death.
[a]Unexplained (or uncertain) syncope is defined as any syncope that does not meet the class I diagnostic criteria defined in section 4. In the presence of clinical features described in this section, unexplained syncope is considered a risk factor for ventricular tachyarrhythmias.
[b]Class of recommendation.
[c]Level of evidence.

5.6.5.3 Other forms

Due to a lack of studies examining unexplained syncope in other forms of inheritable arrhythmic diseases such as catecholaminergic polymorphic VT, early repolarization syndrome, and short QT syndrome, this Task Force is unable to give specific recommendations for the investigation and treatment of unexplained syncope. For further information refer to the 2015 ESC Guidelines for VA and the prevention of SCD.[46]

6. Special issues

6.1 Syncope in patients with comorbidity and frailty

The approach to the assessment and management of an older patient with syncope is similar to that of other age groups; however, there are a number of additional features pertinent to age-related comorbidity and frailty that warrant special attention.[372–374]

6.1.1 Comorbidity and polypharmacy

Comorbidity influences the diagnosis of syncope and management decisions.[33,375] Older patients frequently have abnormal findings on more than one investigation and may have more than one possible cause of syncope.[372,374,376] Conversely, coincidental findings of

cardiovascular diagnoses such as aortic stenosis or atrial fibrillation[377] may not necessarily be the attributable cause of events.[378–380]

The prescription of polypharmacy, cardiovascular medications, and psychotropic (neuroleptics and antidepressants) and dopaminergic drugs also increases the risk of syncope and falls.[381–385] Conversely, the discontinuation or reduction of hypotensive therapy reduces such risk.[260] Negative dromotropic and chronotropic medications should be carefully evaluated in older patients presenting with syncope or falls.

Focal neurological events can occasionally occur due to hypotension and syncope, even in patients without significant carotid artery stenosis (so called '*hypotensive TIA*'). Although these neurological events occur in only 6% of patients with recurrent syncope, their misdiagnosis is particularly important because they may lead to a lowering of BP with antihypertensive medications (e.g. if focal neurology is mistakenly attributed to vascular pathology rather than hypotension), and to a further increase of the risk of syncope and neurologic events.[386]

Despite the lack of large controlled trials and an overall modest quality of studies, there is strong consensus that reduction or discontinuation of hypotensive drugs and psychotropic drugs clearly outweighs the undesirable effects (e.g. complications) of high BP. Further research is likely to have an important impact on our confidence in the estimate of effect.

6.1.2 Falls

Syncopal events may be unwitnessed in over half of older patients meaning that collateral histories may not available, which makes discrimination between falls and syncope challenging.[387] If unwitnessed falls are not due to mechanical slips or trips (i.e. are unexplained or non-accidental), it is likely that the patient experienced a syncopal event and displayed lack of awareness for LOC (*Figure 16*).[388,389] Management of falls in such circumstances is the same as that for syncope.[191,194,390]

Despite the lack of controlled trials and an overall modest quality of studies, there is strong consensus that the management of unexplained falls should be the same as that for unexplained syncope.

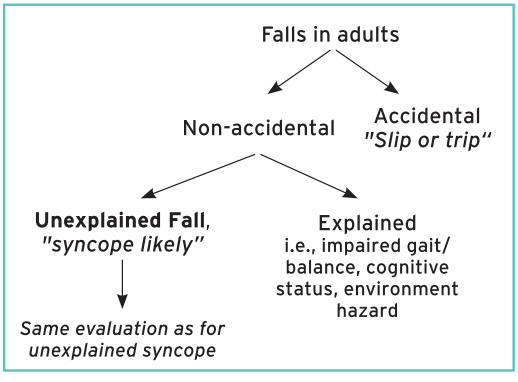


Figure 16 Flow diagram for the identification of unexplained falls.

6.1.3 Cognitive assessment and physical performance tests

Age-related memory impairment or more established forms of cognitive impairment are frequently associated with poor recall and therefore the lack of an accurate history of events. In such circumstances, details of prodromal symptoms, whether or not LOC occurred, and symptoms after the event may be unreliable.[373,389,391–394] Cognitive assessment to inform the accuracy of historical data, and general physical assessment to identify comorbid disorders that influence diagnosis and response to treatments (such as Parkinson's disease, gait and balance abnormalities, previous stroke, and polyneuropathies, etc.), are recommended.

Despite the lack of large controlled trials and an overall modest quality of studies, there is strong consensus that the assessment of older patients with syncope or unexplained falls may require cognitive assessment and physical performance tests in addition to syncope evaluation. Further research is likely to have an important impact on our confidence in the estimate of effect.

Syncope in patients with comorbidity and frailty

Recommendations	Class[a]	Level[b]
Multifactorial evaluation and intervention is recommended in older patients because more than one possible cause for syncope and unexplained fall may be present.[33,372–374,376–380]	I	B
Cognitive assessment and physical performance tests are indicated in older patients with syncope or unexplained fall.[373,389,391–394]	I	C
Modification or discontinuation of possible culprit medications, particularly hypotensive drugs and psychotropic drugs, should be considered in older patients with syncope or unexplained fall.[260,381–385]	IIa	B
In patients with unexplained fall, the same assessment as for unexplained syncope should be considered.[191,194,387–390]	IIa	C

Additional advice and clinical perspectives

- In some frail elderly patients, the rigour of assessment will depend on compliance with tests and on prognosis. Otherwise, the evaluation of mobile, non-frail, cognitively normal older adults must be performed as for younger individuals.[393,395]
- Orthostatic BP measurements, CSM, and tilt testing are well tolerated, even in the frail elderly with cognitive impairment.[96,396,397]
- Not infrequently, patients who present with unexplained falls—although orthostatic BP measurements, CSM, and tilt testing reproduce syncope—may deny TLOC, thus demonstrating amnesia for TLOC.[388,389]
- Failure of orthostatic BP to stabilize is present in up to 40% of community-dwelling people >80 years of age when BP is measured using phasic BP technology.[398] Such failure of systolic BP to stabilize is a risk factor for subsequent falls and syncope.
- In the absence of a witness account, the differential diagnosis between falls, epilepsy, TIA, and syncope may be difficult.

BP = blood pressure; CSM = carotid sinus massage; TIA = transient ischaemic attack; TLOC = transient loss of consciousness.
[a]Class of recommendation.
[b]Level of evidence.

6.2 Syncope in paediatric patients

6.2.1 Diagnostic evaluation

Diagnostic evaluation in paediatric patients is similar to that in adults.

Two specific conditions[399] occur in early childhood:

- Infantile reflex syncopal attacks (also called pallid breath-holding spells or reflex anoxic seizures), elicited by a brief unpleasant stimulus, caused by vagally mediated cardiac inhibition.
- Cyanotic breath-holding spells, characterized by stopping breathing during crying, leading to cyanosis and usually TLOC.

Careful taking of personal and family history and a standard ECG are the most important methods of distinguishing benign reflex syncope (also including reflex anoxic seizure or breath-holding spells) from other causes. If the family history is positive, genetic causes of electrical disease of the heart should be considered first. Some children with reflex syncope also have a positive family history.[400] Tilt testing seems to have high false-negative and false-positive rates and should be used with caution for the primary identification of reflex syncope. Since tilt protocols commonly used in adults may lack specificity in teenagers, in one study, a shorter tilt test duration of 10 min at 60 or 70 degrees was used and showed a specificity of >85%.[401]

In young patients, syncope can rarely be the initial manifestation of unusual but life-threatening conditions such as LQTS, Kearns–Sayre syndrome (external ophthalmoplegia and progressive heart block), Brugada syndrome, catecholaminergic polymorphic VT, Wolff-Parkinson-White syndrome, ARVC, HCM, pulmonary arterial hypertension, myocarditis, arrhythmia after repaired congenital heart disease, and anomalous origin of a coronary artery.

Some aspects of the history can suggest a cardiac origin, and should prompt cardiac evaluation.

- Family history: premature SCD at age <40 years and/or familial heart disease.
- Known or suspected heart disease.
- Event triggers: loud noise, fright, and/or extreme emotional stress.
- Syncope during exercise, including swimming.
- Syncope without prodromes, while supine or sleeping, or preceded by chest pain or palpitations.

6.2.2. Therapy

The therapeutic approach is the same as in adults. However, it should be stressed that the effectiveness of pharmacological agents and tilt training for recurrent reflex syncope is undetermined in the absence of well-designed paediatric trials. Furthermore, even in the presence of VVS with prolonged asystole, pacemakers should be avoided due to the relatively transient and benign nature of the syndrome.[402]

In summary, the key points for the evaluation of syncope in paediatrics are as follows:

- Syncope in childhood is common, the majority being of reflex origin, with only a minority having a potentially life-threatening cause.
- Discriminating benign from serious causes is made primarily by history, physical examination, and ECG results.
- Children with a history suggesting VVS, a normal ECG, and no family history of arrhythmia should not undergo further cardiac investigations.
- The cornerstone of therapy for young patients with reflex syncope includes education and reassurance.

7. Psychogenic transient loss of consciousness and its evaluation

In psychogenic TLOC there is no gross somatic brain dysfunction, but the attacks fulfil the criteria for TLOC (see section 3.1). There are two types: PPS and PNES. In PPS movements are absent, so PPS resembles syncope or longer-lasting LOC, whereas in PNES impressive limb movements mean the attacks resemble epileptic seizures. PPS and PNES differ pathophysiologically from the TLOC forms that they resemble: in PPS, BP and HR are normal or high rather than low, and the EEG is normal instead of showing the slowing or flattening typical of syncope; in contrast to epileptic seizures, the EEG in PNES shows no epileptiform brain activity during an attack.[9,116]

The frequency of PPS and PNES probably depends on the setting. The rate of PPS varies from 1% of patients referred to general syncope clinics[94] to 8% of patients referred to specialist neurological clinics,[116] but PPS is probably insufficiently recognized.[154]

7.1 Diagnosis

7.1.1 Historical criteria for attacks

The presence of a psychological trauma is not a prerequisite for a diagnosis of conversion. The diagnosis of PPS rests on positive clues taken from the patient's history and from documenting normal EEG results, HR, or BP during an attack. History taking in PPS usually reveals a combination of the following features[116,154,403]:

(1) In most cases, the duration of PPS is as short as in syncope, but a much longer duration is a useful diagnostic finding: patients may lie immobile on the floor for 15–30 min.
(2) The eyes are usually open in epileptic seizures and syncope but are usually closed in psychogenic TLOC.
(3) The attack frequency is high, with several attacks occurring over a week or in a day.
(4) There is usually no recognisable trigger, and no sweating, pallor, or nausea beforehand.
(5) Injury does not exclude PNES or PPS.

These features should occur together in most attacks. The presence of another pattern of features suggesting a true syncope type, usually VVS, does not argue against a diagnosis of PPS.

7.1.2 Documentation of key features during an attack

The following features are relevant during an attack:

- Video recording or clinical observation, including provocation of an attack during tilt testing. Primary features: sleep-like body position with closed eyes and lack of response to speech or touch, if

tested. Secondary features: subtle signs incompatible with LOC such as eyelid flicker, eyeball movements, swallowing, intact muscle tone, normal movements absent in true unconsciousness, and resistance to eye opening.
- BP: normal or elevated during TLOC.
- EEG: normal waking eye-closed EEG pattern, i.e. usually with alpha activity, during TLOC.

The gold standard for PPS is documenting an attack with a home video recorder or with a tilt testing during which BP, HR, and EEG are normal.[116,204,404] The gold standard for PNES is documenting an attack with video-EEG monitoring.[204,404]

7.1.2.1 Management of psychogenic pseudosyncope

Announcing a psychological diagnosis to patients may be considered difficult, but is necessary for reasons of honesty and as the first step of treatment.[404] It should be done by the somatic specialist who diagnoses PPS.[116,404] Important aspects are to assure patients that they are taken seriously and that attacks are as involuntary as syncope or an epileptic seizure. Acceptance of the diagnosis by patients may be critical for therapy. In one observational study,[405] communicating and explaining the diagnosis resulted in an immediate reduction of attack frequency, with 39% of patients being asymptomatic during a mean follow-up period of 4 years. Some advice on how to inform the patient is provided in *Web Practical Instructions* section 10: *European Society of Cardiology information sheet for patients affected by psychogenic pseudosyncope.*

Cognitive behavioural therapy is the usual treatment of PNES and PPS, if attacks remain present after explanation. One pilot randomized treatment trial, conducted in PNES,[406] showed that psychological therapy provided more attack reduction than no treatment or treatment with sertraline. There are currently no trials on PPS.

Diagnosis and management of psychogenic pseudosyncope

Recommendations	Class[a]	Level[b]
Diagnosis		
The recording of spontaneous attacks with a video by an eyewitness should be considered for diagnosis of PPS.[116,154]	IIa	C
Tilt testing, preferably with concurrent EEG recording and video monitoring, may be considered for diagnosis of PPS.[116,403,407]	IIb	C
Management		
Doctors who diagnose PPS should present the diagnosis of PPS to the patient.[116,404]	IIa	C
Cognitive behavioural therapy may be considered in the treatment of PPS if attacks persist after explanation.	IIb	C

EEG = electroencephalogram; PPS = psychogenic pseudosyncope.
[a]Class of recommendation.
[b]Level of evidence.

8. Neurological causes and mimics of syncope

This section discusses neurological disorders causing syncope or resembling it, and tests to be performed in patients with syncope.

8.1 Clinical conditions

8.1.1 Autonomic failure

Neurological evaluation should be considered in OH due to autonomic failure. Warning signs are early impotence, disturbed micturition, hyposmia, rapid eye movement, sleep behaviour disorders,[408,409] Parkinsonism, ataxia, cognitive impairment, and sensory deficits. A multidisciplinary approach may be required in secondary autonomic failure and in drug-induced OH, depending on the underlying disease.

8.1.2 Epilepsy and ictal asystole

Table 10 provides a number of clues that aid the differentiation of syncope from epileptic seizures.[9,50,410,411] Epilepsy and syncope may evoke one another on rare occasions, resulting in epileptic seizures triggering syncope as well as syncope triggering an epileptic seizure. The first form concerns *ictal asystole*. Whereas approximately 90% of all epileptic seizures are accompanied by tachycardia, ictal bradycardia and asystole occur in 0.3–0.5% of seizures.[412,413] Bradycardia precedes asystole and AV block may occur, resembling the ECG pattern of reflex syncope.[412,414] Epileptic asystole occurs during partial complex seizures, not during generalized seizures. Epileptic asystole occurs in only a fraction of the seizures of one person, and then occurs after a variable interval of 5–100 s from seizure onset.[415,416] If asystole lasts for more than about 8 s, syncope ensues.[416] A typical history is for a partial complex seizure to progress as usual for that patient, and then the patient suddenly falls flaccidly, with or without brief myoclonic jerking.[416,417] Ictal bradycardia, asystole, and ictal AV block are likely self-terminating,[412] and are due to vagal activation brought about by the seizure. Cessation of cortical activity due to syncopal cerebral hypoperfusion will end the seizure. Therapy requires anti-epileptic drugs and possibly a pacemaker.[418] Ictal asystole is probably not involved in sudden death in epilepsy, as this typically occurs in patients after unwitnessed nocturnal generalized tonic-clonic seizures, i.e. another type of epilepsy.[414,419] Note that most cases of sudden cardiac arrest in patients with epilepsy are due to cardiovascular disease and not to ictal asystole.[420]

The second form concerns a syncopal epileptic seizure. Hypoxia can trigger epileptic seizures.[208,421] Such syncopal epileptic seizures have been described in infants with reflex syncope or cyanotic breath-holding spells. A typical syncopal spell suddenly transforms into prolonged clonic movements that last for minutes; note that shorter epileptic seizures may remain unnoticed.

8.1.3 Cerebrovascular disorders

In general, a TIA concerns a focal neurological deficit without LOC, and syncope the opposite. Subclavian steal refers to the rerouting of blood flow to the arm through the vertebral artery due to proximal

Table 10 Differentiating syncope from epileptic seizures[9,50,410,411]

Clinical feature	Syncope	Epileptic seizures
Useful features		
Presence of trigger	Very often	Rare
Nature of trigger	Differs between types: pain, standing, emotions for VVS; specific trigger for situational syncope; standing for OH	Flashing lights is best known; also range of rare triggers
Prodromes	Often presyncope (autonomic activation in reflex syncope, light-headedness in OH, palpitations in cardiac syncope)	Epileptic aura: repetitive, specific for each patient. Includes *déjà vu*. Rising sensation in the abdomen (epigastric aura) and/or an unusual unpleasant smell
Detailed characteristics of myoclonus	• <10, irregular in amplitude, asynchronous, asymmetrical • Starts after the onset of LOC	• 20–100, synchronous, symmetrical, hemilateral • The onset mostly coincides with LOC • Clear long-lasting automatisms as chewing or lip smacking at the mouth
Tongue bite	Rare, tip of tongue	Side of tongue (rarely bilateral)
Duration of restoration of consciousness	10–30 seconds	May be many minutes
Confusion after attack	No understanding of situation for <10 seconds in most syncope, full alertness and awareness afterwards	Memory deficit, i.e. repeated questions without imprinting for many minutes
Features of limited utility		
Incontinence	Not uncommon	Common
Presence of myoclonus (see below for nature of myoclonus)	Very often	~60%, dependent on accuracy of observation
Eyes open during LOC	Frequent	Nearly always
Fatigue and sleep afterwards	Common, particularly in children	Very common
Blue face	Rare	Fairly often

LOC = loss of consciousness; OH = orthostatic hypotension; VVS = vasovagal syncope.

stenosis or occlusion of the subclavian artery. A TIA may occur when flow through the vertebral artery cannot supply both the arm and part of the brain during forceful use of the arm. Steal most often affects the left side. When detected with ultrasound, steal is asymptomatic in 64% of cases.[422] A TIA is likely due to steal only when it is vertebrobasilar (see below) and associated with exercise of one arm. There are no reliable reports of isolated LOC without focal neurological symptoms and signs in subclavian steal.

A TIA related to a carotid artery does not usually cause TLOC. An exception concerns *orthostatic TIAs*, concerning a combination of multiple stenoses of cerebral arteries and OH. This may rarely result in repetitive, orthostatic, short-lasting, and stereotyped TIAs.[423,424]

A TIA of the vertebrobasilar system can cause LOC, but there are always focal signs, usually limb weakness, gait and limb ataxia, vertigo, diplopia, nystagmus, dysarthria, and oropharyngeal dysfunction. Fewer than 1% of patients with vertebrobasilar ischaemia present with a single presenting symptom.[425]

8.1.4 Migraine

Syncope, presumable VVS, and orthostatic intolerance occur more often in patients with migraine, who have a higher lifetime prevalence of syncope and often frequent syncope.[426] In migraineurs, syncope and migraine attacks rarely occur simultaneously.

8.1.5 Cataplexy

Cataplexy concerns paresis or paralysis triggered by emotions, usually laughter, but also by a range of other triggers.[427] Patients are conscious even when considered unconscious by eyewitnesses, and there is no amnesia. Cataplexy is a key feature of narcolepsy; other cardinal symptoms are excessive daytime sleepiness, sleep-onset paralysis, and hypnagogic hallucinations. Cataplexy may be mistaken for syncope, but also for PPS: a partial awareness of events may be present in PPS, and the falls of cataplexy are partly controlled because paralysis need not be immediately complete.

8.1.6 Drop attacks

The term drop attacks is confusing as it is variably used for Menière's disease, atonic epileptic seizures, and unexplained falls.[387] A specific condition also labelled drop attacks concerns middle-aged women (rarely men) who suddenly find themselves falling.[428] They usually remember hitting the floor and can stand up immediately afterwards.

Neurological evaluation

Recommendations	Class[a]	Level[b]
Neurological evaluation is indicated when syncope is due to autonomic failure to evaluate the underlying disease.	I	C
Neurological evaluation is indicated in patients in whom TLOC is suspected to be epilepsy.	I	C

TLOC = transient loss of consciousness.
[a]Class of recommendation.
[b]Level of evidence.

8.2 Neurological tests

A schematic comprehensive figure of neurological tests used for autonomic failure is shown in *Figure 17*.

8.2.1 Electroencephalography

The results of interictal EEGs are normal in syncope.[410,430] An interictal normal EEG cannot rule out epilepsy and the EEG in epilepsy must always be interpreted in a clinical context. An EEG is not recommended when syncope is the most likely cause of TLOC, but it is when epilepsy is the likely cause or when clinical data are equivocal. The EEG is also useful to establish PPS, if recorded during a provoked attack.

8.2.2 Brain computed tomography and magnetic resonance imaging

Computed tomography and MRI in uncomplicated syncope should be avoided. If neurological examination points out Parkinsonism, ataxia, or cognitive impairment, MRI is recommended. In cases of contraindication for MRI, computed tomography is recommended to exclude brain lesions.

8.2.3 Neurovascular studies

No studies suggest that carotid Doppler ultrasonography is valuable in patients with typical syncope.

8.2.4 Blood tests

An acute or subacute onset of multidomain autonomic failure suggests a paraneoplastic or autoimmune cause. Screening for specific paraneoplastic antibodies is recommended: the most common paraneoplastic antibodies are anti-Hu, while others are anti-Purkinje cell cytoplasmic autoantibody type 2 and anti-collapsin response mediator protein 5.[431] Seropositivity for any of the above-mentioned antibodies may therefore prompt further investigation for occult malignancy (e.g. whole-body fluorodeoxyglucose-positron emission tomography).[432]

Seropositivity for antiganglionic acetylcholine receptor antibodies is the serological hallmark of autoimmune autonomic ganglionopathy.[433,434]

Neurological tests

Recommendations	Class[a]	Level[b]
Brain MRI is recommended if neurological examination indicates Parkinsonism, ataxia, or cognitive impairment.	I	C
Screening for paraneoplastic antibodies and antiganglionic acetylcholine receptor antibodies is recommended in cases of acute or subacute onset of multidomain autonomic failure.[432,433]	I	B
EEG, ultrasound of neck arteries, and computed tomography or magnetic resonance imaging of the brain are not indicated in patients with syncope.[178,435–440]	III	B
Additional advice and clinical perspectives Seropositivity for any paraneoplastic antibody or for antiganglionic acetylcholine receptor antibodies should prompt further investigations for occult malignancy.		

EEG = electroencephalogram; MRI = magnetic resonance imaging.
[a]Class of recommendation.
[b]Level of evidence.

9. Organizational aspects

9.1 Syncope (transient loss of consciousness) management unit

Since the publication of the 2009 ECS Guidelines, the EHRA Task Force has published a further position statement on the rationale and requirement for syncope units.[63] The position paper offers a pragmatic approach to the rationale and requirement for a syncope unit. It is addressed to physicians and others in administration who are

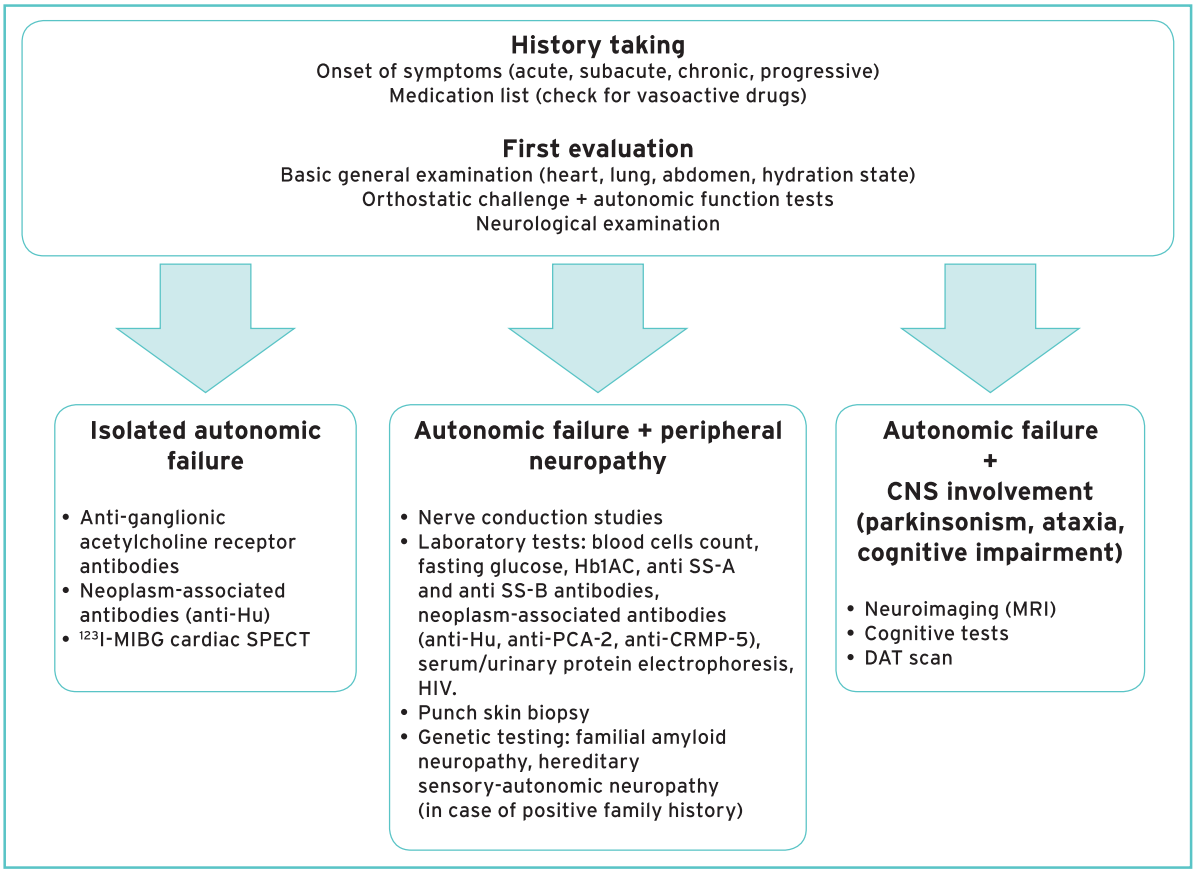


Figure 17 Diagnostic work-up of cardiovascular autonomic failure (adapted from Fanciulli *et al.*[429]). CNS = central nervous system; CRMP-5 = collapsin response mediator protein 5; DAT = dopamine active transporter; HbA1c = haemoglobin A1c; HIV = human immunodeficiency virus; ^{123}I-MIBG = ^{123}I-metaiodobenzylguanidine; MRI = magnetic resonance imaging; PCA-2 = Purkinje cell cytoplasmic autoantibody type 2; SPECT = single-photon emission computed tomography; SS-A = Sjogren's syndrome-associated antigen A; SS-B = Sjogren's syndrome-associated antigen B.

Table 11 Key components of a syncope unit

• The syncope unit should take the lead in service delivery for syncope, and in education and training of healthcare professionals who encounter syncope.
• The syncope unit should be led by a clinician with specific knowledge of TLOC and additional necessary team members (i.e. clinical nurse specialist) depending on the local model of service delivery.
• The syncope unit should provide minimum core treatments for reflex syncope and OH, and treatments or preferential access for cardiac syncope, falls, psychogenic pseudosyncope, and epilepsy.
• Referrals should be directly from family practitioners, EDs, in-hospital and out-hospital services, or self-referral depending on the risk stratification of referrals. Fast-track access, with a separate waiting list and scheduled follow-up visits, should be recommended.
• Syncope units should employ quality indicators, process indicators, and desirable outcome targets.

ED = emergency department; OH = orthostatic hypotension; TLOC = transient loss of consciousness.

interested in establishing a syncope unit in their hospital so that they can meet the standards proposed by the ESC, the EHRA, and the Heart Rhythm Society. The following is the context and evidence for recommendations regarding syncope units (*Table 11*).

9.1.1 Definition of a syncope unit

A syncope unit is a facility featuring a standardized approach to the diagnosis and management of TLOC and related symptoms, with dedicated staff and access to appropriate diagnostics and therapies.

9.1.2 Definition of syncope specialist

The syncope specialist is defined as one who has responsibility for the comprehensive management of the patient from risk stratification to diagnosis, therapy, and follow-up, through a standardized protocol. A syncope specialist is a physician who has sufficient knowledge of historical clues and physical findings to recognize all major forms of TLOC, including mimics, as well as syndromes of orthostatic intolerance.

9.1.3 Goal of a syncope unit

Although the benefit of a syncope unit or a syncope specialist in the different healthcare systems has not been exposed to rigorous scientific or economic scrutiny, the consensus is that a dedicated service (a syncope unit) affords better management of TLOC, from risk stratification to diagnosis, therapy, and follow-up, and better education and training of stakeholders. Further research is likely to have an important impact on our confidence in the estimate of effect.

9.1.4 Model of a syncope unit

The syncope unit should provide minimum core treatments for reflex syncope and OH, and treatments or preferential access for cardiac syncope, falls, psychogenic syncope, and epilepsy (*Table 12*). The tests and assessments available in the syncope unit are detailed in *Table 13*.

Table 12 Structure of the syncope unit

Staffing of a syncope unit is composed of:

(1) One or more physicians of any specialty who are syncope specialists. Owing to the multidisciplinary nature of TLOC management, each syncope unit should identify specific specialists for the syncope unit and for consultancies.

(2) A staff comprising professionals who will advance the care of patients with syncope. These may be physicians, specialized nurses, or others who bring multidisciplinary skills to the facility, coupled with administrative support. The roles played by members of the team may vary according to local circumstances and individual skill. Nurses may be expected to take very important roles including initial assessment, follow-up clinic evaluation, selection of investigations (including tilt testing), and implantation/insertion of ECG loop recorders according to predefined protocols and local regulations (see *Table 14*).

(3) Given that the syncope unit is integrated within a hospital organization, syncope specialists and staff are not necessarily employed full-time, but frequently have other duties depending on the volume of activity in the unit.

Facility, protocol, and equipment

(1) A syncope unit will deliver most of its care to outpatients in addition to ED and inpatients.

(2) The syncope unit should follow an internal protocol, which applies to diagnosis and management and is agreed by stakeholders.

(3) An equipped facility must be available.

(4) Essential equipment/tests:
- 12-lead ECG and 3-lead ECG monitoring
- Non-invasive beat-to-beat BP monitor with recording facilities for subsequent analysis
- Tilt-table
- Holter monitors/external loop recorders
- ILRs
- Follow-up of ILRs[a]
- 24-hour BP monitoring
- Basic autonomic function tests.

(5) Established procedures for:
- Echocardiography
- EPS
- Stress test
- Neuroimaging tests.

(6) Specialists' consultancies (cardiology, neurology, internal medicine, geriatric, psychology), when needed.

Therapy

Patients with syncope will receive their therapy under the care of the syncope unit unless expertise outside that of the unit is required.

Database management

The syncope unit is required to keep medical records that should also include follow-up when appropriate. The database will also offer the possibility of collaborative research with other syncope units.

BP = blood pressure; ECG = electrocardiogram; ED = emergency department; EPS = electrophysiological study; ILR = implantable loop recorder; TLOC = transient loss of consciousness.

[a]Implantation of loop recorders may be performed either by syncope unit physicians or by external cardiologists at the request of the syncope unit physicians.

Table 13 Test and assessments available in a syncope unit

Initial assessment	
History and physical evaluation including 3-min orthostatic BP measurement[a]	
12-lead standard ECG	
Subsequent tests and assessments (only when indicated)	
Blood tests	Electrolytes, haemoglobin, troponin, B-type natriuretic peptide, glucose, D-dimer, haemogas analysis/oxygen saturation
Provocative tests	CSM, tilt testing
Monitoring	External loop recording, implantable loop recording, ambulatory 1–7 days ECG monitoring, 24–48-hour BP monitoring
Autonomic function tests	Standing test, Valsalva manoeuvre, deep-breathing test, cold pressor test, and/or established procedures for access to other autonomic function tests
Cardiac evaluation	Established procedures for access to echocardiogram, stress test, electrophysiological study, coronary angiography
Neurological evaluation	Established procedures for access to neurological tests (computed tomography, magnetic resonance imaging, EEG, video-EEG)
Geriatric evaluation	Established procedures for access to fall risk assessment (cognitive, gait and balance, visual, environmental) and for gait and balance retraining
Psychological or psychiatric evaluation	Established procedures for access to psychological or psychiatric consultancy (mental health problem or psychogenic syncope)

BP = blood pressure; CSM = carotid sinus massage; ECG = electrocardiogram; EEG = electroencephalogram.
[a]Postural orthostatic tachycardia may require longer period of standing.

9.1.5 Access and referrals to a syncope unit

Referral can be direct from family practitioners, EDs, in-hospital and out-hospital services, or self-referral from the patient. Fast-track access with a separate waiting list and scheduled follow-up visits is recommended. In particular, patients at low/intermediate risk admitted to the ED should benefit from such fast-track facilities (so-called protected discharge or advanced access with an appointment for early assessment) to reduce hospitalization rates, directly from the ED or after a short stay in the short observation unit of the ED (see section 4.1.2).

9.1.6 Outcomes and quality indicators

The EHRA Task Force[63] has developed the following preliminary quality indicators, based on consensus, as a rough guide for practitioners:

(1) Absolute rate of undiagnosed TLOC should be reduced by 20%;
(2) Less than 20% of low-/intermediate-risk TLOC patients should be admitted from the ED;
(3) The syncope unit should have a 20% reduction in costs relative to usual practice and improved outcomes (i.e. <5% readmissions for syncope and <20% of paced patients with recurrence at 1 year).

9.2 The clinical nurse specialist in the syncope unit

9.2.1 Definition

The syncope unit clinical nurse specialist is defined as an experienced practitioner who has sufficient knowledge of history features and physical findings to recognize all major forms of TLOC, as well as syndromes of orthostatic intolerance. The clinical nurse specialist should work in close collaboration with the syncope specialist. The core competencies of the clinical nurse specialist include a specialized clinical focus, patient advocacy, education and training, auditing, research, and inter- and intradisciplinary consultations.

9.2.2 Role and skills of the clinical nurse specialist

The clinical nurse specialist should be skilled in the performance and interpretation of structured history taking, 12-lead ECG and routine blood test results, tilt testing, active stand tests, autonomic function tests, ECG monitoring (Holter and/or external loop recorder), ABPM, ILR monitoring, and subsequent triaging of patients and monitoring responses to therapy. Other skills will depend on the service model, e.g. pacemaker interrogation. The clinical nurse specialist may have responsibility for follow-up clinics for cardiovascular risk factor management, autonomic function testing and monitoring, management (including education in PCM) of VVS and OH, and follow-up

Table 14 The role of physicians and staff in performing procedures and tests

Procedure or test	Syncope unit physician	Syncope unit staff	Non-syncope unit personnel
History taking	X		
Structured history taking (e.g. application of software technologies and algorithms)		X	
12-lead ECG		X	
Blood tests		X	
Echocardiogram and imaging			X
CSM	X		
Active standing test		X	
Tilt testing	(X)[a]	X	
Basic autonomic function test		X	
ECG monitoring (Holter, external loop recorder): administration and interpretation	X	X	
ILR	X	(X)[b]	
Remote monitoring		X	
Other cardiac tests (stress test, EPS, angiograms)			X
Neurological tests (computed tomography, magnetic resonance imaging, EEG, video-EEG)			X
Pacemaker and ICD implantation, catheter ablation			X
Patient education, biofeedback training,[c] and instruction sheet on PCM	X	X	
Final report and clinic note	X		
Communication with patients, referring physicians, and stakeholders.	X	X	
Follow-up	X	X	

BP = blood pressure; CSM = carotid sinus massage; ECG = electrocardiogram; EEG = electroencephalogram; EPS = electrophysiological study; ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; PCM = physical counter-pressure manoeuvres.
[a]Physician need not be in the room, but a physician adequately trained in resuscitation needs to be in the vicinity of the test.
[b]Current practice limited to a few countries.
[c]Biofeedback means that the PCM training session consists of biofeedback training using a continuous BP monitor. Each manoeuvre is demonstrated and explained. The manoeuvres are practised under supervision, with immediate feedback of the recordings to gain optimal performance.

of external and internal loop and Holter monitors and ABPM[63] (*Table 14*).

The clinical nurse specialist should be key in developing and delivering communication strategies and processes for the syncope unit for all stakeholders—patients and practitioners—and play a pivotal role in education and training together with the syncope specialist. The clinical nurse specialist should be involved in regular auditing and collection of data to inform quality indicators. See the video in *Web Practical Instructions* section 11.

Although the skill mix of a clinical nurse specialist has not been exposed to rigorous scientific or economic scrutiny, the consensus is that the clinical nurse specialist should have the necessary skills to deliver assessment and treatment for syncope and TLOC. Further research is required to establish the benefits.

10. Key messages

The ESC Task Force has selected 19 simple rules to guide the diagnosis and management of syncope patients with TLOC according to the 2018 ESC Guidelines on syncope:

Diagnosis: initial evaluation

(1) At the initial evaluation answer the following four key questions:
- Was the event TLOC?
- In cases of TLOC, are they of syncopal or non-syncopal origin?
- In cases of suspected syncope, is there a clear aetiological diagnosis?
- Is there evidence to suggest a high risk of cardiovascular events or death?

(2) At the evaluation of TLOC in the ED, answer the following three key questions:
- Is there a serious underlying cause that can be identified?

- If the cause is uncertain, what is the risk of a serious outcome?
- Should the patient be admitted to hospital?

(3) In all patients, perform a complete history taking, physical examination (including standing BP measurement), and standard ECG.

(4) Perform immediate ECG monitoring (in bed or telemetry) in high-risk patients when there is a suspicion of arrhythmic syncope.

(5) Perform an echocardiogram when there is previous known heart disease, or data suggestive of structural heart disease or syncope secondary to cardiovascular cause.

(6) Perform CSM in patients >40 years of age with syncope of unknown origin compatible with a reflex mechanism.

(7) Perform tilt testing in cases where there is suspicion of syncope due to reflex or an orthostatic cause.

(8) Perform blood tests when clinically indicated, e.g. haematocrit and cell blood count when haemorrhage is suspected, oxygen saturation and blood gas analysis when hypoxic syndromes are suspected, troponin when cardiac ischaemia-related syncope is suspected, and D-dimer when pulmonary embolism is suspected, etc.

Diagnosis: subsequent investigations

9. Perform prolonged ECG monitoring (external or implantable) in patients with recurrent severe unexplained syncope who have all of the following three features:
   - Clinical or ECG features suggesting arrhythmic syncope.
   - A high probability of recurrence of syncope in a reasonable time.
   - Who may benefit from a specific therapy if a cause for syncope is found.
10. Perform EPS in patients with unexplained syncope and bifascicular BBB (impending high-degree AV block) or suspected tachycardia.
11. Perform an exercise stress test in patients who experience syncope during or shortly after exertion.
12. Consider basic autonomic function tests (Valsalva manoeuvre and deep-breathing test) and ABPM for the assessment of autonomic function in patients with suspected neurogenic OH.
13. Consider video recording (at home or in hospital) of TLOC suspected to be of non-syncopal nature.

Treatment

14. To all patients with reflex syncope and OH, explain the diagnosis, reassure, explain the risk of recurrence, and give advice on how to avoid triggers and situations. These measures are the cornerstone of treatment and have a high impact in reducing the recurrence of syncope.
15. In patients with *severe forms of reflex syncope*, select one or more of the following additional specific treatments according to the clinical features:
    - Midodrine or fludrocortisone in young patients with low BP phenotype.
    - Counter-pressure manoeuvres (including tilt training if needed) in young patients with prodromes.
    - ILR-guided management strategy in selected patients without or with short prodromes.
    - Discontinuation/reduction of hypotensive therapy targeting a systolic BP of 140 mmHg in old hypertensive patients.
    - Pacemaker implantation in old patients with dominant cardioinhibitory forms.
16. In patients with *OH*, select one or more of the following additional specific treatments according to clinical severity:
    - Education regarding lifestyle manoeuvres.
    - Adequate hydration and salt intake.
    - Discontinuation/reduction of hypotensive therapy.
    - Counter-pressure manoeuvres.
    - Abdominal binders and/or support stockings.
    - Head-up tilt sleeping.
    - Midodrine or fludrocortisone.
17. Ensure that all patients with cardiac syncope receive the specific therapy of the culprit arrhythmia and/or of the underlying disease.
18. Balance the benefits and harm of ICD implantation in patients with unexplained syncope at high risk of SCD (e.g. those affected by left ventricle systolic dysfunction, HCM, ARVC, or inheritable arrhythmogenic disorders). In this situation, *unexplained syncope* is defined as syncope that does not meet any class I diagnostic criterion defined in the tables of recommendations of the 2018 ESC Guidelines on syncope and is considered a *suspected arrhythmic syncope*.
19. Re-evaluate the diagnostic process and consider alternative therapies if the above rules fail or are not applicable to an individual patient. Bear in mind that Guidelines are only advisory. Even though they are based on the best available scientific evidence, treatment should be tailored to an individual patient's need.

11. Gaps in evidence and areas for future research

Clinicians responsible for managing patients with TLOC must frequently make treatment decisions without adequate evidence or a consensus of expert opinion. The following is a short list of selected, common issues that deserve to be addressed in future clinical research.

Diagnosis: the gap between the best available scientific evidence and the need for the dissemination of these concepts into clinical practice

There is wide variation in the practice of syncope evaluation, and wide variation in the adoption of recommendations from published guidelines. The absence of a systematic approach to TLOC incurs higher health and social care costs, unnecessary hospitalizations and diagnostic procedures, prolongation of hospital stays, lower diagnostic rates, and higher rates of misdiagnoses and symptom recurrence.

Therefore, there is a need for:

1) *Large clinical studies that assess the diagnostic yield and compliance of a guideline-based standardized systematic approach*

Despite the recommendation from the ESC Guidelines on syncope, syncope units are not widely established in clinical practice. Barriers to establishing a syncope unit include lack of resources, lack of trained dedicated staff, and complex presentations to multiple settings, necessitating involvement from multiple disciplines. The evidence for the usefulness of syncope units is controversial.

Therefore, there is a need for:

2) *Large clinical studies that test the superiority of management in a dedicated syncope facility vs. conventional management*

Diagnosis: the need for new diagnostic tests and devices

BP recording is crucial for the majority of clinical TLOC situations and will yield important information for the treatment of syncope. Unfortunately, current long-term BP (or surrogate) recording systems are not optimal for diagnostic use in the syncope evaluation setting.

Therefore, there is a need for:

3) *Development and validation of new diagnostic multiparametric devices that can record heart rhythm and BP (and possibly other physiological parameters such as cerebral saturation or EEG) at the time of a syncopal event.*

Treatment: lack of evidence of efficacy of most available therapies

Only a few small RCTs have been conducted on treatment of syncope. In addition, syncopal recurrences are unpredictable and often decrease spontaneously after medical assessment, even in the absence of a specific therapy. The consequence of the spontaneous decrease is that any therapy for syncope prevention appears to be more effective than it actually is, making the results of observational data on therapy questionable in the absence of a control group. No therapy can be effective for all patients. Any therapy should be assessed in homogeneous subgroups.

Therefore, there is strong urgent need for RCTs on the efficacy of:

4) *Pharmacological therapies targeted to specific subgroups of reflex syncope.*
5) *Pacemaker therapy targeted to specific subgroups of cardioinhibitory reflex syncope.*
6) *Pharmacological therapies of OH-mediated syncope.*
7) *ICD therapy targeted to specific subgroups of patients with unexplained syncope at risk of SCD.*

Treatment: the need for new therapies

There is a need to move towards personalized medicine. Improving our knowledge of the biochemical mechanisms underlying specific forms of reflex syncope will allow the development of new therapies in such specific settings. For example, a low adenosine phenotype and a low norepinephrine phenotype have been recently identified.

Therefore, there is a need for:

8) *Randomized clinical trials on the efficacy of theophylline (and other xantine antagonists) for low adenosine syncope and norepinephrine transport inhibitors for low epinephrine syncope.*

Syncope is a transient phenomenon. The ideal therapy should be one that is administered only when needed.

Therefore, there is a need for:

9) *Randomized clinical trials of on-demand administration of specific therapy based on specific sensors similar to adrenalin injectors in asthma or nasal spray for paroxysmal SVT.*

12. 'What to do' and 'what not to do' messages from the Guidelines

Recommendations	Class	Level
Diagnostic criteria with initial evaluation		
VVS is highly probable if syncope is precipitated by pain, fear, or standing, and is associated with typical progressive prodrome (pallor, sweating, and/or nausea).[8,13–17]	I	C
Situational reflex syncope is highly probable if syncope occurs during or immediately after specific triggers listed in *Table 3*.[8,13–17]	I	C
Syncope due to OH is confirmed when syncope occurs while standing and there is concomitant OH.[18–24]	I	C
Arrhythmic syncope is highly probable when the ECG shows[25–39]: • Persistent sinus bradycardia <40 b.p.m. or sinus pauses >3 s in the awake state and in the absence of physical training. • Mobitz II second- and third-degree AV block. • Alternating left and right BBB. • VT or rapid paroxysmal SVT. • Non-sustained episodes of polymorphic VT and long or short QT interval. • Pacemaker or ICD malfunction with cardiac pauses.	I	C

Continued

Management of syncope in the ED		
It is recommended that patients with low-risk features, likely to have reflex or situational syncope or syncope due to OH, are discharged from the ED.[27,35,36,49–54,58,62,69]	I	B
It is recommended that patients with high-risk features receive an early intensive prompt evaluation in a syncope unit or in an ED observation unit (if available), or are hospitalized.[26,27,35,36,44–46,50,55–57,59,60,70–76]	I	B
It is recommended that patients who have neither high- nor low-risk features are observed in the ED or in a syncope unit instead of being hospitalized.[40,63–65,77]	I	B
CSM		
CSM is indicated in patients >40 years of age with syncope of unknown origin compatible with a reflex mechanism.[92–94]	I	B
CSS is confirmed if CSM causes bradycardia (asystole) and/or hypotension that reproduces spontaneous symptoms, and patients have clinical features compatible with a reflex mechanism of syncope.[89,90,92,93,98–102]	I	B
Active standing		
Intermittent determination by sphygmomanometer of BP and HR while supine and during active standing for 3 min are indicated at initial syncope evaluation.[20,103,104]	I	C
Syncope due to OH is confirmed when there is a fall in systolic BP from a baseline value ≥20 mmHg, diastolic BP ≥10 mmHg, or a decrease in systolic BP to <90 mmHg that reproduces spontaneous symptoms.[6,20,103,104]	I	C
ECG monitoring		
Immediate in-hospital monitoring (in bed or by telemetry) is indicated in high-risk patients (defined in *Table 6*).	I	C
ILR is indicated in an early phase of evaluation in patients with recurrent syncope of uncertain origin, absence of high-risk criteria (listed in *Table 6*), and a high likelihood of recurrence within the battery life of the device.[175,176,181–184,202], *Supplementary Data Table 5*	I	A
ILR is indicated in high-risk (criteria listed in *Table 6*) patients in whom a comprehensive evaluation did not demonstrate a cause of syncope or lead to a specific treatment, and who do not have conventional indications for primary prevention ICD or pacemaker indication.[174,180,187,188,195], *Supplementary Data Tables 5 and 6*	I	A
Arrhythmic syncope is confirmed when a correlation between syncope and an arrhythmia (bradyarrhythmia or tachyarrhythmia) is detected.[172,184–186,188,200]	I	B
EPS		
In patients with syncope and previous myocardial infarction or other scar-related conditions, EPS is indicated when syncope remains unexplained after non-invasive evaluation.[218]	I	B
In patients with unexplained syncope and bifascicular BBB, a pacemaker is indicated in the presence of either a baseline H-V interval of ≥70 ms, second- or third-degree His-Purkinje block during incremental atrial pacing, or with pharmacological challenge.[188,214–217,221]	I	B
In patients with unexplained syncope and previous myocardial infarction or other scar-related conditions, it is recommended that induction of sustained monomorphic VT is managed according to the current ESC Guidelines for VA.[46]	I	B
In patients without structural heart disease with syncope preceded by sudden and brief palpitations, it is recommended that the induction of rapid SVT or VT, which reproduces hypotensive or spontaneous symptoms, is managed with appropriate therapy according to the current ESC Guidelines.[46,222]	I	C
Echocardiography		
Echocardiography is indicated for diagnosis and risk stratification in patients with suspected structural heart disease.[235,236]	I	B
Exercise testing		
Exercise testing is indicated in patients who experience syncope during or shortly after exertion.	I	C
Syncope due to second- or third-degree AV block is confirmed when the AV block develops during exercise, even without syncope.[253–257]	I	C
Reflex syncope is confirmed when syncope is reproduced immediately after exercise in the presence of severe hypotension.[250–252]	I	C

Continued

Treatment of reflex syncope		
Explanation of the diagnosis, provision of reassurance, and explanation of the risk of recurrence and the avoidance of triggers and situations are indicated in all patients. *Supplementary Data Table 10*	I	B
Beta-adrenergic blocking drugs are not indicated.[279,280]	III	A
Cardiac pacing is not indicated in the absence of a documented cardioinhibitory reflex.[299,300]	III	B
Treatment of OH		
Explanation of the diagnosis, provision of reassurance, and explanation of the risk of recurrence and the avoidance of triggers and situations are indicated in all patients.	I	C
Adequate hydration and salt intake are indicated.[310,311]	I	C
Treatment of syncope due to cardiac arrhythmias		
Cardiac pacing is indicated when there is an established relationship between syncope and symptomatic bradycardia.[200,210–212,255,334–338,341]	I	B
Cardiac pacing is indicated in patients with intermittent/paroxysmal intrinsic third- or second-degree AV block (including AF with slow ventricular conduction), although there is no documentation of a correlation between symptoms and ECG.	I	C
Cardiac pacing is not indicated in patients when there are reversible causes for bradycardia.	III	C
Cardiac pacing is indicated in patients with syncope, BBB, and a positive EPS or ILR-documented AV block.[188,217]	I	B
Catheter ablation is indicated in patients with syncope due to SVT or VT in order to prevent syncope recurrence.	I	C
An ICD is indicated in patients with syncope due to VT and ejection fraction ≤35%.[46]	I	A
An ICD is indicated in patients with syncope and previous myocardial infarction who have VT induced during EPS.[218]	I	C
ICD indications in patients with unexplained syncope and left ventricular systolic dysfunction		
ICD therapy is recommended to reduce SCD in patients with symptomatic heart failure (NYHA class II–III) and LVEF ≤35% after ≥3 months of optimal medical therapy, who are expected to survive for ≥1 year with good functional status.[46] **systolic dysfunction**	I	A
Syncope in patients with comorbidity and frailty		
A multifactorial evaluation and intervention is recommended in older patients because more than one possible cause for syncope and unexplained fall may be present.[33,372–374,376–380]	I	B
Neurological evaluation		
Neurological evaluation is indicated when syncope is suspected to be epilepsy or due to autonomic failure to evaluate the underlying disease.	I	C

AF = atrial fibrillation; AV = atrioventricular; BBB = bundle branch block; BP = blood pressure; b.p.m. = beats per minute; CSM = carotid sinus massage; CSS = carotid sinus syndrome; ECG = electrocardiogram; ED = emergency department; EPS = electrophysiological study; ESC = European Society of Cardiology; HR = heart rate; ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; OH = orthostatic hypotension; SCD = sudden cardiac death; SVT = supraventricular tachycardia; VA = ventricular arrhythmia; VT = ventricular tachycardia; VVS = vasovagal syncope.

13. Supplementary Data and Web Practical Instructions

Supplementary Data with additional Web Tables complementing the full text, and an additional Web Practical Instructions document—with a glossary containing definitions of syncope and related concepts with tracings, videos, flow charts, and checklists—are available on the *European Heart Journal* website and via the ESC Website at www.escardio.org/guidelines.

14. Appendix

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15. References

1. Mosqueda-Garcia R, Furlan R, Tank J, Fernandez-Violante R. The elusive pathophysiology of neurally mediated syncope. *Circulation* 2000;**102**:2898–2906.
2. Morillo CA, Eckberg DL, Ellenbogen KA, Beightol LA, Hoag JB, Tahvanainen KU, Kuusela TA, Diedrich AM. Vagal and sympathetic mechanisms in patients with orthostatic vasovagal syncope. *Circulation* 1997;**96**:2509–2513.
3. Alboni P, Alboni M. *Vasovagal syncope*. Heidelberg: Springer; 2015. p3–17.
4. Deharo JC, Guieu R, Mechulan A, Peyrouse E, Kipson N, Ruf J, Gerolami V, Devoto G, Marre V, Brignole M. Syncope without prodromes in patients with normal heart and normal electrocardiogram: a distinct entity. *J Am Coll Cardiol* 2013;**62**:1075–1080.
5. Brignole M, Deharo JC, De Roy L, Menozzi C, Blommaert D, Dabiri L, Ruf J, Guieu R. Syncope due to idiopathic paroxysmal atrioventricular block: long-term follow-up of a distinct form of atrioventricular block. *J Am Coll Cardiol* 2011;**58**:167–173.
6. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, Cheshire WP, Chelimsky T, Cortelli P, Gibbons CH, Goldstein DS, Hainsworth R, Hilz MJ, Jacob G, Kaufmann H, Jordan J, Lipsitz LA, Levine BD, Low PA, Mathias C, Raj SR, Robertson D, Sandroni P, Schatz I, Schondorff R, Stewart JM, van Dijk JG. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res* 2011;**21**:69–72.
7. Fedorowski A, Melander O. Syndromes of orthostatic intolerance: a hidden danger. *J Intern Med* 2013;**273**:322–335.
8. Wieling W, Thijs RD, van Dijk N, Wilde AA, Benditt DG, van Dijk JG. Symptoms and signs of syncope: a review of the link between physiology and clinical clues. *Brain* 2009;**132**:2630–2642.
9. van Dijk JG, Thijs RD, van Zwet E, Tannemaat MR, van Niekerk J, Benditt DG, Wieling W. The semiology of tilt-induced reflex syncope in relation to electroencephalographic changes. *Brain* 2014;**137**:576–585.
10. Breningstall GN. Breath-holding spells. *Pediatr Neurol* 1996;**14**:91–97.
11. Stephenson JBP. *Fits and faints*. London: Mac Keith Press; 1990, 202 pages.
12. van Dijk N, Boer KR, Colman N, Bakker A, Stam J, van Grieken JJ, Wilde AA, Linzer M, Reitsma JB, Wieling W. High diagnostic yield and accuracy of history, physical examination, and ECG in patients with transient loss of consciousness in FAST: the Fainting Assessment study. *J Cardiovasc Electrophysiol* 2008;**19**:48–55.
13. Stephenson J. Chapter 7 - Anoxic seizures or syncope. *Fits and faints*. Oxford: Blackwell Scientific Publications; 1990. p41–57.
14. van Dijk JG, Sheldon R. Is there any point to vasovagal syncope? *Clin Auton Res* 2008;**18**:167–169.
15. Alboni P, Alboni M, Bertorelle G. The origin of vasovagal syncope: to protect the heart or to escape predation? *Clin Auton Res* 2008;**18**:170–178.
16. Ganzeboom KS, Colman N, Reitsma JB, Shen WK, Wieling W. Prevalence and triggers of syncope in medical students. *Am J Cardiol* 2003;**91**:1006–1008, A8.
17. Serletis A, Rose S, Sheldon AG, Sheldon RS. Vasovagal syncope in medical students and their first-degree relatives. *Eur Heart J* 2006;**27**:1965–1970.
18. Shibao C, Lipsitz LA, Biaggioni I. ASH position paper: evaluation and treatment of orthostatic hypotension. *J Clin Hypertens (Greenwich)* 2013;**15**:147–153.
19. Mathias CJ, Mallipeddi R, Bleasdale-Barr K. Symptoms associated with orthostatic hypotension in pure autonomic failure and multiple system atrophy. *J Neurol* 1999;**246**:893–898.
20. Naschitz JE, Rosner I. Orthostatic hypotension: framework of the syndrome. *Postgrad Med J* 2007;**83**:568–574.
21. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *J Neurol Sci* 1996;**144**:218–219.
22. Wieling W, Krediet CT, van Dijk N, Linzer M, Tschakovsky ME. Initial orthostatic hypotension: review of a forgotten condition. *Clin Sci (Lond)* 2007;**112**:157–165.
23. Podoleanu C, Maggi R, Brignole M, Croci F, Incze A, Solano A, Puggioni E, Carasca E. Lower limb and abdominal compression bandages prevent progressive orthostatic hypotension in elderly persons: a randomized single-blind controlled study. *J Am Coll Cardiol* 2006;**48**:1425–1432.
24. Gibbons CH, Freeman R. Delayed orthostatic hypotension: a frequent cause of orthostatic intolerance. *Neurology* 2006;**67**:28–32.
25. Sarasin FP, Hanusa BH, Perneger T, Louis-Simonet M, Rajeswaran A, Kapoor WN. A risk score to predict arrhythmias in patients with unexplained syncope. *Acad Emerg Med* 2003;**10**:1312–1317.
26. Quinn J, McDermott D, Stiell I, Kohn M, Wells G. Prospective validation of the San Francisco Syncope Rule to predict patients with serious outcomes. *Ann Emerg Med* 2006;**47**:448–454.
27. Middlekauff HR, Stevenson WG, Stevenson LW, Saxon LA. Syncope in advanced heart failure: high risk of sudden death regardless of origin of syncope. *J Am Coll Cardiol* 1993;**21**:110–116.
28. Brembilla-Perrot B, Suty-Selton C, Beurrier D, Houriez P, Nippert M, de la Chaise AT, Louis P, Claudon O, Andronache M, Abdelaal A, Sadoul N, Juilliere Y. Differences in mechanisms and outcomes of syncope in patients with coronary disease or idiopathic left ventricular dysfunction as assessed by electrophysiologic testing. *J Am Coll Cardiol* 2004;**44**:594–601.
29. Steinberg JS, Beckman K, Greene HL, Marinchak R, Klein RC, Greer SG, Ehlert F, Foster P, Menchavez E, Raitt M, Wathen MS, Morris M, Hallstrom A. Follow-up of patients with unexplained syncope and inducible ventricular tachyarrhythmias: analysis of the AVID registry and an AVID substudy.

Antiarrhythmics Versus Implantable Defibrillators. *J Cardiovasc Electrophysiol* 2001;**12**:996–1001.
30. Pezawas T, Stix G, Kastner J, Wolzt M, Mayer C, Moertl D, Schmidinger H. Unexplained syncope in patients with structural heart disease and no documented ventricular arrhythmias: value of electrophysiologically guided implantable cardioverter defibrillator therapy. *Europace* 2003;**5**:305–312.
31. Olshansky B, Poole JE, Johnson G, Anderson J, Hellkamp AS, Packer D, Mark DB, Lee KL, Bardy GH, SCD-HeFT Investigators. Syncope predicts the outcome of cardiomyopathy patients: analysis of the SCD-HeFT study. *J Am Coll Cardiol* 2008;**51**:1277–1282.
32. Goldberger JJ, Cain ME, Hohnloser SH, Kadish AH, Knight BP, Lauer MS, Maron BJ, Page RL, Passman RS, Siscovick D, Siscovick D, Stevenson WG, Zipes DP, American Heart Association, American College of Cardiology Foundation, Heart Rhythm Society. American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death: a scientific statement from the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention. *Circulation* 2008;**118**:1497–1518.
33. Del Rosso A, Alboni P, Brignole M, Menozzi C, Raviele A. Relation of clinical presentation of syncope to the age of patients. *Am J Cardiol* 2005;**96**:1431–1435.
34. Martin TP, Hanusa BH, Kapoor WN. Risk stratification of patients with syncope. *Ann Emerg Med* 1997;**29**:459–466.
35. Colivicchi F, Ammirati F, Melina D, Guido V, Imperoli G, Santini M, OESIL (Osservatorio Epidemiologico sulla Sincope nel Lazio) Study Investigators. Development and prospective validation of a risk stratification system for patients with syncope in the emergency department: the OESIL risk score. *Eur Heart J* 2003;**24**:811–819.
36. Del Rosso A, Ungar A, Maggi R, Giada F, Petix NR, De Santo T, Menozzi C, Brignole M. Clinical predictors of cardiac syncope at initial evaluation in patients referred urgently to a general hospital: the EGSYS score. *Heart* 2008;**94**:1620–1626.
37. Mittal S, Hao SC, Iwai S, Stein KM, Markowitz SM, Slotwiner DJ, Lerman BB. Significance of inducible ventricular fibrillation in patients with coronary artery disease and unexplained syncope. *J Am Coll Cardiol* 2001;**38**:371–376.
38. Alboni P, Brignole M, Menozzi C, Raviele A, Del Rosso A, Dinelli M, Solano A, Bottoni N. Diagnostic value of history in patients with syncope with or without heart disease. *J Am Coll Cardiol* 2001;**37**:1921–1928.
39. Berecki-Gisolf J, Sheldon A, Wieling W, van Dijk N, Costantino G, Furlan R, Shen WK, Sheldon R. Identifying cardiac syncope based on clinical history: a literature-based model tested in four independent datasets. *PLoS One* 2013;**8**:e75255.
40. Casagranda I, Brignole M, Cencetti S, Cervellin G, Costantino G, Furlan R, Mossini G, Numeroso F, Pesenti Campagnoni M, Pinna Parpaglia P, Rafanelli M, Ungar A. Management of transient loss of consciousness of suspected syncopal cause, after the initial evaluation in the Emergency Department. *Emergency Care J* 2016;**12**:25–27.
41. Crane SD. Risk stratification of patients with syncope in an accident and emergency department. *Emerg Med J* 2002;**19**:23–27.
42. Sheldon R, Rose S, Ritchie D, Connolly SJ, Koshman ML, Lee MA, Frenneaux M, Fisher M, Murphy W. Historical criteria that distinguish syncope from seizures. *J Am Coll Cardiol* 2002;**40**:142–148.
43. Numeroso F, Mossini G, Giovanelli M, Lippi G, Cervellin G. Short-term prognosis and current management of syncopal patients at intermediate risk: results from the IRiS (Intermediate-Risk Syncope) study. *Acad Emerg Med* 2016;**23**:941–948.
44. Reed MJ, Newby DE, Coull AJ, Prescott RJ, Jacques KG, Gray AJ. The ROSE (Risk Stratification Of Syncope in the Emergency department) study. *J Am Coll Cardiol* 2010;**55**:713–721.
45. Martin GJ, Adams SL, Martin HG, Mathews J, Zull D, Scanlon PJ. Prospective evaluation of syncope. *Ann Emerg Med* 1984;**13**:499–504.
46. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;**36**:2793–2867.
47. Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ, Levy D. Incidence and prognosis of syncope. *N Engl J Med* 2002;**347**:878–885.
48. Ricci F, Fedorowski A, Radico F, Romanello M, Tatasciore A, Di Nicola M, Zimarino M, De Caterina R. Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies. *Eur Heart J* 2015;**36**:1609–1617.
49. Calkins H, Shyr Y, Frumin H, Schork A, Morady F. The value of the clinical history in the differentiation of syncope due to ventricular tachycardia, atrioventricular block, and neurocardiogenic syncope. *Am J Med* 1995;**98**:365–373.
50. Sheldon R, Rose S, Connolly S, Ritchie D, Koshman ML, Frenneaux M. Diagnostic criteria for vasovagal syncope based on a quantitative history. *Eur Heart J* 2006;**27**:344–350.
51. Lipsitz LA. Syncope in the elderly patient. *Hosp Pract (Off Ed)* 1986;**21**:33–44.
52. Dermksian G, Lamb LE. Syncope in a population of healthy young adults; incidence, mechanisms, and significance. *J Am Med Assoc* 1958;**168**:1200–1207.
53. Brignole M, Oddone D, Cogorno S, Menozzi C, Gianfranchi L, Bertulla A. Long-term outcome in symptomatic carotid sinus hypersensitivity. *Am Heart J* 1992;**123**:687–692.
54. Jamjoom AA, Nikkar-Esfahani A, Fitzgerald JE. Operating theatre related syncope in medical students: a cross sectional study. *BMC Med Educ* 2009;**9**:14.
55. Quinn JV, Stiell IG, McDermott DA, Sellers KL, Kohn MA, Wells GA. Derivation of the San Francisco Syncope Rule to predict patients with short-term serious outcomes. *Ann Emerg Med* 2004;**43**:224–232.
56. Costantino G, Perego F, Dipaola F, Borella M, Galli A, Cantoni G, Dell'Orto S, Dassi S, Filardo N, Duca PG, Montano N, Furlan R, STePS Investigators. Short- and long-term prognosis of syncope, risk factors, and role of hospital admission: results from the STePS (Short-Term Prognosis of Syncope) study. *J Am Coll Cardiol* 2008;**51**:276–283.
57. Colman N, Bakker A, Linzer M, Reitsma JB, Wieling W, Wilde AA. Value of history-taking in syncope patients: in whom to suspect long QT syndrome? *Europace* 2009;**11**:937–943.
58. Kapoor WN, Peterson J, Wieand HS, Karpf M. Diagnostic and prognostic implications of recurrences in patients with syncope. *Am J Med* 1987;**83**:700–708.
59. Oh JH, Hanusa BH, Kapoor WN. Do symptoms predict cardiac arrhythmias and mortality in patients with syncope? *Arch Intern Med* 1999;**159**:375–380.
60. Grossman SA, Fischer C, Lipsitz LA, Mottley L, Sands K, Thompson S, Zimetbaum P, Shapiro NI. Predicting adverse outcomes in syncope. *J Emerg Med* 2007;**33**:233–239.
61. Surawicz B, Childers R, Deal BJ, Gettes LS, Bailey JJ, Gorgels A, Hancock EW, Josephson M, Kligfield P, Kors JA, Macfarlane P, Mason JW, Mirvis DM, Okin P, Pahlm O, Rautaharju PM, van Herpen G, Wagner GS, Wellens H, American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology, American College of Cardiology Foundation, Heart Rhythm Society. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol* 2009;**53**:976–981.
62. Costantino G, Sun BC, Barbic F, Bossi I, Casazza G, Dipaola F, McDermott D, Quinn J, Reed MJ, Sheldon RS, Solbiati M, Thiruganasambandamoorthy V, Beach D, Bodemer N, Brignole M, Casagranda I, Del Rosso A, Duca P, Falavigna G, Grossman SA, Ippoliti R, Krahn AD, Montano N, Morillo CA, Olshansky B, Raj SR, Ruwald MH, Sarasin FP, Shen WK, Stiell I, Ungar A, Gert van Dijk J, van Dijk N, Wieling W, Furlan R. Syncope clinical management in the emergency department: a consensus from the first international workshop on syncope risk stratification in the emergency department. *Eur Heart J* 2016;**37**:1493–1498.
63. Kenny RA, Brignole M, Dan GA, Deharo JC, van Dijk JG, Doherty C, Hamdan M, Moya A, Parry SW, Sutton R, Ungar A, Wieling W. Syncope Unit: rationale and requirement–the European Heart Rhythm Association position statement endorsed by the Heart Rhythm Society. *Europace* 2015;**17**:1325–1340.
64. Sun BC, McCreath H, Liang LJ, Bohan S, Baugh C, Ragsdale L, Henderson SO, Clark C, Bastani A, Keeler E, An R, Mangione CM. Randomized clinical trial of an emergency department observation syncope protocol versus routine inpatient admission. *Ann Emerg Med* 2014;**64**:167–175.
65. Shen WK, Decker WW, Smars PA, Goyal DG, Walker AE, Hodge DO, Trusty JM, Brekke KM, Jahangir A, Brady PA, Munger TM, Gersh BJ, Hammill SC, Frye RL. Syncope Evaluation in the Emergency Department Study (SEEDS): a multidisciplinary approach to syncope management. *Circulation* 2004;**110**:3636–3645.
66. Thiruganasambandamoorthy V, Stiell IG, Wells GA, Vaidyanathan A, Mukarram M, Taljaard M. Outcomes in presyncope patients: a prospective cohort study. *Ann Emerg Med* 2015;**65**:268–276.e6.
67. Greve Y, Geier F, Popp S, Bertsch T, Singler K, Meier F, Smolarsky A, Mang H, Muller C, Christ M. The prevalence and prognostic significance of near syncope and syncope: a prospective study of 395 cases in an emergency department (the SPEED study). *Dtsch Arztebl Int* 2014;**111**:197–204.

68. Krahn AD, Klein GJ, Yee R, Skanes AC, REVEAL Investigators. Predictive value of presyncope in patients monitored for assessment of syncope. *Am Heart J* 2001;**141**:817–821.
69. Huff JS, Decker WW, Quinn JV, Perron AD, Napoli AM, Peeters S, Jagoda AS, American College of Emergency Physicians. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with syncope. *Ann Emerg Med* 2007;**49**:431–444.
70. Thiruganasambandamoorthy V, Hess EP, Alreesi A, Perry JJ, Wells GA, Stiell IG. External validation of the San Francisco Syncope Rule in the Canadian setting. *Ann Emerg Med* 2010;**55**:464–472.
71. Brignole M, Menozzi C, Bartoletti A, Giada F, Lagi A, Ungar A, Ponassi I, Mussi C, Maggi R, Re G, Furlan R, Rovelli G, Ponzi P, Scivales A. A new management of syncope: prospective systematic guideline-based evaluation of patients referred urgently to general hospitals. *Eur Heart J* 2006;**27**:76–82.
72. Del Greco M, Cozzio S, Scillieri M, Caprari F, Scivales A, Disertori M. Diagnostic pathway of syncope and analysis of the impact of guidelines in a district general hospital. The ECSIT study (epidemiology and costs of syncope in Trento). *Ital Heart J* 2003;**4**:99–106.
73. McCarthy F, McMahon CG, Geary U, Plunkett PK, Kenny RA, Cunningham CJ, European Society of Cardiology. Management of syncope in the Emergency Department: a single hospital observational case series based on the application of European Society of Cardiology Guidelines. *Europace* 2009;**11**:216–224.
74. Numeroso F, Mossini G, Spaggiari E, Cervellin G. Syncope in the emergency department of a large northern Italian hospital: incidence, efficacy of a short-stay observation ward and validation of the OESIL risk score. *Emerg Med J* 2010;**27**:653–658.
75. Lin M, Wolfe RE, Shapiro NI, Novack V, Lior Y, Grossman SA. Observation vs admission in syncope: can we predict short length of stays? *Am J Emerg Med* 2015;**33**:1684–1686.
76. Grossman AM, Volz KA, Shapiro NI, Salem R, Sanchez LD, Smulowitz P, Grossman SA. Comparison of 1-day emergency department observation and inpatient ward for 1-day admissions in syncope patients. *J Emerg Med* 2016;**50**:217–222.
77. Ungar A, Tesi F, Chisciotti VM, Pepe G, Vanni S, Grifoni S, Balzi D, Rafanelli M, Marchionni N, Brignole M. Assessment of a structured management pathway for patients referred to the Emergency Department for syncope: results in a tertiary hospital. *Europace* 2016;**18**:457–462.
78. Serrano LA, Hess EP, Bellolio MF, Murad MH, Montori VM, Erwin PJ, Decker WW. Accuracy and quality of clinical decision rules for syncope in the emergency department: a systematic review and meta-analysis. *Ann Emerg Med* 2010;**56**:362–373.e1.
79. Dipaola F, Costantino G, Perego F, Borella M, Galli A, Cantoni G, Barbic F, Casella F, Duca PG, Furlan R, STePS investigators. San Francisco Syncope Rule, Osservatorio Epidemiologico sulla Sincope nel Lazio risk score, and clinical judgment in the assessment of short-term outcome of syncope. *Am J Emerg Med* 2010;**28**:432–439.
80. Sheldon RS, Morillo CA, Krahn AD, O'Neill B, Thiruganasambandamoorthy V, Parkash R, Talajic M, Tu JV, Seifer C, Johnstone D, Leather R. Standardized approaches to the investigation of syncope: Canadian Cardiovascular Society position paper. *Can J Cardiol* 2011;**27**:246–253.
81. Perego F, Costantino G, Dipaola F, Scannella E, Borella M, Galli A, Barbic F, Casella F, Solbiati M, Angaroni L, Duca P, Furlan R. Predictors of hospital admission after syncope: relationships with clinical risk scores. *Int J Cardiol* 2012;**161**:182–183.
82. Schladenhaufen R, Feilinger S, Pollack M, Benenson R, Kusmiesz AL. Application of San Francisco Syncope Rule in elderly ED patients. *Am J Emerg Med* 2008;**26**:773–778.
83. Sun BC, Mangione CM, Merchant G, Weiss T, Shlamovitz GZ, Zargaraff G, Shiraga S, Hoffman JR, Mower WR. External validation of the San Francisco Syncope Rule. *Ann Emerg Med* 2007;**49**:420–427, 427.e1–4.
84. Reed MJ, Henderson SS, Newby DE, Gray AJ. One-year prognosis after syncope and the failure of the ROSE decision instrument to predict one-year adverse events. *Ann Emerg Med* 2011;**58**:250–256.
85. Birnbaum A, Esses D, Bijur P, Wollowitz A, Gallagher EJ. Failure to validate the San Francisco Syncope Rule in an independent emergency department population. *Ann Emerg Med* 2008;**52**:151–159.
86. Costantino G, Casazza G, Reed M, Bossi I, Sun B, Del Rosso A, Ungar A, Grossman S, D'Ascenzo F, Quinn J, McDermott D, Sheldon R, Furlan R. Syncope risk stratification tools vs clinical judgment: an individual patient data meta-analysis. *Am J Med* 2014;**127**:1126.e13–25.
87. Canzoniero JV, Afshar E, Hedian H, Koch C, Morgan DJ. Unnecessary hospitalization and related harm for patients with low-risk syncope. *JAMA Intern Med* 2015;**175**:1065–1067.
88. Thiruganasambandamoorthy V, Kwong K, Wells GA, Sivilotti ML, Mukarram M, Rowe BH, Lang E, Perry JJ, Sheldon R, Stiell IG, Taljaard M. Development of the Canadian Syncope Risk Score to predict serious adverse events after emergency department assessment of syncope. *CMAJ* 2016;**188**:E289–E298.
89. Kerr SR, Pearce MS, Brayne C, Davis RJ, Kenny RA. Carotid sinus hypersensitivity in asymptomatic older persons: implications for diagnosis of syncope and falls. *Arch Intern Med* 2006;**166**:515–520.
90. Puggioni E, Guiducci V, Brignole M, Menozzi C, Oddone D, Donateo P, Croci F, Solano A, Lolli G, Tomasi C, Bottoni N. Results and complications of the carotid sinus massage performed according to the "method of symptoms". *Am J Cardiol* 2002;**89**:599–601.
91. Wieling W, Krediet CT, Solari D, de Lange FJ, van Dijk N, Thijs RD, van Dijk JG, Brignole M, Jardine DL. At the heart of the arterial baroreflex: a physiological basis for a new classification of carotid sinus hypersensitivity. *J Intern Med* 2013;**273**:345–358.
92. Solari D, Maggi R, Oddone D, Solano A, Croci F, Donateo P, Brignole M. Clinical context and outcome of carotid sinus syndrome diagnosed by means of the 'method of symptoms'. *Europace* 2014;**16**:928–934.
93. Solari D, Maggi R, Oddone D, Solano A, Croci F, Donateo P, Wieling W, Brignole M. Assessment of the vasodepressor reflex in carotid sinus syndrome. *Circ Arrhythm Electrophysiol* 2014;**7**:505–510.
94. Brignole M, Ungar A, Casagranda I, Gulizia M, Lunati M, Ammirati F, Del Rosso A, Sasdelli M, Santini M, Maggi R, Vitale E, Morrione A, Francese GM, Vecchi MR, Giada F, Syncope Unit Project (SUP) investigators. Prospective multicentre systematic guideline-based management of patients referred to the Syncope Units of general hospitals. *Europace* 2010;**12**:109–118.
95. Munro NC, McIntosh S, Lawson J, Morley CA, Sutton R, Kenny RA. Incidence of complications after carotid sinus massage in older patients with syncope. *J Am Geriatr Soc* 1994;**42**:1248–1251.
96. Ungar A, Rivasi G, Rafanelli M, Toffanello G, Mussi C, Ceccofiglio A, McDonagh R, Drumm B, Marchionni N, Alboni P, Kenny RA. Safety and tolerability of Tilt Testing and Carotid Sinus Massage in the octogenarians. *Age Ageing* 2016;**45**:242–248.
97. Davies AJ, Kenny RA. Frequency of neurologic complications following carotid sinus massage. *Am J Cardiol* 1998;**81**:1256–1257.
98. Brignole M, Menozzi C, Lolli G, Bottoni N, Gaggioli G. Long-term outcome of paced and nonpaced patients with severe carotid sinus syndrome. *Am J Cardiol* 1992;**69**:1039–1043.
99. Claesson JE, Kristensson BE, Edvardsson N, Wahrborg P. Less syncope and milder symptoms in patients treated with pacing for induced cardioinhibitory carotid sinus syndrome: a randomized study. *Europace* 2007;**9**:932–936.
100. Menozzi C, Brignole M, Lolli G, Bottoni N, Oddone D, Gianfranchi L, Gaggioli G. Follow-up of asystolic episodes in patients with cardioinhibitory, neurally mediated syncope and VVI pacemaker. *Am J Cardiol* 1993;**72**:1152–1155.
101. Maggi R, Menozzi C, Brignole M, Podoleanu C, Iori M, Sutton R, Moya A, Giada F, Orazi S, Grovale N. Cardioinhibitory carotid sinus hypersensitivity predicts an asystolic mechanism of spontaneous neurally mediated syncope. *Europace* 2007;**9**:563–567.
102. Thomas JE. Hyperactive carotid sinus reflex and carotid sinus syncope. *Mayo Clin Proc* 1969;**44**:127–139.
103. Smit AA, Halliwill JR, Low PA, Wieling W. Pathophysiological basis of orthostatic hypotension in autonomic failure. *J Physiol* 1999;**519**:1–10.
104. Ricci F, De Caterina R, Fedorowski A. Orthostatic hypotension: epidemiology, prognosis, and treatment. *J Am Coll Cardiol* 2015;**66**:848–860.
105. Kenny RA, Ingram A, Bayliss J, Sutton R. Head-up tilt: a useful test for investigating unexplained syncope. *Lancet* 1986;**1**:1352–1355.
106. Bartoletti A, Alboni P, Ammirati F, Brignole M, Del Rosso A, Foglia Manzillo G, Menozzi C, Raviele A, Sutton R. 'The Italian Protocol': a simplified head-up tilt testing potentiated with oral nitroglycerin to assess patients with unexplained syncope. *Europace* 2000;**2**:339–342.
107. Kenny RA, O'Shea D, Parry SW. The Newcastle protocols for head-up tilt table testing in the diagnosis of vasovagal syncope, carotid sinus hypersensitivity, and related disorders. *Heart* 2000;**83**:564–569.
108. Benditt DG, Ferguson DW, Grubb BP, Kapoor WN, Kugler J, Lerman BB, Maloney JD, Raviele A, Ross B, Sutton R, Wolk MJ, Wood DL. Tilt table testing for assessing syncope. American College of Cardiology. *J Am Coll Cardiol* 1996;**28**:263–275.
109. Morillo CA, Klein GJ, Zandri S, Yee R. Diagnostic accuracy of a low-dose isoproterenol head-up tilt protocol. *Am Heart J* 1995;**129**:901–906.
110. Forleo C, Guida P, Iacoviello M, Resta M, Monitillo F, Sorrentino S, Favale S. Head-up tilt testing for diagnosing vasovagal syncope: a meta-analysis. *Int J Cardiol* 2013;**168**:27–35.
111. Parry SW, Gray JC, Newton JL, Reeve P, O'Shea D, Kenny RA. 'Front-loaded' head-up tilt table testing: validation of a rapid first line nitrate-provoked tilt protocol for the diagnosis of vasovagal syncope. *Age Ageing* 2008;**37**:411–415.
112. Verheyden B, Gisolf J, Beckers F, Karemaker JM, Wesseling KH, Aubert AE, Wieling W. Impact of age on the vasovagal response provoked by sublingual nitroglycerine in routine tilt testing. *Clin Sci (Lond)* 2007;**113**:329–337.

113. Nilsson D, Sutton R, Tas W, Burri P, Melander O, Fedorowski A. Orthostatic changes in hemodynamics and cardiovascular biomarkers in dysautonomic patients. *PLoS One* 2015;**10**:e0128962.
114. Low PA, Sandroni P, Joyner M, Shen WK. Postural tachycardia syndrome (POTS). *J Cardiovasc Electrophysiol* 2009;**20**:352–358.
115. Petersen ME, Williams TR, Sutton R. Psychogenic syncope diagnosed by prolonged head-up tilt testing. *QJM* 1995;**88**:209–213.
116. Tannemaat MR, van Niekerk J, Reijntjes RH, Thijs RD, Sutton R, van Dijk JG. The semiology of tilt-induced psychogenic pseudosyncope. *Neurology* 2013;**81**:752–758.
117. Blad H, Lamberts RJ, van Dijk GJ, Thijs RD. Tilt-induced vasovagal syncope and psychogenic pseudosyncope: Overlapping clinical entities. *Neurology* 2015;**85**:2006–2010.
118. Moya A, Permanyer-Miralda G, Sagrista-Sauleda J, Carne X, Rius T, Mont L, Soler-Soler J. Limitations of head-up tilt test for evaluating the efficacy of therapeutic interventions in patients with vasovagal syncope: results of a controlled study of etilefrine versus placebo. *J Am Coll Cardiol* 1995;**25**:65–69.
119. Brignole M, Croci F, Menozzi C, Solano A, Donateo P, Oddone D, Puggioni E, Lolli G. Isometric arm counter-pressure maneuvers to abort impending vasovagal syncope. *J Am Coll Cardiol* 2002;**40**:2053–2059.
120. Krediet CT, van Dijk N, Linzer M, van Lieshout JJ, Wieling W. Management of vasovagal syncope: controlling or aborting faints by leg crossing and muscle tensing. *Circulation* 2002;**106**:1684–1689.
121. van Dijk N, Quartieri F, Blanc JJ, Garcia-Civera R, Brignole M, Moya A, Wieling W, PCTrial Investigators. Effectiveness of physical counterpressure maneuvers in preventing vasovagal syncope: the Physical Counterpressure Manoeuvres Trial (PC-Trial). *J Am Coll Cardiol* 2006;**48**:1652–1657.
122. Deharo JC, Jego C, Lanteaume A, Djiane P. An implantable loop recorder study of highly symptomatic vasovagal patients: the heart rhythm observed during a spontaneous syncope is identical to the recurrent syncope but not correlated with the head-up tilt test or adenosine triphosphate test. *J Am Coll Cardiol* 2006;**47**:587–593.
123. Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Moya A, Wieling W, Andresen D, Benditt DG, Grovale N, De Santo T, Vardas P, International Study on Syncope of Uncertain Etiology 2 (ISSUE 2) Group. Lack of correlation between the responses to tilt testing and adenosine triphosphate test and the mechanism of spontaneous neurally mediated syncope. *Eur Heart J* 2006;**27**:2232–2239.
124. Flevari P, Leftheriotis D, Komborozos C, Fountoulaki K, Dagres N, Theodorakis G, Kremastinos D. Recurrent vasovagal syncope: comparison between clomipramine and nitroglycerin as drug challenges during head-up tilt testing. *Eur Heart J* 2009;**30**:2249–2253.
125. Petersen ME, Williams TR, Gordon C, Chamberlain-Webber R, Sutton R. The normal response to prolonged passive head up tilt testing. *Heart* 2000;**84**:509–514.
126. Furukawa T, Maggi R, Solano A, Croci F, Brignole M. Effect of clinical triggers on positive responses to tilt-table testing potentiated with nitroglycerin or clomipramine. *Am J Cardiol* 2011;**107**:1693–1697.
127. Petix NR, Del Rosso A, Furlan R, Guarnaccia V, Zipoli A. Nitrate-potentiated head-up tilt testing (HUT) has a low diagnostic yield in patients with likely vasovagal syncope. *Pacing Clin Electrophysiol* 2014;**37**:164–172.
128. Raviele A, Menozzi C, Brignole M, Gasparini G, Alboni P, Musso G, Lolli G, Oddone D, Dinelli M, Mureddu R. Value of head-up tilt testing potentiated with sublingual nitroglycerin to assess the origin of unexplained syncope. *Am J Cardiol* 1995;**76**:267–272.
129. Ungar A, Sgobino P, Russo V, Vitale E, Sutton R, Melissano D, Beiras X, Bottoni N, Ebert HH, Gulizia M, Jorfida M, Moya A, Andresen D, Grovale N, Brignole M, International Study on Syncope of Uncertain Etiology 3 (ISSUE-3) Investigators. Diagnosis of neurally mediated syncope at initial evaluation and with tilt table testing compared with that revealed by prolonged ECG monitoring. An analysis from the Third International Study on Syncope of Uncertain Etiology (ISSUE-3). *Heart* 2013;**99**:1825–1831.
130. Brignole M, Gianfranchi L, Menozzi C, Raviele A, Oddone D, Lolli G, Bottoni N. Role of autonomic reflexes in syncope associated with paroxysmal atrial fibrillation. *J Am Coll Cardiol* 1993;**22**:1123–1129.
131. Leitch JW, Klein GJ, Yee R, Leather RA, Kim YH. Syncope associated with supraventricular tachycardia. An expression of tachycardia rate or vasomotor response? *Circulation* 1992;**85**:1064–1071.
132. Sutton R, Brignole M. Twenty-eight years of research permit reinterpretation of tilt-testing: hypotensive susceptibility rather than diagnosis. *Eur Heart J* 2014;**35**:2211–2212.
133. Taneja I, Marney A, Robertson D. Aortic stenosis and autonomic dysfunction: co-conspirators in syncope. *Am J Med Sci* 2004;**327**:281–283.
134. Thomson HL, Morris-Thurgood J, Atherton J, Frenneaux M. Reduced cardiopulmonary baroreflex sensitivity in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1998;**31**:1377–1382.
135. Brignole M, Menozzi C, Gianfranchi L, Oddone D, Lolli G, Bertulla A. Neurally mediated syncope detected by carotid sinus massage and head-up tilt test in sick sinus syndrome. *Am J Cardiol* 1991;**68**:1032–1036.
136. Alboni P, Menozzi C, Brignole M, Paparella N, Lolli G, Oddone D, Dinelli M. An abnormal neural reflex plays a role in causing syncope in sinus bradycardia. *J Am Coll Cardiol* 1993;**22**:1130–1134.
137. Zaidi A, Clough P, Cooper P, Scheepers B, Fitzpatrick AP. Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. *J Am Coll Cardiol* 2000;**36**:181–184.
138. Goldstein DS, Pechnik S, Holmes C, Eldadah B, Sharabi Y. Association between supine hypertension and orthostatic hypotension in autonomic failure. *Hypertension* 2003;**42**:136–142.
139. Novak P. Assessment of sympathetic index from the Valsalva maneuver. *Neurology* 2011;**76**:2010–2016.
140. Fanciulli A, Strano S, Ndayisaba JP, Goebel G, Gioffre L, Rizzo M, Colosimo C, Caltagirone C, Poewe W, Wenning GK, Pontieri FE. Detecting nocturnal hypertension in Parkinson's disease and multiple system atrophy: proposal of a decision-support algorithm. *J Neurol* 2014;**261**:1291–1299.
141. Jones PK, Gibbons CH. The role of autonomic testing in syncope. *Auton Neurosci* 2014;**184**:40–45.
142. Baschieri F, Calandra-Buonaura G, Doria A, Mastrolilli F, Palareti A, Barletta G, Solieri L, Guaraldi P, Martinelli P, Cortelli P. Cardiovascular autonomic testing performed with a new integrated instrumental approach is useful in differentiating MSA-P from PD at an early stage. *Parkinsonism Relat Disord* 2015;**21**:477–482.
143. Rocchi C, Pierantozzi M, Galati S, Chiaravalloti A, Pisani V, Prosperetti C, Lauretti B, Stampanoni Bassi M, Olivola E, Schillaci O, Stefani A. Autonomic function tests and MIBG in Parkinson's disease: correlation to disease duration and motor symptoms. *CNS Neurosci Ther* 2015;**21**:727–732.
144. Kim AJ, Frishman WH. Laughter-induced syncope. *Cardiol Rev* 2012;**20**:194–196.
145. Ndayisaba JP, Fanciulli A, Granata R, Duerr S, Hintringer F, Goebel G, Krismer F, Wenning GK. Sex and age effects on cardiovascular autonomic function in healthy adults. *Clin Auton Res* 2015;**25**:317–326.
146. Bonuccelli U, Lucetti C, Del Dotto P, Ceravolo R, Gambaccini G, Bernardini S, Rossi G, Piaggesi A. Orthostatic hypotension in de novo Parkinson disease. *Arch Neurol* 2003;**60**:1400–1404.
147. Struhal W, Javor A, Brunner C, Benesch T, Schmidt V, Vosko MR, Ransmayr G. The phoenix from the ashes: cardiovascular autonomic dysfunction in behavioral variant of frontotemporal dementia. *J Alzheimers Dis* 2014;**42**:1041–1046.
148. Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, Clement D, de la Sierra A, de Leeuw P, Dolan E, Fagard R, Graves J, Head GA, Imai Y, Kario K, Lurbe E, Mallion JM, Mancia G, Mengden T, Myers M, Ogedegbe G, Ohkubo T, Omboni S, Palatini P, Redon J, Ruilope LM, Shennan A, Staessen JA, vanMontfrans G, Verdecchia P, Waeber B, Wang J, Zanchetti A, Zhang Y, European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. *J Hypertens* 2014;**32**:1359–1366.
149. Schmidt C, Berg D, Herting, Prieur S, Junghanns S, Schweitzer K, Globas C, Schols L, Reichmann H, Ziemssen T. Loss of nocturnal blood pressure fall in various extrapyramidal syndromes. *Mov Disord* 2009;**24**:2136–2142.
150. Voichanski S, Grossman C, Leibowitz A, Peleg E, Koren-Morag N, Sharabi Y, Shamiss A, Grossman E. Orthostatic hypotension is associated with nocturnal change in systolic blood pressure. *Am J Hypertens* 2012;**25**:159–164.
151. Fanciulli A, Strano S, Colosimo C, Caltagirone C, Spalletta G, Pontieri FE. The potential prognostic role of cardiovascular autonomic failure in alpha-synucleinopathies. *Eur J Neurol* 2013;**20**:231–235.
152. Stuebner E, Vichayanrat E, Low DA, Mathias CJ, Isenmann S, Haensch CA. Twenty-four hour non-invasive ambulatory blood pressure and heart rate monitoring in Parkinson's disease. *Front Neurol* 2013;**4**:49.
153. Norcliffe-Kaufmann L, Kaufmann H. Is ambulatory blood pressure monitoring useful in patients with chronic autonomic failure? *Clin Auton Res* 2014;**24**:189–192.
154. Tannemaat MR, Thijs RD, van Dijk JG. Managing psychogenic pseudosyncope: facts and experiences. *Cardiol J* 2014;**21**:658–664.
155. Braune S, Auer A, Schulte-Monting J, Schwerbrock S, Lucking CH. Cardiovascular parameters: sensitivity to detect autonomic dysfunction and influence of age and sex in normal subjects. *Clin Auton Res* 1996;**6**:3–15.
156. Low PA, Denq JC, Opfer-Gehrking TL, Dyck PJ, O'Brien PC, Slezak JM. Effect of age and gender on sudomotor and cardiovagal function and blood pressure response to tilt in normal subjects. *Muscle Nerve* 1997;**20**:1561–1568.
157. Barnett SR, Morin RJ, Kiely DK, Gagnon M, Azhar G, Knight EL, Nelson JC, Lipsitz LA. Effects of age and gender on autonomic control of blood pressure dynamics. *Hypertension* 1999;**33**:1195–1200.
158. Chiu DT, Shapiro NI, Sun BC, Mottley JL, Grossman SA. Are echocardiography, telemetry, ambulatory electrocardiography monitoring, and cardiac enzymes in

emergency department patients presenting with syncope useful tests? A preliminary investigation. *J Emerg Med* 2014;**47**:113–118.
159. Benezet-Mazuecos J, Ibanez B, Rubio JM, Navarro F, Martin E, Romero J, Farre J. Utility of in-hospital cardiac remote telemetry in patients with unexplained syncope. *Europace* 2007;**9**:1196–1201.
160. Croci F, Brignole M, Alboni P, Menozzi C, Raviele A, Del Rosso A, Dinelli M, Solano A, Bottoni N, Donateo P. The application of a standardized strategy of evaluation in patients with syncope referred to three syncope units. *Europace* 2002;**4**:351–355.
161. Bass EB, Curtiss EI, Arena VC, Hanusa BH, Cecchetti A, Karpf M, Kapoor WN. The duration of Holter monitoring in patients with syncope. Is 24 hours enough? *Arch Intern Med* 1990;**150**:1073–1078.
162. Rockx MA, Hoch JS, Klein GJ, Yee R, Skanes AC, Gula LJ, Krahn AD. Is ambulatory monitoring for "community-acquired" syncope economically attractive? A cost-effectiveness analysis of a randomized trial of external loop recorders versus Holter monitoring. *Am Heart J* 2005;**150**:1065.
163. Kinlay S, Leitch JW, Neil A, Chapman BL, Hardy DB, Fletcher PJ. Cardiac event recorders yield more diagnoses and are more cost-effective than 48-hour Holter monitoring in patients with palpitations. A controlled clinical trial. *Ann Intern Med* 1996;**124**:16–20.
164. Bruining N, Caiani E, Chronaki C, Guzik P, van der Velde E, Task Force of the e-Cardiology Working. Acquisition and analysis of cardiovascular signals on smartphones: potential, pitfalls and perspectives: by the Task Force of the e-Cardiology Working Group of European Society of Cardiology. *Eur J Prev Cardiol* 2014;**21**:4–13.
165. Waks JW, Fein AS, Das S. Wide complex tachycardia recorded with a smartphone cardiac rhythm monitor. *JAMA Intern Med* 2015;**175**:437–439.
166. Locati ET, Moya A, Oliveira M, Tanner H, Willems R, Lunati M, Brignole M. External prolonged electrocardiogram monitoring in unexplained syncope and palpitations: results of the SYNARR-Flash study. *Europace* 2016;**18**:1265–1272.
167. Linzer M, Pritchett EL, Pontinen M, McCarthy E, Divine GW. Incremental diagnostic yield of loop electrocardiographic recorders in unexplained syncope. *Am J Cardiol* 1990;**66**:214–219.
168. Schuchert A, Maas R, Kretzschmar C, Behrens G, Kratzmann I, Meinertz T. Diagnostic yield of external electrocardiographic loop recorders in patients with recurrent syncope and negative tilt table test. *Pacing Clin Electrophysiol* 2003;**26**:1837–1840.
169. Drak-Hernández Y, Toquero-Ramos J, Fernández JM, Pérez-Pereira E, Castro-Urda V, Fernández-Lozano I. Effectiveness and safety of remote monitoring of patients with an implantable loop recorder. *Rev Esp Cardiol (Engl Ed)* 2013;**66**:943–948.
170. Furukawa T, Maggi R, Bertolone C, Ammirati F, Santini M, Ricci R, Giada F, Brignole M. Effectiveness of remote monitoring in the management of syncope and palpitations. *Europace* 2011;**13**:431–437.
171. Rothman SA, Laughlin JC, Seltzer J, Walia JS, Baman RI, Siouffi SY, Sangrigoli RM, Kowey PR. The diagnosis of cardiac arrhythmias: a prospective multicenter randomized study comparing mobile cardiac outpatient telemetry versus standard loop event monitoring. *J Cardiovasc Electrophysiol* 2007;**18**:241–247.
172. Farwell DJ, Freemantle N, Sulke N. The clinical impact of implantable loop recorders in patients with syncope. *Eur Heart J* 2006;**27**:351–356.
173. Krahn AD, Klein GJ, Yee R, Skanes AC. Randomized assessment of syncope trial: conventional diagnostic testing versus a prolonged monitoring strategy. *Circulation* 2001;**104**:46–51.
174. Da Costa A, Defaye P, Romeyer-Bouchard C, Roche F, Dauphinot V, Deharo JC, Jacon P, Lamaison D, Bathelemy JC, Isaaz K, Laurent G. Clinical impact of the implantable loop recorder in patients with isolated syncope, bundle branch block and negative workup: a randomized multicentre prospective study. *Arch Cardiovasc Dis* 2013;**106**:146–154.
175. Podoleanu C, DaCosta A, Defaye P, Taieb J, Galley D, Bru P, Maury P, Mabo P, Boveda S, Cellarier G, Anselme F, Kouakam C, Delarche N, Deharo JC, FRESH investigators. Early use of an implantable loop recorder in syncope evaluation: a randomized study in the context of the French healthcare system (FRESH study). *Arch Cardiovasc Dis* 2014;**107**:546–552.
176. Sulke N, Sugihara C, Hong P, Patel N, Freemantle N. The benefit of a remotely monitored implantable loop recorder as a first line investigation in unexplained syncope: the EaSyAS II trial. *Europace* 2016;**18**:912–918.
177. Edvardsson N, Garutti C, Rieger G, Linker NJ, PICTURE Study Investigators. Unexplained syncope: implications of age and gender on patient characteristics and evaluation, the diagnostic yield of an implantable loop recorder, and the subsequent treatment. *Clin Cardiol* 2014;**37**:618–625.
178. Edvardsson N, Wolff C, Tsintzos S, Rieger G, Linker NJ. Costs of unstructured investigation of unexplained syncope: insights from a micro-costing analysis of the observational PICTURE registry. *Europace* 2015;**17**:1141–1148.
179. Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, Ricci R, Sulke N, Wieling W, Auricchio A, Lip GY, Almendral J, Kirchhof P, Aliot E, Gasparini M, Braunschweig F, Lip GY, Almendral J, Kirchhof P, Botto GL, EHRA Scientific Documents Committee. Indications for the use of diagnostic implantable and external ECG loop recorders. *Europace* 2009;**11**:671–687.
180. Menozzi C, Brignole M, Garcia-Civera R, Moya A, Botto G, Tercedor L, Migliorini R, Navarro X, International Study on Syncope of Uncertain Etiology (ISSUE) Investigators. Mechanism of syncope in patients with heart disease and negative electrophysiologic test. *Circulation* 2002;**105**:2741–2745.
181. Linker NJ, Voulgaraki D, Garutti C, Rieger G, Edvardsson N, PICTURE Study Investigators. Early versus delayed implantation of a loop recorder in patients with unexplained syncope–effects on care pathway and diagnostic yield. *Int J Cardiol* 2013;**170**:146–151.
182. Edvardsson N, Frykman V, van Mechelen R, Mitro P, Mohii-Oskarsson A, Pasquie JL, Ramanna H, Schwertfeger F, Ventura R, Voulgaraki D, Garutti C, Stolt P, Linker NJ, PICTURE Study Investigators. Use of an implantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry. *Europace* 2011;**13**:262–269.
183. Lacunza-Ruiz FJ, Moya-Mitjans A, Martinez-Alday J, Baron-Esquivias G, Ruiz-Granell R, Rivas-Gandara N, Gonzalez-Enriquez S, Leal-del-Ojo J, Arcocha-Torres MF, Perez-Villacastin J, Garcia-Heil N, Garcia-Alberola A. Implantable loop recorder allows an etiologic diagnosis in one-third of patients. Results of the Spanish reveal registry. *Circ J* 2013;**77**:2535–2541.
184. Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Moya A, Wieling W, Andresen D, Benditt DG, Vardas P, International Study on Syncope of Uncertain Etiology 2 (ISSUE 2) Group. Early application of an implantable loop recorder allows effective specific therapy in patients with recurrent suspected neurally mediated syncope. *Eur Heart J* 2006;**27**:1085–1092.
185. Brignole M, Menozzi C, Moya A, Andresen D, Blanc JJ, Krahn AD, Wieling W, Beiras X, Deharo JC, Russo V, Tomaino M, Sutton R, International Study on Syncope of Uncertain Etiology 3 (ISSUE-3) Investigators. Pacemaker therapy in patients with neurally mediated syncope and documented asystole: Third International Study on Syncope of Uncertain Etiology (ISSUE-3): a randomized trial. *Circulation* 2012;**125**:2566–2571.
186. Brignole M, Ammirati F, Arabia F, Quartieri F, Tomaino M, Ungar A, Lunati M, Russo V, Del Rosso A, Gaggioli G, Syncope Unit Project (SUP) Two Investigators. Assessment of a standardized algorithm for cardiac pacing in older patients affected by severe unpredictable reflex syncopes. *Eur Heart J* 2015;**36**:1529–1535.
187. Brignole M, Menozzi C, Moya A, Garcia-Civera R, Mont L, Alvarez M, Errazquin F, Beiras J, Bottoni N, Donateo P, International Study on Syncope of Uncertain Etiology (ISSUE) Investigators. Mechanism of syncope in patients with bundle branch block and negative electrophysiological test. *Circulation* 2001;**104**:2045–2050.
188. Moya A, Garcia-Civera R, Croci F, Menozzi C, Brugada J, Ammirati F, Del Rosso A, Bellver-Navarro A, Garcia-Sacristan J, Bortnik M, Mont L, Ruiz-Granell R, Navarro X, Bradycardia detection in Bundle Branch Block (B4) study. Diagnosis, management, and outcomes of patients with syncope and bundle branch block. *Eur Heart J* 2011;**32**:1535–1541.
189. Ho RT, Wicks T, Wyeth D, Nei M. Generalized tonic-clonic seizures detected by implantable loop recorder devices: diagnosing more than cardiac arrhythmias. *Heart Rhythm* 2006;**3**:857–861.
190. Petkar S, Hamid T, Iddon P, Clifford A, Rice N, Claire R, McKee D, Curtis N, Cooper PN, Fitzpatrick AP. Prolonged implantable electrocardiographic monitoring indicates a high rate of misdiagnosis of epilepsy–REVISE study. *Europace* 2012;**14**:1653–1660.
191. Maggi R, Rafanelli M, Ceccofiglio A, Solari D, Brignole M, Ungar A. Additional diagnostic value of implantable loop recorder in patients with initial diagnosis of real or apparent transient loss of consciousness of uncertain origin. *Europace* 2014;**16**:1226–1230.
192. Armstrong VL, Lawson J, Kamper AM, Newton J, Kenny RA. The use of an implantable loop recorder in the investigation of unexplained syncope in older people. *Age Ageing* 2003;**32**:185–188.
193. Ryan DJ, Nick S, Colette SM, Roseanne K. Carotid sinus syndrome, should we pace? A multicentre, randomised control trial (Safepace 2). *Heart* 2010;**96**:347–351.
194. Bhangu J, McMahon CG, Hall P, Bennett K, Rice C, Crean P, Sutton R, Kenny RA. Long-term cardiac monitoring in older adults with unexplained falls and syncope. *Heart* 2016;**102**:681–686.
195. Krahn AD, Klein GJ, Norris C, Yee R. The etiology of syncope in patients with negative tilt table and electrophysiological testing. *Circulation* 1995;**92**:1819–1824.
196. Krahn AD, Klein GJ, Yee R, Takle-Newhouse T, Norris C. Use of an extended monitoring strategy in patients with problematic syncope. Reveal Investigators. *Circulation* 1999;**99**:406–410.
197. Krahn AD, Klein GJ, Yee R, Skanes AC. Detection of asymptomatic arrhythmias in unexplained syncope. *Am Heart J* 2004;**148**:326–332.
198. Ermis C, Zhu AX, Pham S, Li JM, Guerrero M, Vrudney A, Hiltner L, Lu F, Sakaguchi S, Lurie KG, Benditt DG. Comparison of automatic and patient-

activated arrhythmia recordings by implantable loop recorders in the evaluation of syncope. *Am J Cardiol* 2003;**92**:815–819.
199. Moya A, Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Wieling W, Andresen D, Benditt DG, Garcia-Sacristan JF, Beiras X, Grovale N, Vardas P, International Study on Syncope of Uncertain Etiology 2 (ISSUE 2) Group. Reproducibility of electrocardiographic findings in patients with suspected reflex neurally-mediated syncope. *Am J Cardiol* 2008;**102**:1518–1523.
200. Sud S, Klein GJ, Skanes AC, Gula LJ, Yee R, Krahn AD. Implications of mechanism of bradycardia on response to pacing in patients with unexplained syncope. *Europace* 2007;**9**:312–318.
201. Olmos C, Franco E, Suarez-Barrientos A, Fortuny E, Martin-Garcia A, Viliani D, Macaya C, Perez de Isla L. Wearable wireless remote monitoring system: an alternative for prolonged electrocardiographic monitoring. *Int J Cardiol* 2014;**172**:e43–44.
202. Moya A, Brignole M, Menozzi C, Garcia-Civera R, Tognarini S, Mont L, Botto G, Giada F, Cornacchia D, International Study on Syncope of Uncertain Etiology (ISSUE) Investigators. Mechanism of syncope in patients with isolated syncope and in patients with tilt-positive syncope. *Circulation* 2001;**104**:1261–1267.
203. Furukawa T, Maggi R, Bertolone C, Fontana D, Brignole M. Additional diagnostic value of very prolonged observation by implantable loop recorder in patients with unexplained syncope. *J Cardiovasc Electrophysiol* 2012;**23**:67–71.
204. LaFrance WC Jr, Baker GA, Duncan R, Goldstein LH, Reuber M. Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: a staged approach: a report from the International League Against Epilepsy Nonepileptic Seizures Task Force. *Epilepsia* 2013;**54**:2005–2018.
205. Saal DP, Thijs RD, van Zwet EW, Bootsma M, Brignole M, Benditt DG, van Dijk JG. Temporal relationship of asystole to onset of transient loss of consciousness in tilt-induced reflex syncope. *JACC: Clinical Electrophysiology* 2017;**3**:1592–1598.
206. Whittaker RG. Video telemetry: current concepts and recent advances. *Pract Neurol* 2015;**15**:445–450.
207. Goodwin E, Kandler RH, Alix JJ. The value of home video with ambulatory EEG: a prospective service review. *Seizure* 2014;**23**:480–482.
208. Stephenson J, Breningstall G, Steer C, Kirkpatrick M, Horrocks I, Nechay A, Zuberi S. Anoxic-epileptic seizures: home video recordings of epileptic seizures induced by syncopes. *Epileptic Disord* 2004;**6**:15–19.
209. Linzer M, Yang EH, Estes NA III, Wang P, Vorperian VR, Kapoor WN. Diagnosing syncope. Part 2: Unexplained syncope. Clinical Efficacy Assessment Project of the American College of Physicians. *Ann Intern Med* 1997;**127**:76–86.
210. Dhingra RC. Sinus node dysfunction. *Pacing Clin Electrophysiol* 1983;**6**:1062–1069.
211. Gann D, Tolentino A, Samet P. Electrophysiologic evaluation of elderly patients with sinus bradycardia: a long-term follow-up study. *Ann Intern Med* 1979;**90**:24–29.
212. Menozzi C, Brignole M, Alboni P, Boni L, Paparella N, Gaggioli G, Lolli G. The natural course of untreated sick sinus syndrome and identification of the variables predictive of unfavorable outcome. *Am J Cardiol* 1998;**82**:1205–1209.
213. McAnulty JH, Rahimtoola SH, Murphy E, DeMots H, Ritzmann L, Kanarek PE, Kauffman S. Natural history of "high-risk" bundle-branch block: final report of a prospective study. *N Engl J Med* 1982;**307**:137–143.
214. Gronda M, Magnani A, Occhetta E, Sauro G, D'Aulerio M, Carfora A, Rossi P. Electrophysiological study of atrio-ventricular block and ventricular conduction defects. Prognostic and therapeutical implications. *G Ital Cardiol* 1984;**14**:768–773.
215. Bergfeldt L, Edvardsson N, Rosenqvist M, Vallin H, Edhag O. Atrioventricular block progression in patients with bifascicular block assessed by repeated electrocardiography and a bradycardia-detecting pacemaker. *Am J Cardiol* 1994;**74**:1129–1132.
216. Kaul U, Dev V, Narula J, Malhotra AK, Talwar KK, Bhatia ML. Evaluation of patients with bundle branch block and "unexplained" syncope: a study based on comprehensive electrophysiologic testing and ajmaline stress. *Pacing Clin Electrophysiol* 1988;**11**:289–297.
217. Kalscheur MM, Donateo P, Wenzke KE, Aste M, Oddone D, Solano A, Maggi R, Croci F, Page RL, Brignole M, Hamdan MH. Long-term outcome of patients with bifascicular block and unexplained syncope following cardiac pacing. *Pacing Clin Electrophysiol* 2016;**39**:1126–1131.
218. Olshansky B, Hahn EA, Hartz VL, Prater SP, Mason JW. Clinical significance of syncope in the electrophysiologic study versus electrocardiographic monitoring (ESVEM) trial. The ESVEM Investigators. *Am Heart J* 1999;**137**:878–886.
219. Link MS, Kim KM, Homoud MK, Estes NA III, Wang PJ. Long-term outcome of patients with syncope associated with coronary artery disease and a nondiagnostic electrophysiologic evaluation. *Am J Cardiol* 1999;**83**:1334–1337.
220. Sroubek J, Probst V, Mazzanti A, Delise P, Hevia JC, Ohkubo K, Zorzi A, Champagne J, Kostopoulou A, Yin X, Napolitano C, Milan DJ, Wilde A, Sacher F, Borggrefe M, Ellinor PT, Theodorakis G, Nault I, Corrado D, Watanabe I, Antzelevitch C, Allocca G, Priori SG, Lubitz SA. Programmed ventricular stimulation for risk stratification in the Brugada syndrome: a pooled analysis. *Circulation* 2016;**133**:622–630.
221. Scheinman MM, Peters RW, Suave MJ, Desai J, Abbott JA, Cogan J, Wohl B, Williams K. Value of the H-Q interval in patients with bundle branch block and the role of prophylactic permanent pacing. *Am J Cardiol* 1982;**50**:1316–1322.
222. Blomström-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ, Campbell WB, Haines DE, Kuck KH, Lerman BB, Miller DD, Shaeffer CW Jr, Stevenson WG, Tomaselli GF, Antman EM, Smith SC Jr, Alpert JS, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Hiratzka LF, Hunt SA, Jacobs AK, Russell RO Jr, Priori SG, Blanc JJ, Budaj A, Burgos EF, Cowie M, Deckers JW, Garcia MA, Klein WW, Lekakis J, Lindahl B, Mazzotta G, Morais JC, Oto A, Smiseth O, Trappe HJ, American College of Cardiology, American Heart Association Task Force on Practice Guidelines, European Society of Cardiology Committee for Practice Guidelines, Writing Committee to Develop Guidelines for the management of Patients With Supraventricular Arrhythmias. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias–executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias). *Circulation* 2003;**108**:1871–1909.
223. Pfister R, Hagemeister J, Esser S, Hellmich M, Erdmann E, Schneider CA. NT-pro-BNP for diagnostic and prognostic evaluation in patients hospitalized for syncope. *Int J Cardiol* 2012;**155**:268–272.
224. Costantino G, Solbiati M, Casazza G, Bonzi M, Vago T, Montano N, McDermott D, Quinn J, Furlan R. Usefulness of N-terminal pro-B-type natriuretic Peptide increase as a marker for cardiac arrhythmia in patients with syncope. *Am J Cardiol* 2014;**113**:98–102.
225. Thiruganasambandamoorthy V, Ramaekers R, Rahman MO, Stiell IG, Sikora L, Kelly SL, Christ M, Claret PG, Reed MJ. Prognostic value of cardiac biomarkers in the risk stratification of syncope: a systematic review. *Intern Emerg Med* 2015;**10**:1003–1014.
226. Guieu R, Deharo JC, Ruf J, Mottola G, Kipson N, Bruzzese L, Gerolami V, Franceschi F, Ungar A, Tomaino M, Iori M, Brignole M. Adenosine and clinical forms of neurally-mediated syncope. *J Am Coll Cardiol* 2015;**66**:204–205.
227. Flammang D, Church TR, De Roy L, Blanc JJ, Leroy J, Mairesse GH, Otmani A, Graux PJ, Frank R, Purnode P, ATP Multicenter Study. Treatment of unexplained syncope: a multicenter, randomized trial of cardiac pacing guided by adenosine 5'-triphosphate testing. *Circulation* 2012;**125**:31–36.
228. Brignole M, Gaggioli G, Menozzi C, Gianfranchi L, Bartoletti A, Bottoni N, Lolli G, Oddone D, Del Rosso A, Pellinghelli G. Adenosine-induced atrioventricular block in patients with unexplained syncope: the diagnostic value of ATP testing. *Circulation* 1997;**96**:3921–3927.
229. Donateo P, Brignole M, Menozzi C, Bottoni N, Alboni P, Dinelli M, Del Rosso A, Croci F, Oddone D, Solano A, Puggioni E. Mechanism of syncope in patients with positive adenosine triphosphate tests. *J Am Coll Cardiol* 2003;**41**:93–98.
230. Krishnan B, Patarroyo-Aponte M, Duprez D, Pritzker M, Missov E, Benditt DG. Orthostatic hypotension of unknown cause: unanticipated association with elevated circulating N-terminal brain natriuretic peptide (NT-proBNP). *Heart Rhythm* 2015;**12**:1287–1294.
231. Fedorowski A, Burri P, Struck J, Juul-Moller S, Melander O. Novel cardiovascular biomarkers in unexplained syncopal attacks: the SYSTEMA cohort. *J Intern Med* 2013;**273**:359–367.
232. Li H, Kem DC, Reim S, Khan M, Vanderlinde-Wood M, Zillner C, Collier D, Liles C, Hill MA, Cunningham MW, Aston CE, Yu X. Agonistic autoantibodies as vasodilators in orthostatic hypotension: a new mechanism. *Hypertension* 2012;**59**:402–408.
233. Li H, Yu X, Liles C, Khan M, Vanderlinde-Wood M, Galloway A, Zillner C, Benbrook A, Reim S, Collier D, Hill MA, Raj SR, Okamoto LE, Cunningham MW, Aston CE, Kem DC. Autoimmune basis for postural tachycardia syndrome. *J Am Heart Assoc* 2014;**3**:e000755.
234. Fedorowski A, Li H, Yu X, Koelsch KA, Harris VM, Liles C, Murphy TA, Quadri SMS, Scofield RH, Sutton R, Melander O, Kem DC. Antiadrenergic autoimmunity in postural tachycardia syndrome. *Europace* 2017;**19**:1211–1219.
235. Recchia D, Barzilai B. Echocardiography in the evaluation of patients with syncope. *J Gen Intern Med* 1995;**10**:649–655.
236. Sarasin FP, Junod AF, Carballo D, Slama S, Unger PF, Louis-Simonet M. Role of echocardiography in the evaluation of syncope: a prospective study. *Heart* 2002;**88**:363–367.
237. Hoegholm A, Clementsen P, Mortensen SA. Syncope due to right atrial thromboembolism: diagnostic importance of two-dimensional echocardiography. *Acta Cardiol* 1987;**42**:469–473.
238. Omran H, Fehske W, Rabahieh R, Hagendorff A, Pizzulli L, Zirbes M, Luderitz B. Valvular aortic stenosis: risk of syncope. *J Heart Valve Dis* 1996;**5**:31–34.

239. Bogaert AM, De Scheerder I, Colardyn F. Successful treatment of aortic rupture presenting as a syncope: the role of echocardiography in diagnosis. *Int J Cardiol* 1987;**16**:212–214.
240. Acikel M, Yekeler I, Ates A, Erkut B. A giant left atrial myxoma: an unusual cause of syncope and cerebral emboli. *Int J Cardiol* 2004;**94**:325–326.
241. Nogueira DC, Bontempo D, Menardi AC, Vicente WV, Ribeiro PJ, Evora PR. Left atrial myxoma as the cause of syncope in an adolescent. *Arq Bras Cardiol* 2003;**81**:206–209, 202–205.
242. Sinha AK, Singh BP. LA myxoma presenting as recurrent syncope. *Indian Heart J* 2013;**65**:643.
243. Rahman MS, Michael H. A rare presentation of chest pain and syncope: massive right atrial myxoma. *Postgrad Med J* 2012;**88**:671–672.
244. Han H, Li Y, Guo S, Yu X. Right atrial myxoma-induced syncope. *Postgrad Med J* 2011;**87**:438–439.
245. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;**35**:2733–2779.
246. Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, Kuvin JT, Nistri S, Cecchi F, Udelson JE, Maron BJ. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. *Circulation* 2006;**114**:2232–2239.
247. Shah JS, Esteban MT, Thaman R, Sharma R, Mist B, Pantazis A, Ward D, Kohli SK, Page SP, Demetrescu C, Sevdalis E, Keren A, Pellerin D, McKenna WJ, Elliott PM. Prevalence of exercise-induced left ventricular outflow tract obstruction in symptomatic patients with non-obstructive hypertrophic cardiomyopathy. *Heart* 2008;**94**:1288–1294.
248. Dimitrow PP, Bober M, Michalowska J, Sorysz D. Left ventricular outflow tract gradient provoked by upright position or exercise in treated patients with hypertrophic cardiomyopathy without obstruction at rest. *Echocardiography* 2009;**26**:513–520.
249. Marwick TH, Nakatani S, Haluska B, Thomas JD, Lever HM. Provocation of latent left ventricular outflow tract gradients with amyl nitrite and exercise in hypertrophic cardiomyopathy. *Am J Cardiol* 1995;**75**:805–809.
250. Sneddon JF, Scalia G, Ward DE, McKenna WJ, Camm AJ, Frenneaux MP. Exercise induced vasodepressor syncope. *Br Heart J* 1994;**71**:554–557.
251. Sakaguchi S, Shultz JJ, Remole SC, Adler SW, Lurie KG, Benditt DG. Syncope associated with exercise, a manifestation of neurally mediated syncope. *Am J Cardiol* 1995;**75**:476–481.
252. Colivicchi F, Ammirati F, Biffi A, Verdile L, Pelliccia A, Santini M. Exercise-related syncope in young competitive athletes without evidence of structural heart disease. Clinical presentation and long-term outcome. *Eur Heart J* 2002;**23**:1125–1130.
253. Woelfel AK, Simpson RJ Jr, Gettes LS, Foster JR. Exercise-induced distal atrioventricular block. *J Am Coll Cardiol* 1983;**2**:578–581.
254. Byrne JM, Marais HJ, Cheek GA. Exercise-induced complete heart block in a patient with chronic bifascicular block. *J Electrocardiol* 1994;**27**:339–342.
255. Aste M, Oddone D, Donateo P, Solano A, Maggi R, Croci F, Solari D, Brignole M. Syncope in patients paced for atrioventricular block. *Europace* 2016;**18**:1735–1739.
256. Sumiyoshi M, Nakata Y, Yasuda M, Tokano T, Ogura S, Nakazato Y, Yamaguchi H. Clinical and electrophysiologic features of exercise-induced atrioventricular block. *Am Heart J* 1996;**132**:1277–1281.
257. Wissocq L, Ennezat PV, Mouquet F. Exercise-induced high-degree atrioventricular block. *Arch Cardiovasc Dis* 2009;**102**:733–735.
258. Anderson LL, Dai D, Miller AL, Roe MT, Messenger JC, Wang TY. Percutaneous coronary intervention for older adults who present with syncope and coronary artery disease? Insights from the National Cardiovascular Data Registry. *Am Heart J* 2016;**176**:1–9.
259. El-Sayed H, Hainsworth R. Salt supplement increases plasma volume and orthostatic tolerance in patients with unexplained syncope. *Heart* 1996;**75**:134–140.
260. Solari D, Tesi F, Unterhuber M, Gaggioli G, Ungar A, Tomaino M, Brignole M. Stop vasodepressor drugs in reflex syncope: a randomised controlled trial. *Heart* 2017;**103**:449–455.
261. SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC Jr, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med* 2015;**373**:2103–2116.
262. Brignole M, Menozzi C, Gaggioli G, Musso G, Foglia-Manzillo G, Mascioli G, Fradella G, Bottoni N, Mureddu R. Effects of long-term vasodilator therapy in patients with carotid sinus hypersensitivity. *Am Heart J* 1998;**136**:264–268.
263. Kim KH, Cho JG, Lee KO, Seo TJ, Shon CY, Lim SY, Yun KH, Sohn IS, Hong YJ, Park HW, Kim JH, Kim W, Ahn YK, Jeong MH, Park JC, Kang JC. Usefulness of physical maneuvers for prevention of vasovagal syncope. *Circ J* 2005;**69**:1084–1088.
264. Tomaino M, Romeo C, Vitale E, Kus T, Moya A, van Dijk N, Giuli S, D'Ippolito G, Gentili A, Sutton R, International Study on Syncope of Uncertain Etiology 3 (ISSUE 3) Investigators. Physical counter-pressure manoeuvres in preventing syncopal recurrence in patients older than 40 years with recurrent neurally mediated syncope: a controlled study from the Third International Study on Syncope of Uncertain Etiology (ISSUE-3)†. *Europace* 2014;**16**:1515–1520.
265. Reybrouck T, Heidbuchel H, Van De Werf F, Ector H. Long-term follow-up results of tilt training therapy in patients with recurrent neurocardiogenic syncope. *Pacing Clin Electrophysiol* 2002;**25**:1441–1446.
266. Zeng H, Ge K, Zhang W, Wang G, Guo L. The effect of orthostatic training in the prevention of vasovagal syncope and its influencing factors. *Int Heart J* 2008;**49**:707–712.
267. Jang WJ, Yim HR, Lee SH, Park SJ, Kim JS, On YK. Prognosis after tilt training in patients with recurrent vasovagal syncope. *Int J Cardiol* 2013;**168**:4264–4265.
268. Foglia-Manzillo G, Giada F, Gaggioli G, Bartoletti A, Lolli G, Dinelli M, Del Rosso A, Santarone M, Raviele A, Brignole M. Efficacy of tilt training in the treatment of neurally mediated syncope. A randomized study. *Europace* 2004;**6**:199–204.
269. Kinay O, Yazici M, Nazli C, Acar G, Gedikli O, Altinbas A, Kahraman H, Dogan A, Ozaydin M, Tuzun N, Ergene O. Tilt training for recurrent neurocardiogenic syncope: effectiveness, patient compliance, and scheduling the frequency of training sessions. *Jpn Heart J* 2004;**45**:833–843.
270. On YK, Park J, Huh J, Kim JS. Is home orthostatic self-training effective in preventing neurally mediated syncope? *Pacing Clin Electrophysiol* 2007;**30**:638–643.
271. Duygu H, Zoghi M, Turk U, Akyuz S, Ozerkan F, Akilli A, Erturk U, Onder R, Akin M. The role of tilt training in preventing recurrent syncope in patients with vasovagal syncope: a prospective and randomized study. *Pacing Clin Electrophysiol* 2008;**31**:592–596.
272. Tan MP, Newton JL, Chadwick TJ, Gray JC, Nath S, Parry SW. Home orthostatic training in vasovagal syncope modifies autonomic tone: results of a randomized, placebo-controlled pilot study. *Europace* 2010;**12**:240–246.
273. Verheyden B, Liu J, van Dijk N, Westerhof BE, Reybrouck T, Aubert AE, Wieling W. Steep fall in cardiac output is main determinant of hypotension during drug-free and nitroglycerine-induced orthostatic vasovagal syncope. *Heart Rhythm* 2008;**5**:1695–1701.
274. Burklow TR, Moak JP, Bailey JJ, Makhlouf FT. Neurally mediated cardiac syncope: autonomic modulation after normal saline infusion. *J Am Coll Cardiol* 1999;**33**:2059–2066.
275. Sheldon R, Raj SR, Rose MS, Morillo CA, Krahn AD, Medina E, Talajic M, Kus T, Seifer CM, Lelonek M, Klingenheben T, Parkash R, Ritchie D, McRae M, POST 2 Investigators. Fludrocortisone for the prevention of vasovagal syncope: a randomized, placebo-controlled trial. *J Am Coll Cardiol* 2016;**68**:1–9.
276. Salim MA, Di Sessa TG. Effectiveness of fludrocortisone and salt in preventing syncope recurrence in children: a double-blind, placebo-controlled, randomized trial. *J Am Coll Cardiol* 2005;**45**:484–488.
277. Raviele A, Brignole M, Sutton R, Alboni P, Giani P, Menozzi C, Moya A. Effect of etilefrine in preventing syncopal recurrence in patients with vasovagal syncope: a double-blind, randomized, placebo-controlled trial. The Vasovagal Syncope International Study. *Circulation* 1999;**99**:1452–1457.
278. Izcovich A, Gonzalez Malla C, Manzotti M, Catalano HN, Guyatt G. Midodrine for orthostatic hypotension and recurrent reflex syncope: a systematic review. *Neurology* 2014;**83**:1170–1177.
279. Madrid AH, Ortega J, Rebollo JG, Manzano JG, Segovia JG, Sanchez A, Pena G, Moro C. Lack of efficacy of atenolol for the prevention of neurally mediated syncope in a highly symptomatic population: a prospective, double-blind, randomized and placebo-controlled study. *J Am Coll Cardiol* 2001;**37**:554–559.
280. Sheldon R, Connolly S, Rose S, Klingenheben T, Krahn A, Morillo C, Talajic M, Ku T, Fouad-Tarazi F, Ritchie D, Koshman ML, POST Investigators. Prevention of Syncope Trial (POST): a randomized, placebo-controlled study of metoprolol in the prevention of vasovagal syncope. *Circulation* 2006;**113**:1164–1170.
281. Di Girolamo E, Di Iorio C, Sabatini P, Leonzio L, Barbone C, Barsotti A. Effects of paroxetine hydrochloride, a selective serotonin reuptake inhibitor, on refractory vasovagal syncope: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol* 1999;**33**:1227–1230.
282. Theodorakis GN, Markianos M, Zarvalis E, Livanis EG, Flevari P, Kremastinos DT. Provocation of neurocardiogenic syncope by clomipramine administration during the head-up tilt test in vasovagal syndrome. *J Am Coll Cardiol* 2000;**36**:174–178.
283. Marquez MF, Urias-Medina K, Gomez-Flores J, Sobrino A, Sotomayor-Gonzalez A, Gonzalez-Hermosillo A, Cardenas M. [Comparison of metoprolol vs

clonazepam as a first treatment choice among patients with neurocardiogenic syncope]. *Gac Med Mex* 2008;**144**:503–507.
284. Kanjwal K, Saeed B, Karabin B, Kanjwal Y, Grubb BP. Use of octreotide in the treatment of refractory orthostatic intolerance. *Am J Ther* 2012;**19**:7–10.
285. Brignole M, Solari D, Iori M, Bottoni N, Guieu R, Deharo JC. Efficacy of theophylline in patients affected by low adenosine syncope. *Heart Rhythm* 2016;**13**:1151–1154.
286. Brignole M, Guieu R, Tomaino M, Iori M, Ungar A, Bertolone C, Unterhuber M, Bottoni N, Tesi F, Claude Deharo J. Mechanism of syncope without prodromes with normal heart and normal electrocardiogram. *Heart Rhythm* 2017;**14**:234–239.
287. Vaddadi G, Guo L, Esler M, Socratous F, Schlaich M, Chopra R, Eikelis N, Lambert G, Trauer T, Lambert E. Recurrent postural vasovagal syncope: sympathetic nervous system phenotypes. *Circ Arrhythm Electrophysiol* 2011;**4**:711–718.
288. Schroeder C, Birkenfeld AL, Mayer AF, Tank J, Diedrich A, Luft FC, Jordan J. Norepinephrine transporter inhibition prevents tilt-induced pre-syncope. *J Am Coll Cardiol* 2006;**48**:516–522.
289. Sheldon RS, Ritchie D, McRae M, Raj S. Norepinephrine transport inhibition for treatment of vasovagal syncope. *J Cardiovasc Electrophysiol* 2013;**24**:799–803.
290. Pachon JC, Pachon EI, Cunha Pachon MZ, Lobo TJ, Pachon JC, Santillana TG. Catheter ablation of severe neurally meditated reflex (neurocardiogenic or vasovagal) syncope: cardioneuroablation long-term results. *Europace* 2011;**13**:1231–1242.
291. Aksu T, Güler TE, Bozyel S, Özcan KS, Yalin K, Mutluer FO. Cardioneuroablation in the treatment of neurally mediated reflex syncope: a review of the current literature. *Turk Kardiyol Dern Ars* 2017;**45**:33–41.
292. Brignole M, Arabia F, Ammirati F, Tomaino M, Quartieri F, Rafanelli M, Del Rosso A, Rita Vecchi M, Russo V, Gaggioli G, Syncope Unit Project 2 (SUP 2) investigators. Standardized algorithm for cardiac pacing in older patients affected by severe unpredictable reflex syncope: 3-year insights from the Syncope Unit Project 2 (SUP 2) study. *Europace* 2016;**18**:1427–1433.
293. Brignole M, Menozzi C. The natural history of carotid sinus syncope and the effect of cardiac pacing. *Europace* 2011;**13**:462–464.
294. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J* 2013;**34**:2281–2329.
295. Gaggioli G, Brignole M, Menozzi C, Devoto G, Oddone D, Gianfranchi L, Gostoli E, Bottoni N, Lolli G. A positive response to head-up tilt testing predicts syncopal recurrence in carotid sinus syndrome patients with permanent pacemakers. *Am J Cardiol* 1995;**76**:720–722.
296. Connolly SJ, Sheldon R, Roberts RS, Gent M. The North American Vasovagal Pacemaker Study (VPS). A randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. *J Am Coll Cardiol* 1999;**33**:16–20.
297. Sutton R, Brignole M, Menozzi C, Raviele A, Alboni P, Giani P, Moya A. Dual-chamber pacing in the treatment of neurally mediated tilt-positive cardioinhibitory syncope: pacemaker versus no therapy: a multicenter randomized study. The Vasovagal Syncope International Study (VASIS) Investigators. *Circulation* 2000;**102**:294–299.
298. Ammirati F, Colivicchi F, Santini M, Syncope Diagnosis and Treatment Study Investigators. Permanent cardiac pacing versus medical treatment for the prevention of recurrent vasovagal syncope: a multicenter, randomized, controlled trial. *Circulation* 2001;**104**:52–57.
299. Connolly SJ, Sheldon R, Thorpe KE, Roberts RS, Ellenbogen KA, Wilkoff BL, Morillo C, Gent M, VPS II Investigators. Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: Second Vasovagal Pacemaker Study (VPS II): a randomized trial. *JAMA* 2003;**289**:2224–2229.
300. Raviele A, Giada F, Menozzi C, Speca G, Orazi S, Gasparini G, Sutton R, Brignole M, Vasovagal Syncope and Pacing Trial Investigators. A randomized, double-blind, placebo-controlled study of permanent cardiac pacing for the treatment of recurrent tilt-induced vasovagal syncope. The Vasovagal Syncope and Pacing Trial (SYNPACE). *Eur Heart J* 2004;**25**:1741–1748.
301. Sud S, Massel D, Klein GJ, Leong-Sit P, Yee R, Skanes AC, Gula LJ, Krahn AD. The expectation effect and cardiac pacing for refractory vasovagal syncope. *Am J Med* 2007;**120**:54–62.
302. Brignole M, Donateo P, Tomaino M, Massa R, Iori M, Beiras X, Moya A, Kus T, Deharo JC, Giuli S, Gentili A, Sutton R, International Study on Syncope of Uncertain Etiology 3 (ISSUE-3) Investigators. Benefit of pacemaker therapy in patients with presumed neurally mediated syncope and documented asystole is greater when tilt test is negative: an analysis from the third International Study on Syncope of Uncertain Etiology (ISSUE-3). *Circ Arrhythm Electrophysiol* 2014;**7**:10–16.
303. Baron-Esquivias G, Morillo CA, Moya-Mitjans A, Martinez-Alday J, Ruiz-Granell R, Lacunza-Ruiz J, Garcia-Civera R, Gutierrez-Carretero E, Romero-Garrido R. Dual-chamber pacing with closed loop stimulation in recurrent reflex vasovagal syncope: the SPAIN Study. *J Am Coll Cardiol* 2017;**70**:1720–1728.
304. Madigan NP, Flaker GC, Curtis JJ, Reid J, Mueller KJ, Murphy TJ. Carotid sinus hypersensitivity: beneficial effects of dual-chamber pacing. *Am J Cardiol* 1984;**53**:1034–1040.
305. Brignole M, Sartore B, Barra M, Menozzi C, Lolli G. Is DDD superior to VVI pacing in mixed carotid sinus syndrome? An acute and medium-term study. *Pacing Clin Electrophysiol* 1988;**11**:1902–1910.
306. Sutton R. Pacing in patients with carotid sinus and vasovagal syndromes. *Pacing Clin Electrophysiol* 1989;**12**:1260–1263.
307. Palmisano P, Dell'Era G, Russo V, Zaccaria M, Mangia R, Bortnik M, De Vecchi F, Giubertoni A, Patti F, Magnani A, Nigro G, Rago A, Occhetta E, Accogli M. Effects of closed-loop stimulation vs. DDD pacing on haemodynamic variations and occurrence of syncope induced by head-up tilt test in older patients with refrac\tory cardioinhibitory vasovagal syncope: the Tilt test-Induced REsponse in Closed-loop Stimulation multicentre, prospective, single blind, randomized study. *Europace*; doi:10.1093/europace/eux015. Published online ahead of print 12 April 2017.
308. Russo V, Rago A, Papa AA, Golino P, Calabro R, Russo MG, Nigro G. The effect of dual-chamber closed-loop stimulation on syncope recurrence in healthy patients with tilt-induced vasovagal cardioinhibitory syncope: a prospective, randomised, single-blind, crossover study. *Heart* 2013;**99**:1609–1613.
309. Brignole M, Deharo JC, Menozzi C, Moya A, Sutton R, Tomaino M, Ungar A. The benefit of pacemaker therapy in patients with neurally-mediated syncope and documented asystole: a meta-analysis of implantable loop recorder studies. *Europace*; doi:10.1093/europace/eux321. Published online ahead of print 15 December 2017.
310. Claydon VE, Hainsworth R. Salt supplementation improves orthostatic cerebral and peripheral vascular control in patients with syncope. *Hypertension* 2004;**43**:809–813.
311. Schroeder C, Bush VE, Norcliffe LJ, Luft FC, Tank J, Jordan J, Hainsworth R. Water drinking acutely improves orthostatic tolerance in healthy subjects. *Circulation* 2002;**106**:2806–2811.
312. Zia A, Kamaruzzaman SB, Tan MP. Blood pressure lowering therapy in older people: does it really cause postural hypotension or falls? *Postgrad Med* 2015;**127**:186–193.
313. Verwoert GC, Mattace-Raso FU, Hofman A, Heeringa J, Stricker BH, Breteler MM, Witteman JC. Orthostatic hypotension and risk of cardiovascular disease in elderly people: the Rotterdam study. *J Am Geriatr Soc* 2008;**56**:1816–1820.
314. Kamaruzzaman S, Watt H, Carson C, Ebrahim S. The association between orthostatic hypotension and medication use in the British Women's Heart and Health Study. *Age Ageing* 2010;**39**:51–56.
315. Valbusa F, Labat C, Salvi P, Vivian ME, Hanon O, Benetos A, PARTAGE investigators. Orthostatic hypotension in very old individuals living in nursing homes: the PARTAGE study. *J Hypertens* 2012;**30**:53–60.
316. Romero-Ortuno R, O'Connell MD, Finucane C, Soraghan C, Fan CW, Kenny RA. Insights into the clinical management of the syndrome of supine hypertension–orthostatic hypotension (SH-OH): the Irish Longitudinal Study on Ageing (TILDA). *BMC Geriatr* 2013;**13**:73.
317. Canney M, O'Connell MD, Murphy CM, O'Leary N, Little MA, O'Seaghdha CM, Kenny RA. Single agent antihypertensive therapy and orthostatic blood pressure behaviour in older adults using beat-to-beat measurements: the Irish Longitudinal Study on Ageing. *PLoS One* 2016;**11**:e0146156.
318. Fogari R, Zoppi A, Mugellini A, Corradi L, Lazzari P, Preti P, Derosa G. Efficacy and safety of two treatment combinations of hypertension in very elderly patients. *Arch Gerontol Geriatr* 2009;**48**:401–405.
319. van Lieshout JJ, ten Harkel AD, Wieling W. Physical manoeuvres for combating orthostatic dizziness in autonomic failure. *Lancet* 1992;**339**:897–898.
320. Smit AA, Wieling W, Fujimura J, Denq JC, Opfer-Gehrking TL, Akarriou M, Karemaker JM, Low PA. Use of lower abdominal compression to combat orthostatic hypotension in patients with autonomic dysfunction. *Clin Auton Res* 2004;**14**:167–175.
321. Fanciulli A, Goebel G, Metzler B, Sprenger F, Poewe W, Wenning GK, Seppi K. Elastic abdominal binders attenuate orthostatic hypotension in Parkinson's disease. *Mov Dis Clin Practice* 2015;**3**:156–160.
322. Ten Harkel AD, Van Lieshout JJ, Wieling W. Treatment of orthostatic hypotension with sleeping in the head-up tilt position, alone and in combination with fludrocortisone. *J Intern Med* 1992;**232**:139–145.
323. Omboni S, Smit AA, van Lieshout JJ, Settels JJ, Langewouters GJ, Wieling W. Mechanisms underlying the impairment in orthostatic tolerance after nocturnal recumbency in patients with autonomic failure. *Clin Sci (Lond)* 2001;**101**:609–618.

324. Jankovic J, Gilden JL, Hiner BC, Kaufmann H, Brown DC, Coghlan CH, Rubin M, Fouad-Tarazi FM. Neurogenic orthostatic hypotension: a double-blind, placebo-controlled study with midodrine. *Am J Med* 1993;**95**:38–48.
325. Low PA, Gilden JL, Freeman R, Sheng KN, McElligott MA. Efficacy of midodrine vs placebo in neurogenic orthostatic hypotension. A randomized, double-blind multicenter study. Midodrine Study Group. *JAMA* 1997;**277**:1046–1051.
326. Wright RA, Kaufmann HC, Perera R, Opfer-Gehrking TL, McElligott MA, Sheng KN, Low PA. A double-blind, dose-response study of midodrine in neurogenic orthostatic hypotension. *Neurology* 1998;**51**:120–124.
327. van Lieshout JJ, ten Harkel AD, Wieling W. Fludrocortisone and sleeping in the head-up position limit the postural decrease in cardiac output in autonomic failure. *Clin Auton Res* 2000;**10**:35–42.
328. Finke J, Sagemuller I. [Fludrocortisone in the treatment of orthostatic hypotension: ophthalmodynamography during standing(author's transl)]. *Dtsch Med Wochenschr* 1975;**100**:1790–1792.
329. Kaufmann H, Freeman R, Biaggioni I, Low P, Pedder S, Hewitt LA, Mauney J, Feirtag M, Mathias CJ, NOH301 Investigators. Droxidopa for neurogenic orthostatic hypotension: a randomized, placebo-controlled, phase 3 trial. *Neurology* 2014;**83**:328–335.
330. Hauser RA, Isaacson S, Lisk JP, Hewitt LA, Rowse G. Droxidopa for the short-term treatment of symptomatic neurogenic orthostatic hypotension in Parkinson's disease (nOH306B). *Mov Disord* 2015;**30**:646–654.
331. Biaggioni I, Freeman R, Mathias CJ, Low P, Hewitt LA, Kaufmann H, Droxidopa 302 Investigators. Randomized withdrawal study of patients with symptomatic neurogenic orthostatic hypotension responsive to droxidopa. *Hypertension* 2015;**65**:101–107.
332. Hauser RA, Hewitt LA, Isaacson S. Droxidopa in patients with neurogenic orthostatic hypotension associated with Parkinson's disease (NOH306A). *J Parkinsons Dis* 2014;**4**:57–65.
333. Elgebaly A, Abdelazeim B, Mattar O, Gadelkarim M, Salah R, Negida A. Meta-analysis of the safety and efficacy of droxidopa for neurogenic orthostatic hypotension. *Clin Auton Res* 2016;**26**:171–180.
334. Alboni P, Menozzi C, Brignole M, Paparella N, Gaggioli G, Lolli G, Cappato R. Effects of permanent pacemaker and oral theophylline in sick sinus syndrome the THEOPACE study: a randomized controlled trial. *Circulation* 1997;**96**:260–266.
335. Breivik K, Ohm OJ, Segadal L. Sick sinus syndrome treated with permanent pacemaker in 109 patients. A follow-up study. *Acta Med Scand* 1979;**206**:153–159.
336. Hartel G, Talvensaari T. Treatment of sinoatrial syndrome with permanent cardiac pacing in 90 patients. *Acta Med Scand* 1975;**198**:341–347.
337. Rasmussen K. Chronic sinus node disease: natural course and indications for pacing. *Eur Heart J* 1981;**2**:455–459.
338. Sasaki Y, Shimotori M, Akahane K, Yonekura H, Hirano K, Endoh R, Koike S, Kawa S, Furuta S, Homma T. Long-term follow-up of patients with sick sinus syndrome: a comparison of clinical aspects among unpaced, ventricular inhibited paced, and physiologically paced groups. *Pacing Clin Electrophysiol* 1988;**11**:1575–1583.
339. Sgarbossa EB, Pinski SL, Jaeger FJ, Trohman RG, Maloney JD. Incidence and predictors of syncope in paced patients with sick sinus syndrome. *Pacing Clin Electrophysiol* 1992;**15**:2055–2060.
340. Ng Kam Chuen MJ, Kirkfeldt RE, Andersen HR, Nielsen JC. Syncope in paced patients with sick sinus syndrome from the DANPACE trial: incidence, predictors and prognostic implication. *Heart* 2014;**100**:842–847.
341. Langenfeld H, Grimm W, Maisch B, Kochsiek K. Course of symptoms and spontaneous ECG in pacemaker patients: a 5-year follow-up study. *Pacing Clin Electrophysiol* 1988;**11**:2198–2206.
342. Donateo P, Brignole M, Alboni P, Menozzi C, Raviele A, Del Rosso A, Dinelli M, Solano A, Bottoni N, Croci F. A standardized conventional evaluation of the mechanism of syncope in patients with bundle branch block. *Europace* 2002;**4**:357–360.
343. Azocar D, Ruiz-Granell R, Ferrero A, Martinez-Brotons A, Izquierdo M, Dominguez E, Palau P, Morell S, Garcia-Civera R. Syncope and bundle branch block. Diagnostic yield of a stepped use of electrophysiology study and implantable loop recorders. *Rev Esp Cardiol* 2011;**64**:213–219.
344. Santini M, Castro A, Giada F, Ricci R, Inama G, Gaggioli G, Calo L, Orazi S, Viscusi M, Chiodi L, Bartoletti A, Foglia-Manzillo G, Ammirati F, Loricchio ML, Pedrinazzi C, Turreni F, Gasparini G, Accardi F, Raciti G, Raviele A. Prevention of syncope through permanent cardiac pacing in patients with bifascicular block and syncope of unexplained origin: the PRESS study. *Circ Arrhythm Electrophysiol* 2013;**6**:101–107.
345. Englund A, Bergfeldt L, Rehnqvist N, Astrom H, Rosenqvist M. Diagnostic value of programmed ventricular stimulation in patients with bifascicular block: a prospective study of patients with and without syncope. *J Am Coll Cardiol* 1995;**26**:1508–1515.
346. Morady F, Higgins J, Peters RW, Schwartz AB, Shen EN, Bhandari A, Scheinman MM, Sauve MJ. Electrophysiologic testing in bundle branch block and unexplained syncope. *Am J Cardiol* 1984;**54**:587–591.
347. Tabrizi F, Rosenqvist M, Bergfeldt L, Englund A. Long-term prognosis in patients with bifascicular block–the predictive value of noninvasive and invasive assessment. *J Intern Med* 2006;**260**:31–38.
348. Ruwald MH, Okumura K, Kimura T, Aonuma K, Shoda M, Kutyifa V, Ruwald AC, McNitt S, Zareba W, Moss AJ. Syncope in high-risk cardiomyopathy patients with implantable defibrillators: frequency, risk factors, mechanisms, and association with mortality: results from the multicenter automatic defibrillator implantation trial-reduce inappropriate therapy (MADIT-RIT) study. *Circulation* 2014;**129**:545–552.
349. Sacher F, Probst V, Maury P, Babuty D, Mansourati J, Komatsu Y, Marquie C, Rosa A, Diallo A, Cassagneau R, Loizeau C, Martins R, Field ME, Derval N, Miyazaki S, Denis A, Nogami A, Ritter P, Gourraud JB, Ploux S, Rollin A, Zemmoura A, Lamaison D, Bordachar P, Pierre B, Jais P, Pasquie JL, Hocini M, Legal F, Defaye P, Boveda S, Iesaka Y, Mabo P, Haissaguerre M. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study-part 2. *Circulation* 2013;**128**:1739–1747.
350. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM, Hypertrophic Cardiomyopathy Outcomes Investigators. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J* 2014;**35**:2010–2020.
351. Corrado D, Calkins H, Link MS, Leoni L, Favale S, Bevilacqua M, Basso C, Ward D, Boriani G, Ricci R, Piccini JP, Dalal D, Santini M, Buja G, Iliceto S, Estes NA III, Wichter T, McKenna WJ, Thiene G, Marcus FI. Prophylactic implantable defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior ventricular fibrillation or sustained ventricular tachycardia. *Circulation* 2010;**122**:1144–1152.
352. Liu JF, Jons C, Moss AJ, McNitt S, Peterson DR, Qi M, Zareba W, Robinson JL, Barsheshet A, Ackerman MJ, Benhorin J, Kaufman ES, Locati EH, Napolitano C, Priori SG, Schwartz PJ, Towbin J, Vincent M, Zhang L, Goldenberg I, International Long QT Syndrome Registry. Risk factors for recurrent syncope and subsequent fatal or near-fatal events in children and adolescents with long QT syndrome. *J Am Coll Cardiol* 2011;**57**:941–950.
353. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, Babuty D, Sacher F, Giustetto C, Schulze-Bahr E, Borggrefe M, Haissaguerre M, Mabo P, Le Marec H, Wolpert C, Wilde AA. Long-term prognosis of patients diagnosed with Brugada syndrome: Results from the FINGER Brugada Syndrome Registry. *Circulation* 2010;**121**:635–643.
354. Spirito P, Autore C, Rapezzi C, Bernabo P, Badagliacca R, Maron MS, Bongioanni S, Coccolo F, Estes NA, Barilla CS, Biagini E, Quarta G, Conte MR, Bruzzi P, Maron BJ. Syncope and risk of sudden death in hypertrophic cardiomyopathy. *Circulation* 2009;**119**:1703–1710.
355. Conte G, Sieira J, Ciconte G, de Asmundis C, Chierchia GB, Baltogiannis G, Di Giovanni G, La Meir M, Wellens F, Czapla J, Wauters K, Levinstein M, Saitoh Y, Irfan G, Julia J, Pappaert G, Brugada P. Implantable cardioverter-defibrillator therapy in Brugada syndrome: a 20-year single-center experience. *J Am Coll Cardiol* 2015;**65**:879–888.
356. Olde Nordkamp LR, Vink AS, Wilde AA, de Lange FJ, de Jong JS, Wieling W, van Dijk N, Tan HL. Syncope in Brugada syndrome: prevalence, clinical significance, and clues from history taking to distinguish arrhythmic from nonarrhythmic causes. *Heart Rhythm* 2015;**12**:367–375.
357. Olde Nordkamp LR, Wilde AA, Tijssen JG, Knops RE, van Dessel PF, de Groot JR. The ICD for primary prevention in patients with inherited cardiac diseases: indications, use, and outcome: a comparison with secondary prevention. *Circ Arrhythm Electrophysiol* 2013;**6**:91–100.
358. Spezzacatene A, Sinagra G, Merlo M, Barbati G, Graw SL, Brun F, Slavov D, Di Lenarda A, Salcedo EE, Towbin JA, Saffitz JE, Marcus FI, Zareba W, Taylor MR, Mestroni L, Familial Cardiomyopathy Registry. Arrhythmogenic Phenotype in Dilated Cardiomyopathy: Natural History and Predictors of Life-Threatening Arrhythmias. *J Am Heart Assoc* 2015;**4**:e002149.
359. Russo AM, Verdino R, Schorr C, Nicholas M, Dias D, Hsia H, Callans D, Marchlinski FE. Occurrence of implantable defibrillator events in patients with syncope and nonischemic dilated cardiomyopathy. *Am J Cardiol* 2001;**88**:1444–1446, A1449.
360. Phang RS, Kang D, Tighiouart H, Estes NA III, Link MS. High risk of ventricular arrhythmias in patients with nonischemic dilated cardiomyopathy presenting with syncope. *Am J Cardiol* 2006;**97**:416–420.
361. Christiaans I, van Engelen K, van Langen IM, Birnie E, Bonsel GJ, Elliott PM, Wilde AA. Risk stratification for sudden cardiac death in hypertrophic cardiomyopathy: systematic review of clinical risk markers. *Europace* 2010;**12**:313–321.
362. Corrado D, Wichter T, Link MS, Hauer R, Marchlinski F, Anastasakis A, Bauce B, Basso C, Brunckhorst C, Tsatsopoulou A, Tandri H, Paul M, Schmied C,

Pelliccia A, Duru F, Protonotarios N, Estes NA III, McKenna WJ, Thiene G, Marcus FI, Calkins H. Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement. *Eur Heart J* 2015;**36**:3227–3237.
363. Bhonsale A, James CA, Tichnell C, Murray B, Gagarin D, Philips B, Dalal D, Tedford R, Russell SD, Abraham T, Tandri H, Judge DP, Calkins H. Incidence and predictors of implantable cardioverter-defibrillator therapy in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy undergoing implantable cardioverter-defibrillator implantation for primary prevention. *J Am Coll Cardiol* 2011;**58**:1485–1496.
364. Jons C, Moss AJ, Goldenberg I, Liu J, McNitt S, Zareba W, Qi M, Robinson JL. Risk of fatal arrhythmic events in long QT syndrome patients after syncope. *J Am Coll Cardiol* 2010;**55**:783–788.
365. Giustetto C, Cerrato N, Ruffino E, Gribaudo E, Scrocco C, Barbonaglia L, Bianchi F, Bortnik M, Rossetti G, Carvalho P, Riccardi R, Castagno D, Anselmino M, Bergamasco L, Gaita F. Etiological diagnosis, prognostic significance and role of electrophysiological study in patients with Brugada ECG and syncope. *Int J Cardiol* 2017;**241**:188–193.
366. Kubala M, Aissou L, Traulle S, Gugenheim AL, Hermida JS. Use of implantable loop recorders in patients with Brugada syndrome and suspected risk of ventricular arrhythmia. *Europace* 2012;**14**:898–902.
367. Delise P, Allocca G, Marras E, Giustetto C, Gaita F, Sciarra L, Calo L, Proclemer A, Marziali M, Rebellato L, Berton G, Coro L, Sitta N. Risk stratification in individuals with the Brugada type 1 ECG pattern without previous cardiac arrest: usefulness of a combined clinical and electrophysiologic approach. *Eur Heart J* 2011;**32**:169–176.
368. Maury P, Rollin A, Sacher F, Gourraud JB, Raczka F, Pasquie JL, Duparc A, Mondoly P, Cardin C, Delay M, Derval N, Chatel S, Bongard V, Sadron M, Denis A, Davy JM, Hocini M, Jais P, Jesel L, Haissaguerre M, Probst V. Prevalence and prognostic role of various conduction disturbances in patients with the Brugada syndrome. *Am J Cardiol* 2013;**112**:1384–1389.
369. Maury P, Sacher F, Gourraud JB, Pasquie JL, Raczka F, Bongard V, Duparc A, Mondoly P, Sadron M, Chatel S, Derval N, Denis A, Cardin C, Davy JM, Hocini M, Jais P, Jesel L, Carrie D, Galinier M, Haissaguerre M, Probst V, Rollin A. Increased Tpeak-Tend interval is highly and independently related to arrhythmic events in Brugada syndrome. *Heart Rhythm* 2015;**12**:2469–2476.
370. Morita H, Kusano KF, Miura D, Nagase S, Nakamura K, Morita ST, Ohe T, Zipes DP, Wu J. Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. *Circulation* 2008;**118**:1697–1704.
371. Priori SG, Gasparini M, Napolitano C, Della Bella P, Ottonelli AG, Sassone B, Giordano U, Pappone C, Mascioli G, Rossetti G, De Nardis R, Colombo M. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. *J Am Coll Cardiol* 2012;**59**:37–45.
372. McIntosh SJ, Lawson J, Kenny RA. Clinical characteristics of vasodepressor, cardioinhibitory, and mixed carotid sinus syndrome in the elderly. *Am J Med* 1993;**95**:203–208.
373. Ungar A, Mussi C, Del Rosso A, Noro G, Abete P, Ghirelli L, Cellai T, Landi A, Salvioli G, Rengo F, Marchionni N, Masotti G, Italian Group for the Study of Syncope in the Elderly. Diagnosis and characteristics of syncope in older patients referred to geriatric departments. *J Am Geriatr Soc* 2006;**54**:1531–1536.
374. Galizia G, Abete P, Mussi C, Noro G, Morrione A, Langellotto A, Landi A, Cacciatore F, Masotti G, Rengo F, Marchionni N, Ungar A. Role of early symptoms in assessment of syncope in elderly people: results from the Italian group for the study of syncope in the elderly. *J Am Geriatr Soc* 2009;**57**:18–23.
375. Romme JJ, van Dijk N, Boer KR, Dekker LR, Stam J, Reitsma JB, Wieling W. Influence of age and gender on the occurrence and presentation of reflex syncope. *Clin Auton Res* 2008;**18**:127–133.
376. Bhangu JS, King-Kallimanis B, Cunningham C, Kenny RA. The relationship between syncope, depression and anti-depressant use in older adults. *Age Ageing* 2014;**43**:502–509.
377. Jansen S, Frewen J, Finucane C, de Rooij SE, van der Velde N, Kenny RA. AF is associated with self-reported syncope and falls in a general population cohort. *Age Ageing* 2015;**44**:598–603.
378. Jansen S, Kenny RA, de Rooij SE, van der Velde N. Self-reported cardiovascular conditions are associated with falls and syncope in community-dwelling older adults. *Age Ageing* 2015;**44**:525–529.
379. Aronow WS. Heart disease and aging. *Med Clin North Am* 2006;**90**:849–862.
380. Jansen S, Bhangu J, de Rooij S, Daams J, Kenny RA, van der Velde N. The Association of Cardiovascular Disorders and Falls: a systematic review. *J Am Med Dir Assoc* 2016;**17**:193–199.
381. van der Velde N, van den Meiracker AH, Pols HA, Stricker BH, van der Cammen TJ. Withdrawal of fall-risk-increasing drugs in older persons: effect on tilt-table test outcomes. *J Am Geriatr Soc* 2007;**55**:734–739.
382. Ruwald MH, Hansen ML, Lamberts M, Hansen CM, Nume AK, Vinther M, Kober L, Torp-Pedersen C, Hansen J, Gislason GH. Comparison of incidence, predictors, and the impact of co-morbidity and polypharmacy on the risk of recurrent syncope in patients <85 versus >/=85 years of age. *Am J Cardiol* 2013;**112**:1610–1615.
383. Mossello E, Pieraccioli M, Nesti N, Bulgaresi M, Lorenzi C, Caleri V, Tonon E, Cavallini MC, Baroncini C, Di Bari M, Baldasseroni S, Cantini C, Biagini CA, Marchionni N, Ungar A. Effects of low blood pressure in cognitively impaired elderly patients treated with antihypertensive drugs. *JAMA Intern Med* 2015;**175**:578–585.
384. McLachlan CY, Yi M, Ling A, Jardine DL. Adverse drug events are a major cause of acute medical admission. *Intern Med J* 2014;**44**:633–638.
385. Ungar A, Mussi C, Ceccofiglio A, Bellelli G, Nicosia F, Bo M, Riccio D, Martone AM, Guadagno L, Noro G, Ghidoni G, Rafanelli M, Marchionni N, Abete P. Etiology of syncope and unexplained falls in elderly adults with Dementia: Syncope and Dementia (SYD) study. *J Am Geriatr Soc* 2016;**64**:1567–1573.
386. Ryan DJ, Harbison JA, Meaney JF, Rice CP, King-Kallimanis B, Kenny RA. Syncope causes transient focal neurological symptoms. *QJM* 2015;**108**:711–718.
387. Parry SW, Kenny RA. Drop attacks in older adults: systematic assessment has a high diagnostic yield. *J Am Geriatr Soc* 2005;**53**:74–78.
388. Parry SW, Steen IN, Baptist M, Kenny RA. Amnesia for loss of consciousness in carotid sinus syndrome: implications for presentation with falls. *J Am Coll Cardiol* 2005;**45**:1840–1843.
389. O'Dwyer C, Bennett K, Langan Y, Fan CW, Kenny RA. Amnesia for loss of consciousness is common in vasovagal syncope. *Europace* 2011;**13**:1040–1045.
390. Rafanelli M, Ruffolo E, Chisciotti VM, Brunetti MA, Ceccofiglio A, Tesi F, Morrione A, Marchionni N, Ungar A. Clinical aspects and diagnostic relevance of neuroautonomic evaluation in patients with unexplained falls. *Aging Clin Exp Res* 2014;**26**:33–37.
391. Shaw FE, Bond J, Richardson DA, Dawson P, Steen IN, McKeith IG, Kenny RA. Multifactorial intervention after a fall in older people with cognitive impairment and dementia presenting to the accident and emergency department: randomised controlled trial. *BMJ* 2003;**326**:73.
392. Frewen J, Finucane C, Savva GM, Boyle G, Kenny RA. Orthostatic hypotension is associated with lower cognitive performance in adults aged 50 plus with supine hypertension. *J Gerontol A Biol Sci Med Sci* 2014;**69**:878–885.
393. Robertson DA, Savva GM, Coen RF, Kenny RA. Cognitive function in the prefrailty and frailty syndrome. *J Am Geriatr Soc* 2014;**62**:2118–2124.
394. Frewen J, King-Kallimanis B, Boyle G, Kenny RA. Recent syncope and unexplained falls are associated with poor cognitive performance. *Age Ageing* 2015;**44**:282–286.
395. Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment–a review of the evidence and causal mechanisms. *Ageing Res Rev* 2013;**12**:840–851.
396. Kenny RA, Richardson DA, Steen N, Bexton RS, Shaw FE, Bond J. Carotid sinus syndrome: a modifiable risk factor for nonaccidental falls in older adults (SAFE PACE). *J Am Coll Cardiol* 2001;**38**:1491–1496.
397. Ungar A, Galizia G, Morrione A, Mussi C, Noro G, Ghirelli L, Masotti G, Rengo F, Marchionni N, Abete P. Two-year morbidity and mortality in elderly patients with syncope. *Age Ageing* 2011;**40**:696–702.
398. Finucane C, O'Connell MD, Fan CW, Savva GM, Soraghan CJ, Nolan H, Cronin H, Kenny RA. Age-related normative changes in phasic orthostatic blood pressure in a large population study: findings from The Irish Longitudinal Study on Ageing (TILDA). *Circulation* 2014;**130**:1780–1789.
399. DiMario FJ Jr. Prospective study of children with cyanotic and pallid breath-holding spells. *Pediatrics* 2001;**107**:265–269.
400. Vlahos AP, Kolettis TM. Family history of children and adolescents with neurocardiogenic syncope. *Pediatr Cardiol* 2008;**29**:227.
401. Vlahos AP, Tzoufi M, Katsouras CS, Barka T, Sionti I, Michalis LK, Siamopoulou A, Kolettis TM. Provocation of neurocardiogenic syncope during head-up tilt testing in children: comparison between isoproterenol and nitroglycerin. *Pediatrics* 2007;**119**:e419–425.
402. McLeod KA, Wilson N, Hewitt J, Norrie J, Stephenson JB. Cardiac pacing for severe childhood neurally mediated syncope with reflex anoxic seizures. *Heart* 1999;**82**:721–725.
403. Raj V, Rowe AA, Fleisch SB, Paranjape SY, Arain AM, Nicolson SE. Psychogenic pseudosyncope: diagnosis and management. *Auton Neurosci* 2014;**184**:66–72.
404. LaFrance WC Jr, Reuber M, Goldstein LH. Management of psychogenic nonepileptic seizures. *Epilepsia* 2013;**54**:53–67.
405. Saal DP, Overdijk MJ, Thijs RD, van Vliet IM, van Dijk JG. Long-term follow-up of psychogenic pseudosyncope. *Neurology* 2016;**87**:2214–2219.
406. LaFrance WC Jr, Baird GL, Barry JJ, Blum AS, Frank Webb A, Keitner GI, Machan JT, Miller I, Szaflarski JP, NES Treatment Trial (NEST-T) Consortium. Multicenter pilot treatment trial for psychogenic nonepileptic seizures: a randomized clinical trial. *JAMA Psychiatry* 2014;**71**:997–1005.
407. Benbadis SR, Chichkova R. Psychogenic pseudosyncope: an underestimated and provable diagnosis. *Epilepsy Behav* 2006;**9**:106–110.
408. Jecmenica-Lukic M, Poewe W, Tolosa E, Wenning GK. Premotor signs and symptoms of multiple system atrophy. *Lancet Neurol* 2012;**11**:361–368.

409. Siderowf A, Lang AE. Premotor Parkinson's disease: concepts and definitions. *Mov Disord* 2012;**27**:608–616.
410. Hoefnagels WA, Padberg GW, Overweg J, van der Velde EA, Roos RA. Transient loss of consciousness: the value of the history for distinguishing seizure from syncope. *J Neurol* 1991;**238**:39–43.
411. Benbadis SR, Wolgamuth BR, Goren H, Brener S, Fouad-Tarazi F. Value of tongue biting in the diagnosis of seizures. *Arch Intern Med* 1995;**155**:2346–2349.
412. van der Lende M, Surges R, Sander JW, Thijs RD. Cardiac arrhythmias during or after epileptic seizures. *J Neurol Neurosurg Psychiatry* 2016;**87**:69–74.
413. Rugg-Gunn FJ, Simister RJ, Squirrell M, Holdright DR, Duncan JS. Cardiac arrhythmias in focal epilepsy: a prospective long-term study. *Lancet* 2004;**364**:2212–2219.
414. Benditt DG, van Dijk G, Thijs RD. Ictal asystole: life-threatening vagal storm or a benign seizure self-termination mechanism? *Circ Arrhythm Electrophysiol* 2015;**8**:11–14.
415. Rocamora R, Kurthen M, Lickfett L, Von Oertzen J, Elger CE. Cardiac asystole in epilepsy: clinical and neurophysiologic features. *Epilepsia* 2003;**44**:179–185.
416. Schuele SU, Bermeo AC, Alexopoulos AV, Locatelli ER, Burgess RC, Dinner DS, Foldvary-Schaefer N. Video-electrographic and clinical features in patients with ictal asystole. *Neurology* 2007;**69**:434–441.
417. Ghearing GR, Munger TM, Jaffe AS, Benarroch EE, Britton JW. Clinical cues for detecting ictal asystole. *Clin Auton Res* 2007;**17**:221–226.
418. Bestawros M, Darbar D, Arain A, Abou-Khalil B, Plummer D, Dupont WD, Raj SR. Ictal asystole and ictal syncope: insights into clinical management. *Circ Arrhythm Electrophysiol* 2015;**8**:159–164.
419. Lamberts RJ, Thijs RD, Laffan A, Langan Y, Sander JW. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. *Epilepsia* 2012;**53**:253–257.
420. Lamberts RJ, Blom MT, Wassenaar M, Bardai A, Leijten FS, de Haan GJ, Sander JW, Thijs RD, Tan HL. Sudden cardiac arrest in people with epilepsy in the community: Circumstances and risk factors. *Neurology* 2015;**85**:212–218.
421. Horrocks IA, Nechay A, Stephenson JB, Zuberi SM. Anoxic-epileptic seizures: observational study of epileptic seizures induced by syncopes. *Arch Dis Child* 2005;**90**:1283–1287.
422. Hennerici M, Klemm C, Rautenberg W. The subclavian steal phenomenon: a common vascular disorder with rare neurologic deficits. *Neurology* 1988;**38**:669–673.
423. Melgar MA, Weinand ME. Thyrocervical trunk-external carotid artery bypass for positional cerebral ischemia due to common carotid artery occlusion. Report of three cases. *Neurosurg Focus* 2003;**14**:e7.
424. Dobkin BH. Orthostatic hypotension as a risk factor for symptomatic occlusive cerebrovascular disease. *Neurology* 1989;**39**:30–34.
425. Savitz SI, Caplan LR. Vertebrobasilar disease. *N Engl J Med* 2005;**352**:2618–2626.
426. Thijs RD, Kruit MC, van Buchem MA, Ferrari MD, Launer LJ, van Dijk JG. Syncope in migraine: the population-based CAMERA study. *Neurology* 2006;**66**:1034–1037.
427. Overeem S, van Nues SJ, van der Zande WL, Donjacour CE, van Mierlo P, Lammers GJ. The clinical features of cataplexy: a questionnaire study in narcolepsy patients with and without hypocretin-1 deficiency. *Sleep Med* 2011;**12**:12–18.
428. Stevens DL, Matthews WB. Cryptogenic drop attacks: an affliction of women. *Br Med J* 1973;**1**:439–442.
429. Fanciulli A, Indelicato E, Wenning GK. Autonomic history taking and key symptoms: where is the autonomic disease? In: A Fanciulli et al (eds). *Bedside Approach to Autonomic Disorders A Clinical Tutor*. Cham: Springer Verlag; 2017, 15–36.
430. Abubakr A, Wambacq I. The diagnostic value of EEGs in patients with syncope. *Epilepsy Behav* 2005;**6**:433–434.
431. Freeman R. Clinical practice. Neurogenic orthostatic hypotension. *N Engl J Med* 2008;**358**:615–624.
432. Lucchinetti CF, Kimmel DW, Lennon VA. Paraneoplastic and oncologic profiles of patients seropositive for type 1 antineuronal nuclear autoantibodies. *Neurology* 1998;**50**:652–657.
433. Vernino S, Low PA, Fealey RD, Stewart JD, Farrugia G, Lennon VA. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. *N Engl J Med* 2000;**343**:847–855.
434. McKeon A, Lennon VA, Lachance DH, Fealey RD, Pittock SJ. Ganglionic acetylcholine receptor autoantibody: oncological, neurological, and serological accompaniments. *Arch Neurol* 2009;**66**:735–741.
435. Dantas FG, Cavalcanti AP, Rodrigues Maciel BD, Ribeiro CD, Napy Charara GC, Lopes JM, Martins Filho PF, Junior LA. The role of EEG in patients with syncope. *J Clin Neurophysiol* 2012;**29**:55–57.
436. Kapoor WN, Karpf M, Maher Y, Miller RA, Levey GS. Syncope of unknown origin. The need for a more cost-effective approach to its diagnosis evaluation. *JAMA* 1982;**247**:2687–2691.
437. Farwell DJ, Sulke AN. Does the use of a syncope diagnostic protocol improve the investigation and management of syncope? *Heart* 2004;**90**:52–58.
438. Mendu ML, McAvay G, Lampert R, Stoehr J, Tinetti ME. Yield of diagnostic tests in evaluating syncopal episodes in older patients. *Arch Intern Med* 2009;**169**:1299–1305.
439. Schnipper JL, Ackerman RH, Krier JB, Honour M. Diagnostic yield and utility of neurovascular ultrasonography in the evaluation of patients with syncope. *Mayo Clin Proc* 2005;**80**:480–488.
440. Kadian-Dodov D, Papolos A, Olin JW. Diagnostic utility of carotid artery duplex ultrasonography in the evaluation of syncope: a good test ordered for the wrong reason. *Eur Heart J Cardiovasc Imaging* 2015;**16**:621–625.