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ESC Guidelines

Guidelines for the diagnosis and management of syncope (Version 2018)

The Multidisciplinary Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC)

Developed in collaboration with:

European Heart Rhythm Association (EHRA)
ESC WG “Myocardial and pericardial diseases”
ESC Council of CV nursing and allied professions

Endorsement to be requested to the following societies:

European Society of Emergency Medicine (EuSEM)
European Federation of Internal Medicine (EFIM)
European Union Geriatric Medicine Society (EUGMS)
European Neurological Society (ENS)
European Federation of Autonomic Societies (EFAS)

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Key words: syncope, transient loss of consciousness

Table of Contents

1. Preamble.....	6
2. Introduction.....	6
3. Definitions, classification and pathophysiology.....	9
3.1 Definitions.....	9
3.2 Classification and pathophysiology of syncope and transient loss of consciousness.....	11
3.2.1 Syncope.....	11
3.2.2 Non-syncope forms of (real or apparent) transient loss of consciousness.....	14
4. Diagnostic evaluation and management according to risk stratification.....	15
4.1 Initial evaluation.....	15
4.1.1. Diagnosis of syncope.....	16
4.1.2 Management of syncope in the emergency department based on risk stratification.....	19
4.2 Diagnostic tests.....	26
4.2.1 Carotid sinus massage.....	26
4.2.2 Orthostatic challenge.....	27
4.2.2.1 Active standing.....	27
4.2.2.2 Tilt testing.....	29
4.2.3 Basic autonomic function tests.....	32
4.2.3.1 Valsalva manoeuvre.....	32
4.2.3.2 Deep breathing.....	32
4.2.3.3 Other autonomic function tests.....	32
4.2.3.4 Twenty-four-hour ambulatory and home blood pressure monitoring.....	33
4.2.4 Electrocardiographic monitoring (non-invasive and invasive).....	34
4.2.4.1 In-hospital monitoring.....	34
4.2.4.2 Holter monitoring.....	34
4.2.4.3 Prospective external event recorders.....	34
4.2.4.4 Smartphone applications.....	34
4.2.4.5 External loop recorders.....	35
4.2.4.6 Remote (at home) telemetry.....	35
4.2.4.7 Implantable loop recorders.....	35
4.2.4.8 Diagnostic criteria.....	36
4.2.5 Video recording in suspected syncope.....	37
4.2.5.1 In-hospital video recording.....	37
4.2.5.2 Home video recording.....	38
4.2.6 Electrophysiological study.....	38
4.2.6.1 Asymptomatic sinus bradycardia – suspected sinus arrest causing syncope.....	38
4.2.6.2 Syncope in bifascicular bundle branch block (impending high-degree atrioventricular block).....	39
4.2.6.3 Suspected tachycardia.....	39
4.2.7 Endogenous adenosine and other biomarkers.....	41
4.2.7.1 Adenosine (triphosphate) test and plasma concentration.....	41
4.2.7.2 Cardiovascular biomarkers.....	41
4.2.7.3 Immunological biomarkers.....	41
4.2.8 Echocardiography.....	41
4.2.8.1 Exercise stress echocardiography.....	42
4.2.9 Exercise stress testing.....	42
4.2.10 Coronary angiography.....	43
5. Treatment.....	444
5.1 General principles of treatment of syncope.....	444
5.2 Treatment of reflex syncope.....	45
5.2.1 Education and lifestyle modifications.....	47
5.2.2 Discontinuation/reduction of hypotensive therapy.....	47
5.2.3 Physical counter-pressure manoeuvres.....	47
5.2.4 Tilt training.....	48
5.2.5 Pharmacological therapy.....	48
5.2.5.1 Fludrocortisone.....	48

85	5.2.5.2 Alpha-agonists	49
86	5.2.5.3 Beta-blockers	49
87	5.2.5.4 Other drugs	49
88	5.2.5.5 Emerging new therapies in specific subgroups	49
89	5.2.6 Cardiac pacing	50
90	5.2.6.1 Evidence from trials in suspected or certain reflex syncope and electrocardiogram-documented asystole	51
91	5.2.6.2 Evidence from the trials in patients with carotid sinus syndrome	52
92	5.2.6.3 Evidence from trials in patients with tilt-induced vasovagal syncope	52
93	5.2.6.4 Evidence from trials in patients with adenosine-sensitive syncope	53
94	5.2.6.5 Choice of pacing mode.....	54
95	5.2.6.6 Selection of patients for pacing and proposed algorithm.....	54
96	5.3 Treatment of orthostatic hypotension and orthostatic intolerance syndromes	57
97	5.3.1 Education and lifestyle measures.....	57
98	5.3.2 Adequate hydration and salt intake.....	57
99	5.3.3 Discontinuation/reduction of vasoactive drugs	58
100	5.3.4 Counter-pressure manoeuvres	58
101	5.3.5 Abdominal binders and/or support stockings.....	58
102	5.3.6 Head-up tilt sleeping	58
103	5.3.7 Midodrine.....	58
104	5.3.8 Fludrocortisone	58
105	5.3.9 Additional therapies	59
106	5.3.10 Emerging new pharmacological therapy in specific subgroups	59
107	5.4 Cardiac arrhythmias as the primary cause	60
108	5.4.1 Syncope due to intrinsic sinoatrial or atrioventricular conduction system disease	60
109	5.4.1.1 Sinus node disease.....	61
110	5.4.1.2 Atrioventricular conduction system disease	61
111	5.4.1.3 Bundle branch block and unexplained syncope	62
112	5.4.2 Syncope due to intrinsic cardiac tachyarrhythmias	63
113	5.4.2.1 Paroxysmal supraventricular tachycardia.....	64
114	5.4.2.2 Paroxysmal ventricular tachycardia.....	64
115	5.5 Treatment of syncope secondary to structural cardiac, cardiopulmonary, and great vessel disease.....	66
116	5.6 Treatment of unexplained syncope in patients at high risk of sudden cardiac death	67
117	5.6.1 Definition	67
118	5.6.2 Left ventricular systolic dysfunction.....	67
119	5.6.3 Hypertrophic cardiomyopathy	68
120	5.6.4 Arrhythmogenic right ventricular cardiomyopathy	69
121	5.6.5 Patients with inheritable arrhythmogenic disorders	70
122	5.6.5.1 Long QT syndrome	70
123	5.6.5.2 Brugada syndrome.....	70
124	5.6.5.3 Other forms	71
125	6. Special issues	72
126	6.1 Syncope in patients with comorbidity and frailty	72
127	6.1.1 Comorbidity and polypharmacy.....	72
128	6.1.2 Falls.....	72
129	6.1.3 Cognitive assessment and physical performance tests	73
130	6.2 Syncope in paediatric patients.....	74
131	6.2.1 Diagnostic evaluation.....	74
132	6.2.2. Therapy.....	75
133	7. Psychogenic transient loss of consciousness and its evaluation	75
134	7.1 Diagnosis.....	75
135	7.1.1 Historical criteria for attacks	75
136	7.1.2 Documentation of key features during an attack	76
137	7.1.2.1 Management of psychogenic pseudosyncope	76
138		
139		

140	8. Neurological causes and mimics of syncope.....	77
141	8.1 Clinical conditions.....	77
142	8.1.1. Autonomic failure	77
143	8.1.2 Epilepsy and ictal asystole	77
144	8.1.3 Cerebrovascular disorders	79
145	8.1.4 Migraine	79
146	8.1.5 Cataplexy.....	79
147	8.1.6 Drop attacks	79
148	8.2 Neurological tests.....	80
149	8.2.1 Electroencephalography.....	81
150	8.2.2 Brain computed tomography and magnetic resonance imaging	81
151	8.2.3 Neurovascular studies	81
152	8.2.4 Blood tests	81
153	9. Organizational aspects	82
154	9.1 Syncope (transient loss of consciousness) management unit	82
155	9.1.1 Definition of a syncope unit	82
156	9.1.2 Definition of syncope specialist.....	82
157	9.1.3 Goal of a syncope unit	82
158	9.1.4 Model of a syncope unit.....	83
159	9.1.5 Access and referrals to syncope unit.....	85
160	9.1.6 Outcomes and quality indicators.....	85
161	9.2 The clinical nurse specialist in the syncope unit.....	85
162	9.2.1 Definition	85
163	9.2.2 Role and skills of clinical nurse specialist	85
164	10. Key messages	87
165	11. Gaps in evidence and areas for future research	89
166	12. “What to do” and “what not to do” messages from the guidelines	90
167	13. References.....	93
168		
169		

170	Abbreviations and Acronyms	
171	ABPM	ambulatory blood pressure monitoring
172	AF	atrial fibrillation
173	ARVC	arrhythmogenic right ventricular cardiomyopathy
174	AV	atrioventricular
175	BBB	bundle branch block
176	BP	blood pressure
177	b.p.m.	beats per minute
178	CI	confidence interval
179	CI-CSS	cardioinhibitory carotid sinus syndrome
180	CRT-D	cardiac resynchronization therapy defibrillator
181	CSM	carotid sinus massage
182	CSS	carotid sinus syndrome
183	DCM	dilated cardiomyopathy
184	ECG	electrocardiogram/electrocardiographic
185	ED	emergency department
186	EEG	electroencephalogram
187	EHRA	European Heart Rhythm Association
188	EPS	electrophysiological study
189	ESC	European Society of Cardiology
190	HBPM	home blood pressure monitoring
191	HCM	hypertrophic cardiomyopathy
192	HR	heart rate
193	ICD	implantable cardioverter defibrillator
194	ILR	implantable loop recorder
195	ISSUE	International Study on Syncope of Unknown Etiology
196	LOC	loss of consciousness
197	LQTS	long QT syndrome
198	LVEF	left ventricular ejection fraction
199	MRI	magnetic resonance imaging
200	NYHA	New York Heart Association
201	OH	orthostatic hypotension
202	PC-Trial	Physical Counterpressure Manoeuvres Trial
203	PCM	physical counter-pressure
204	PNES	psychogenic non-epileptic seizures
205	POST	Prevention of Syncope Trial
206	POTS	postural orthostatic tachycardia syndrome
207	PPS	psychogenic pseudosyncope
208	SCD	sudden cardiac death
209	SNRT	sinus node recovery time
210	SU	syncope unit
211	SUP	Syncope Unit Project
212	SVT	supraventricular tachycardia
213	TIA	transient ischaemic attack
214	TLOC	transient loss of consciousness
215	TNG	trinitroglycerin
216	VA	ventricular arrhythmia
217	VF	ventricular fibrillation
218	VT	ventricular tachycardia
219	VVS	vasovagal syncope
220		

221

1. Preamble

TO BE INSERTED

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.	
<i>Class IIa</i>	<i>Weight of evidence/opinion is in favour of usefulness/efficacy.</i>	Should be considered
<i>Class IIb</i>	<i>Usefulness/efficacy is less well established by evidence/opinion.</i>	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

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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.

2. Introduction

The first European Society of Cardiology (ESC) guidelines for the management of syncope were published in 2001, with subsequent versions in 2004 and 2009. In March 2015, the ESC Committee for Practice Guidelines considered that there were enough new data to justify 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 Web Addenda as an integral part. While the print text is mainly aimed to give formal evidence-based

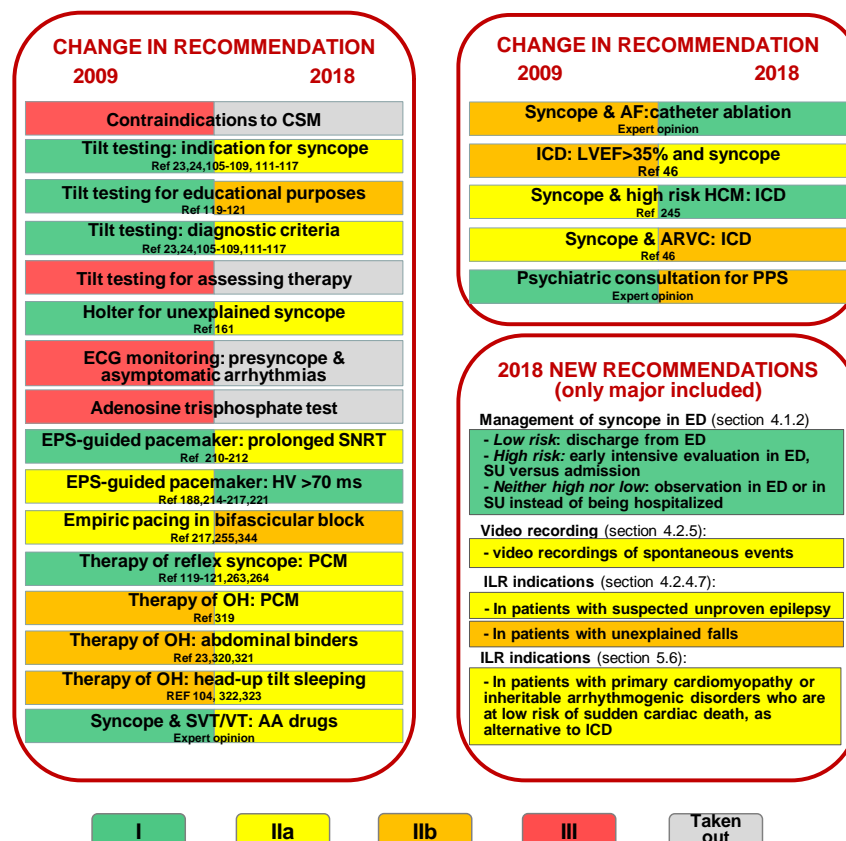
241 recommendations according to the standardized rules of the ESC, this new web-only feature allows
242 expansion of the content to practical issues and aims to fill the gap between the best available scientific
243 evidence and the need for dissemination of these concepts into clinical practice (*"We have the knowledge,
244 we need to teach it"*). Thanks to the web addenda, we can give explanations and practical instructions on
245 how to evaluate patients with loss of consciousness (LOC) and how to perform and interpret tests properly;
246 whenever possible we provide tracings, videos, flow-charts, and check lists.

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

252 Finally, we recognize that one major challenge in syncope management is reduction of inappropriate
253 admissions and inappropriate use of tests while maintaining the safety of the patient. We give strong focus to
254 pathways and organizational issues (*"We have the knowledge; we need to apply it"*). In particular, we
255 propose a care pathway for management of the patient with TLOC from their arrival in the emergency
256 department (ED), and give practical instructions on how to set up outpatient syncope clinics (syncope units)
257 aimed at reducing hospitalization, under- and misdiagnoses, and costs.

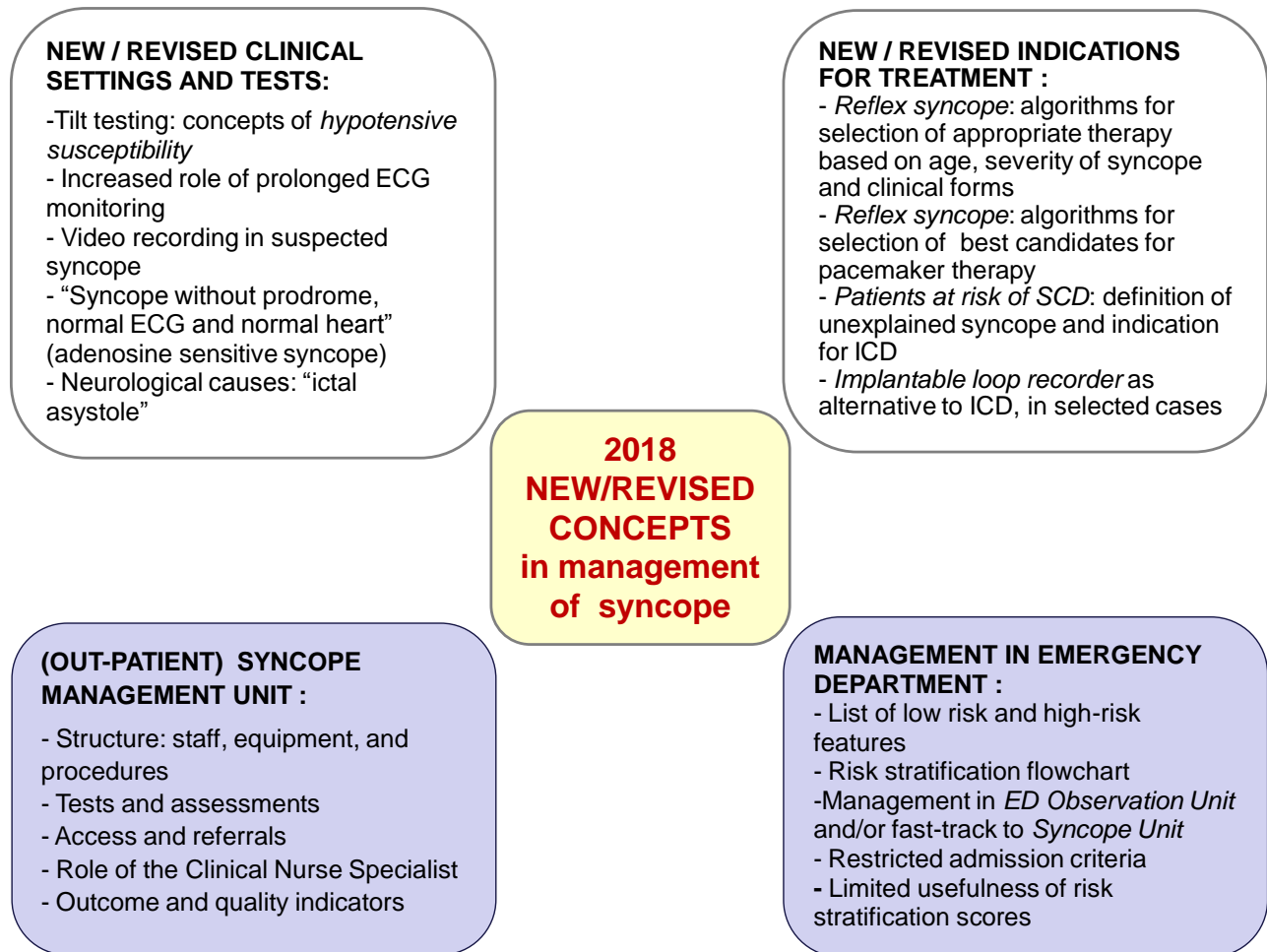
258 259 **2.1 What is new in the 2018 version?**

260 The changes in recommendations made in 2018 version compared with the 2009 version, the new
261 recommendations, and the most important new/revised concepts are summarized in *Figure 1*.
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Figure 1 What is new in 2018 syncope guidelines. AA = antiarrhythmic; AF = atrial fibrillation; ARVC = arrhythmogenic right ventricular cardiomyopathy; CSM = carotid sinus massage; ECG = electrocardiogram; ED = emergency department; LVEF = 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.

3. Definitions, classification and pathophysiology

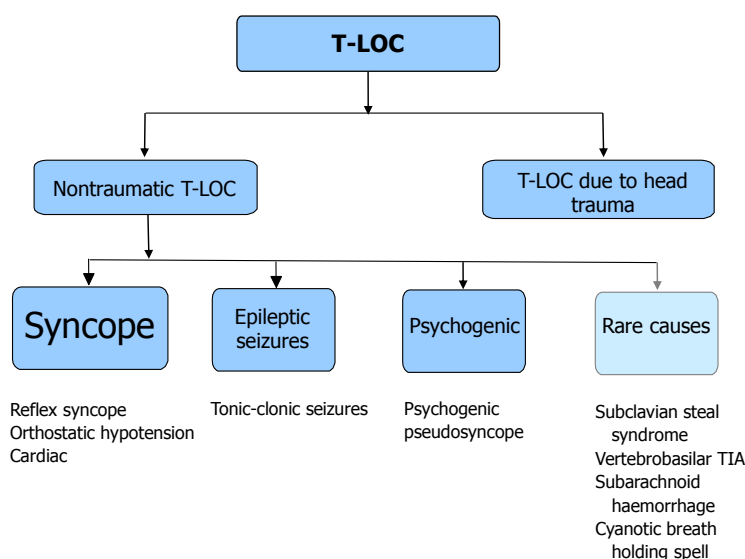
3.1 Definitions

- *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, which therefore feature in one another's differential diagnosis. 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.

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



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

299
 300 The clinical features characterizing TLOC are usually derived from history taking from patients and
 301 eyewitnesses. Specific characteristics that aid diagnosis are outlined in the *Web Practical Instructions*
 302 *section 3*.

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

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

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

315

316 **3.2 Classification and pathophysiology of syncope and transient loss of** 317 **consciousness**

318 **3.2.1 Syncope**

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

322

323 **Table 3 Classification of syncope**

Reflex (neurally mediated) syncope Vasovagal: <ul style="list-style-type: none"> - orthostatic VVS: standing, less common sitting - emotional: fear, pain (somatic or visceral), instrumentation, blood phobia Situational: <ul style="list-style-type: none"> - 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 <i>Note that hypotension may be exacerbated by venous pooling during exercise (exercise-induced), after meals (postprandial hypotension), and after prolonged bed rest (deconditioning).</i> Drug-induced OH (most common cause of OH): <ul style="list-style-type: none"> - e.g. vasodilators, diuretics, phenothiazine, antidepressants Volume depletion: <ul style="list-style-type: none"> - haemorrhage, diarrhoea, vomiting, etc. Primary autonomic failure (neurogenic OH): <ul style="list-style-type: none"> - pure autonomic failure, multiple system atrophy, Parkinson’s disease, dementia with Lewy bodies Secondary autonomic failure (neurogenic OH): <ul style="list-style-type: none"> - 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 valves 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 hypovolemia), 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.

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 seconds 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}

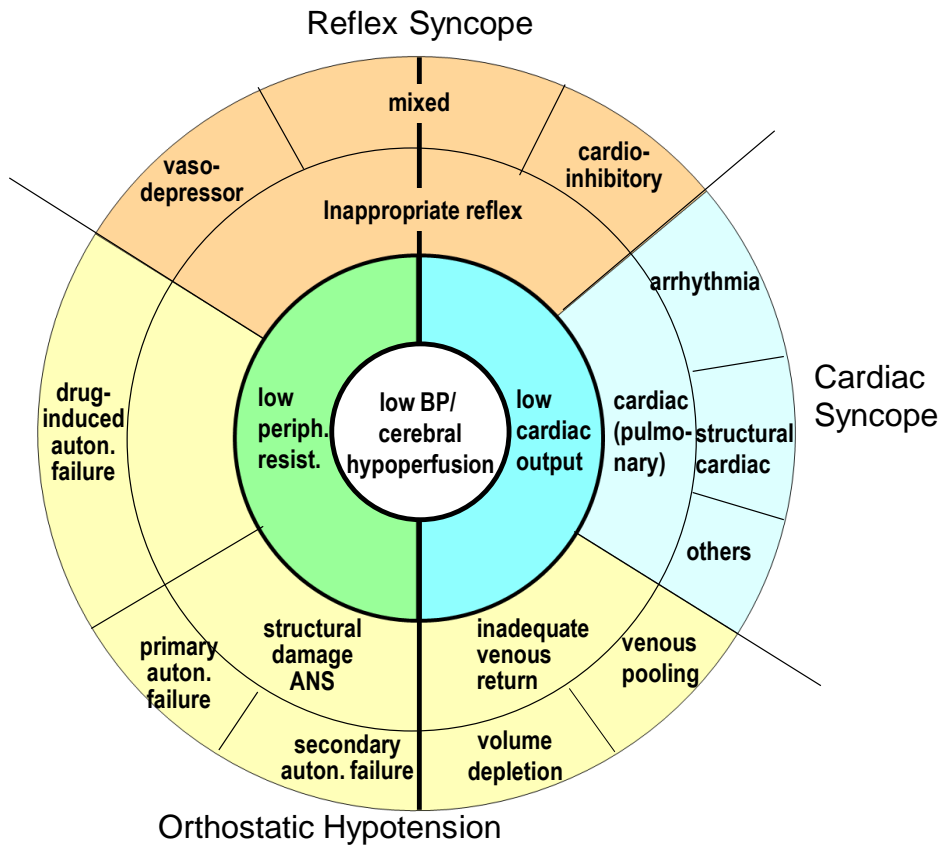
Systemic BP is the product of cardiac output and total peripheral resistance; a fall in either can cause syncope. However, in syncope, often both mechanisms act together to a varying degree.

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

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

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

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



352

353 **Figure 3** Pathophysiological basis of the classification of syncope. ANS = autonomic nervous system; auton.
 354 = autonomic; BP = blood pressure; OH = orthostatic hypotension; periph. = peripheral; resist. = resistance.
 355

356 **3.2.2 Non-syncopal forms of (real or apparent) transient loss of consciousness**

357 Only those forms of epilepsy in which normal motor control is lost, so patients may fall, are included in *Figure*
 358 2. These are tonic, clonic, tonic-clonic, and atonic generalized seizures, and can be classified as primary or
 359 secondary. The forms of epilepsy in which people remain actively upright sitting or standing (e.g. complex
 360 partial seizures, absence epilepsy) are not regarded as TLOC, but sometimes they are incorrectly diagnosed
 361 as syncope.

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

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

372 *Table 4* lists the main features that distinguish syncope from disorders that may be mistaken for
 373 syncope.
 374

375 **Table 4** Conditions which may be incorrectly diagnosed as syncope

Condition	Characteristic features that distinguish from syncope
Generalized seizures	See section 8, <i>Table 10</i> .
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,	Duration much longer than in TLOC; consciousness may be impaired instead of lost

hypoxia, hyperventilation with hypocapnia	
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?
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 4 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 the *Web Practical Instructions to section 4.1*).

TLOC is probably syncope when: a) there are signs and symptoms specific for reflex syncope, syncope due to OH, or cardiac syncope, and; b) signs and symptoms specific for other forms of TLOC (head trauma, epileptic seizures, psychogenic TLOC, rare causes) are absent. Practical instructions for history taking are given in the *Web Practical Instructions sections 3 and 4: ESC guidelines checklist of historical clues to diagnose TLOC*.

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.

Presentation of patient with probable TLOC

(may include ambulance or referral data)

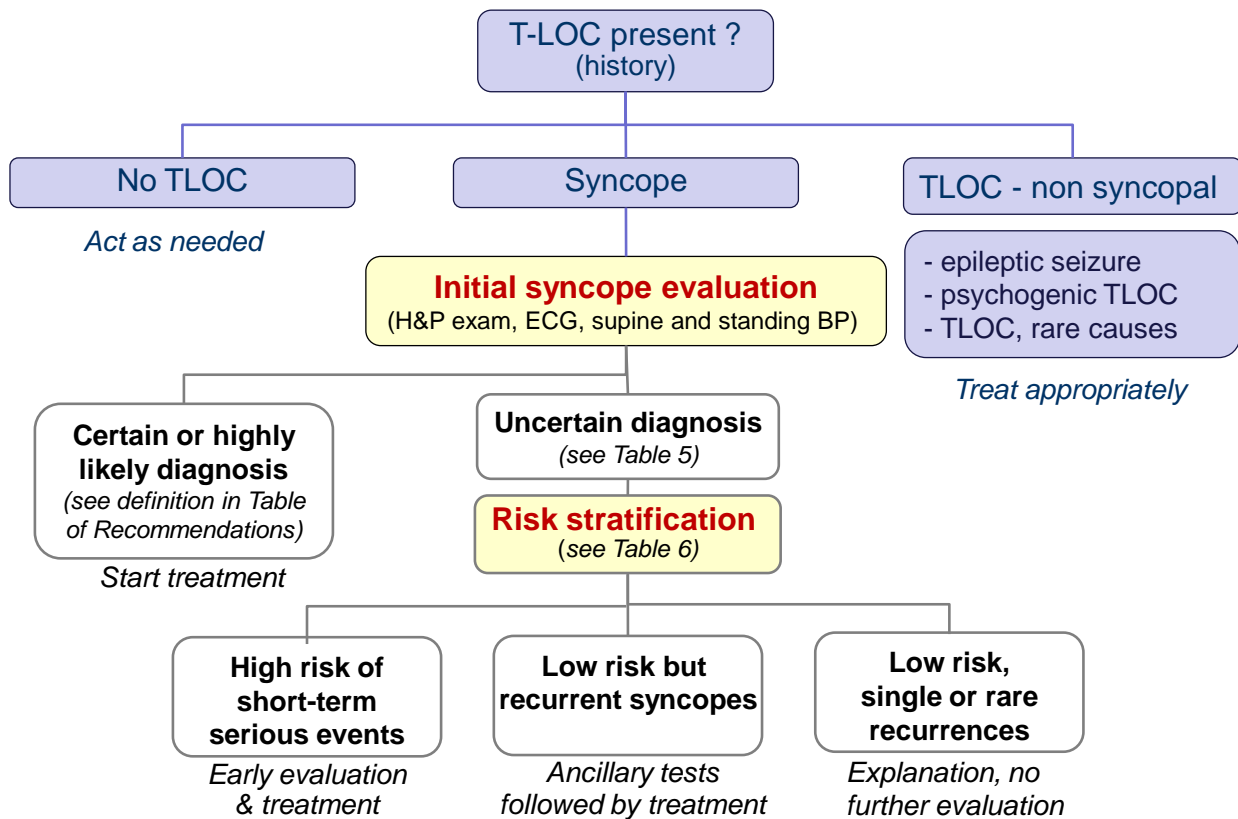


Figure 4 Flow diagram for initial evaluation and risk stratification of patients with syncope. BP = blood pressure; ECG = electrocardiogram; H&P exam = history and physical examination; TLOC = transient loss of consciousness.

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; and
- 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 or data suggestive of structural heart disease or syncope secondary to cardiovascular cause;

- Carotid sinus massage (CSM) in patients age >40 years;
- Head-up tilt testing when there is suspicion of syncope due to OH or reflex syncope; and
- 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-ischemia related syncope is suspected, 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		
1. VVS is highly probable if syncope is precipitated by pain or fear or standing, and is associated with typical progressive prodrome (pallor, sweating, nausea). ^{8,13-17}	I	C
2. Situational reflex syncope is highly probable if syncope occurs during or immediately after specific triggers, listed in <i>Table 3</i> . ^{8,13-17}	I	C
3. Syncope due to OH is confirmed when syncope occurs while standing and there is concomitant significant OH. ¹⁸⁻²⁴	I	C
4. 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 <i>Table 5</i>).	Ila	C
Cardiac syncope		
5. Arrhythmic syncope is highly probable when the ECG shows ²⁵⁻³⁹ : <ul style="list-style-type: none"> • Persistent sinus bradycardia <40 b.p.m. or sinus pauses >3 seconds 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 • Pacemaker or ICD malfunction with cardiac pauses. 	I	C
6. Cardiac-ischaemia-related syncope is confirmed when syncope presents with evidence of acute myocardial ischaemia with or without myocardial infarction. ²⁵⁻³⁹	I	C
7. 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 vasovagal 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

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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 flowchart for the management and risk stratification of patients referred to the ED for TLOC suspected to be syncope (modified from Casagrande *et al*⁴⁰).

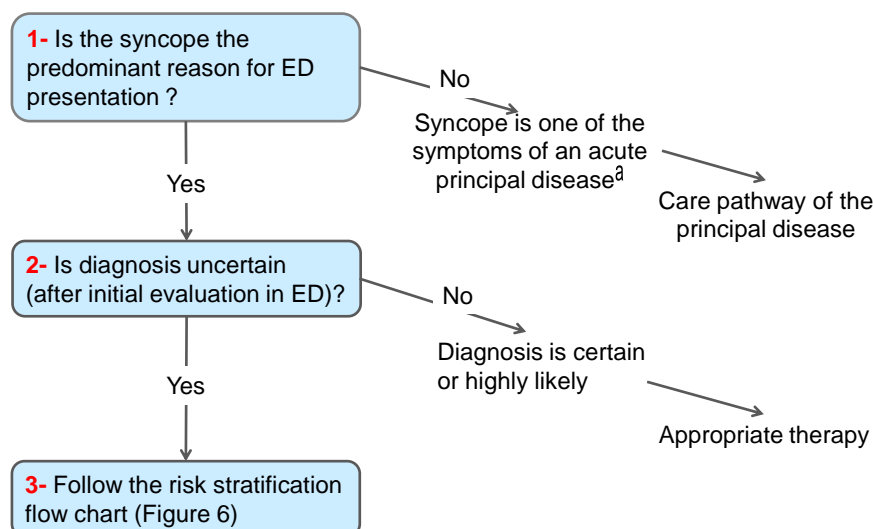


Figure 5 The management of patients presenting to the ED for TLOC suspected to be syncope (modified from Casagrande *et al*⁴⁰). ED = emergency department; TLOC = transient loss of consciousness.

^a e.g. this includes pulmonary embolism presenting with shortness of breath, pleuritic chest pain, and syncope, but not trauma secondary to syncope.

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.

473 High-risk patients are more likely to have cardiac syncope. Structural heart disease^{25-27,31,35,36,45} and primary
 474 electrical disease⁴⁶ are major risk factors for sudden cardiac death (SCD) and overall mortality in patients
 475 with syncope. Low-risk patients are more likely to have reflex syncope and have an excellent prognosis.⁴⁷
 476 OH is associated with a twofold higher risk of death owing to the severity of comorbidities compared with the
 477 general population.⁴⁸

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

Low risk	High risk (red flag)
Syncopal event	
1. Associated with prodrome typical of reflex syncope (e.g. light-headedness, feeling of warmth, sweating, nausea, vomiting) ^{36,49} 2. After sudden unexpected unpleasant sight, sound, smell, or pain ^{36,49,50} 3. After prolonged standing or crowded, hot places ³⁶ 4. During a meal or postprandial ⁵¹ 5. Triggered by cough, defaecation, or micturition ⁵² 6. With head rotation or pressure on carotid sinus (e.g. tumour, shaving, tight collars) ⁵³ 7. Standing from supine/sitting position ⁵⁴	Major 1. New onset of chest discomfort, breathlessness, abdominal pain, or headache ^{26,44,55} 2. Syncope during exertion or when supine ³⁶ 3. Sudden onset palpitation immediately followed by syncope ³⁶ Minor (high risk only if associated with structural heart disease or abnormal ECG): 4. No warning symptoms or short (<10 s) prodrome ^{36,38,49,56} 5. Family history of SCD at young age ⁵⁷ 6. Syncope in the sitting position ⁵⁴
Past medical history	
8. Long history (years) of recurrent syncope with low-risk features with the same characteristics of the current episode ⁵⁸ 9. Absence of structural heart disease ^{27,58}	Major 7. Severe structural or coronary artery disease (heart failure, low LVEF or previous myocardial infarction) ^{26,27,35,55,59}
Physical examination	
10. Normal examination	Major 8. Unexplained systolic BP in the ED <90 mmHg ^{26,55} 9. Suggestion of gastrointestinal bleed on rectal examination ⁴⁴ 10. Persistent bradycardia (<40 b.p.m.) in awake state and in absence of physical training 11. Undiagnosed systolic murmur ⁶⁰
ECG^a	
11. Normal ECG ^{26,35,36,55}	Major 12. ECG changes consistent with acute ischaemia 13. Mobitz II second- and third-degree AV block

	<p>14. Slow AF (<40 b.p.m.)</p> <p>12. 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</p> <p>15. Bundle branch block, intraventricular conduction disturbance, ventricular hypertrophy, or Q waves consistent with ischaemic heart disease or cardiomyopathy^{44,56}</p> <p>16. Sustained and non-sustained VT</p> <p>17. Dysfunction of an implantable cardiac device (pacemaker or ICD)</p> <p>18. ST-segment elevation with type 1 morphology in leads V1–V3 (Brugada pattern)</p> <p>19. QTc >460 ms in repeated 12-lead ECGs indicating LQTS⁴⁶</p> <p>Minor (high risk only if history consistent with arrhythmic syncope)</p> <p>20. Mobitz I second-degree AV block and 1° degree AV block with markedly prolonged PR interval</p> <p>21. Asymptomatic inappropriate mild sinus bradycardia (40–50 b.p.m.), or slow AF (40–50 b.p.m.)⁵⁶</p> <p>22. Paroxysmal SVT or atrial fibrillation.⁵⁰</p> <p>23. Pre-excited QRS complex</p> <p>24. Short QTc interval (≤ 340 ms)⁴⁶</p> <p>25. Atypical Brugada patterns⁴⁶</p> <p>26. Negative T waves in right precordial leads, epsilon waves suggestive of ARVC⁴⁶</p>
<p>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.</p> <p>^a Some ECG criteria are <i>per se</i> 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</p>	

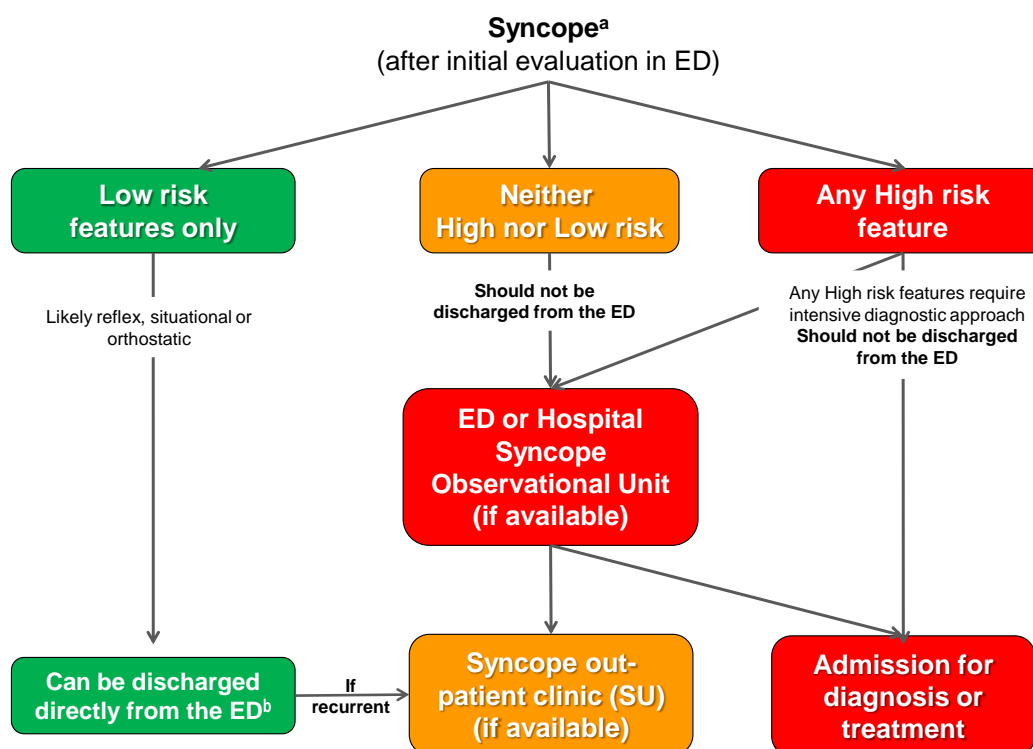


Figure 6. ED risk stratification flowchart. Low- and high-risk features are listed in Table 6. ED = emergency department; SU = syncope unit.

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}

^aRecent studies have suggested that outcomes in patients presenting with presyncope are similar to those presenting with syncope.⁶⁶⁻⁶⁸

^bThese 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.

503 **Management of syncope in the ED**

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 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
Risk stratification scores may be considered for risk stratification in the ED. ⁷⁸⁻⁸⁶	IIb	B
Additional advice and clinical perspectives <ul style="list-style-type: none"> • 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, D-dimer and cardiac markers have a low diagnostic yield and 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 (<i>Web Data Supplement Table 4</i>). 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 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 clinician judgement and should not be used alone to perform risk stratification in the ED. 		

504 ED = emergency department; OH = orthostatic hypotension.

505 ^a Class of recommendation.

506 ^b Level of evidence.

507

508 **Question 3: Should the patient be admitted to hospital?**

509 Approximately 50% of patients who present to the ED with syncope are admitted (although the rate varies
510 between 12% and 86%) (*Web Data Supplement Table 4*). The use of clinical decision rules and standardized
511 protocols has not changed this rate significantly. The composite estimate of outcomes is that in the next
512 7–30 days, only 0.8% die, 6.9% have a non-fatal severe outcome whilst in the ED, and another 3.6% have a
513 post-ED serious outcome (*Web Data Supplement Table 4*). Unnecessary admission in low-risk patients can
514 be harmful.⁸⁷ Whereas it is crucial to identify these high-risk patients to ensure early, rapid, and intensive
515 investigation, not all patients at high risk need hospitalization.⁸⁰

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

524

525 **Table 7 High-risk syncope patients – criteria favouring stay in an ED observation unit and/or fast-**
 526 **track to syncope unit versus 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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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.	

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529 **Risk stratification scores**

530 There are several ED syncope clinical decision rules that aim to stratify patients with syncope based on
 531 medical history, examination, and ECG findings (*Web Data Supplement Table 3*).^{26,34-36,44,88} None of these
 532 rules are used widely in EDs due to poor sensitivity and specificity on external validation or to a lack of
 533 external validation.^{70,78-85} Syncope clinical decision rules perform no better than clinician judgment at
 534 predicting short-term serious outcomes.⁸⁶ Clinical decision rules can predict poor outcomes, but most
 535 syncope deaths and many poor outcomes are associated with underlying illness rather than syncope *per*
 536 *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 seconds 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 (up to 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 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 seconds.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 study⁹⁴ aimed at validation of 2009 ESC guidelines, CSM was indicated after the initial evaluation in 73% of 700 patients and was diagnostic in 12%. The precise methodology and results of CSM are shown in the *Web Practical Instructions section 5*.

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 estimate of effect and may change the estimate.

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 <ul style="list-style-type: none">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 up to 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.⁹⁰Albeit 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-hour 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 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 consensus⁶ 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 hypovolemia. 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 OH

		History of syncope and orthostatic complaints	
		Highly suggestive of OH: <i>syncope and presyncope 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"</i>	Possibly due to OH: <i>not all of the features highly suggestive of OH are present</i>
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 minutes 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 minutes 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 minute; 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 μ g of sublingual TNG after a 20-minute 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 μ g/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% to 14%; the test differentiated patients with syncope from controls with an odds ratio of 12. Methodology and classification of responses are described in the *Web Practical Instructions section 6..* Adding video recording to a tilt table permits review of clinical signs in relation to BP and HR objectively and repeatedly, helps to assess the relative contribution of bradycardia and hypotension to syncope (see section 5.2.6.3 and explanatory video in *Web Practical Instruction 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: 1) to confirm a diagnosis of reflex syncope in patients in whom this diagnosis was suspected but not confirmed by initial evaluation^{105-109,111}; 2) for the assessment of autonomic failure especially for the reproduction of delayed OH (which could not be detected by active standing

640 because of its delayed onset)^{23,24,112,113} and postural orthostatic tachycardia syndrome (POTS).¹¹⁴ Tilt testing
641 may be helpful in separating syncope from PPS.¹¹⁵⁻¹¹⁷

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

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

650 **Interpretation of tilt testing results in patients with reflex syncope**

651 Some studies^{122,123} compared the response to tilt testing with spontaneous syncope recorded by an
652 implantable loop recorder (ILR). While a positive cardioinhibitory response to tilt testing predicts, with a high
653 probability, an asystolic spontaneous syncope, the presence of a positive vasodepressor, mixed response,
654 or even a negative response, does not exclude the presence of asystole during spontaneous syncope.^{122,123}

655 Tilt testing has an acceptable sensitivity¹²⁴ and specificity^{106,124,125} when these are calculated in
656 patients with true VVS or without a history of syncope. However, there is an inability to apply the test to
657 populations with syncope of uncertain cause where it is hoped tilt testing might prove decisive. In these
658 clinical settings, tilt testing fails to deliver (*Figure 7*). Indeed, tilt testing was positive in 51–56% of patients
659 with atypical clinical features suggesting a reflex mechanism,^{106,124-128} in 30–36% with unexplained syncope
660 after full investigation,^{124,129} and in 45–47% with true cardiac arrhythmic syncope.^{130,131} In other words, tilt
661 testing offers little diagnostic value in patients for whom it is most needed. In these patients, a positive tilt test
662 reveals a susceptibility to orthostatic stress.¹³² This *hypotensive susceptibility* plays a role in causing syncope
663 irrespective of the aetiology and mechanism of syncope. For example, in arrhythmic syncope caused by
664 paroxysmal atrial tachyarrhythmias, the mechanism is a combination of onset of the arrhythmia itself and
665 hypotensive susceptibility, corroborated by positive tilt testing.^{130,131} Similarly, multifactorial mechanisms are
666 likely in other types of cardiac syncope, e.g. aortic stenosis,¹³³ hypertrophic cardiomyopathy (HCM),¹³⁴ and
667 sick sinus syndrome.^{135,136} The presence or absence of susceptibility explains the occurrence of syncope in
668 some and not in others affected by the same severity of arrhythmia or structural defect. Tilt testing should
669 now be considered a means of exposing a hypotensive tendency rather than being diagnostic of VVS. This
670 concept has practical implications for therapy (see sections 5.1 and 5.2).

Tilt testing: positivity rate

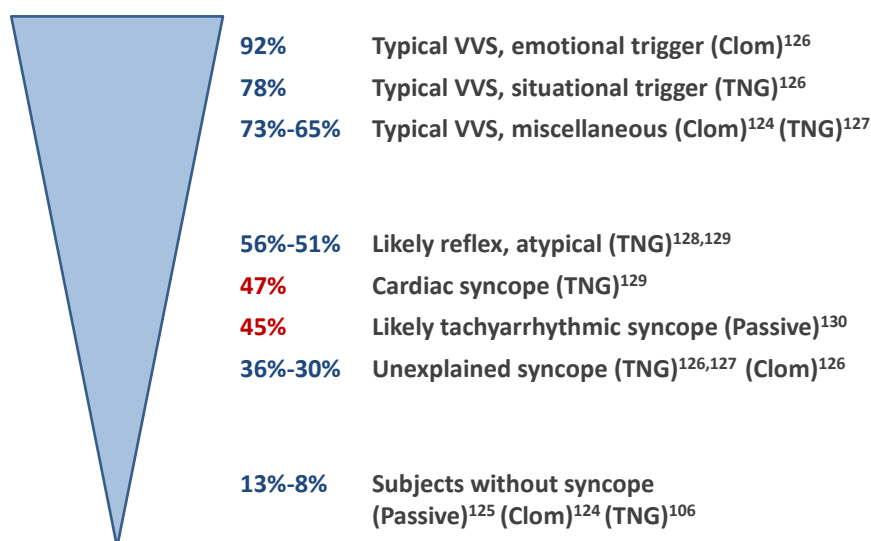


Figure 7 Rates of tilt testing positivity in different clinical conditions. These studies used the Westminster protocol for passive tilt,¹²⁵ the Italian protocol for TNG tilt,¹⁰⁶ and the clomipramine protocol,¹²⁴ for a total of 1453 syncope patients and 407 controls without syncope. Studies using other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

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		
<ul style="list-style-type: none"> 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 <i>hypotensive susceptibility</i>, 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 or 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 efficacy of 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.

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 the *Web Practical Instructions section 7.1.1* and in *Web video 2*. There is strong evidence that the absence of a BP overshoot and 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 suspect of situational syncope, i.e. syncope occurring during some forms of situational syncope, e.g. cough, brass instrument playing, singing, and weight lifting.¹⁴⁴

4.2.3.2 Deep breathing

The methodology of the deep breathing test is described in the *Web Practical Instructions section 7.1.2*. Under physiological conditions, HR rises during inspiration and falls during expiration. HR variability during deep breathing (also called 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, cold

701 pressure test, sustained hand grip, and mental arithmetic. There is weak evidence that these tests may be
 702 useful.^{13,142,143,147}

703
 704 **4.2.3.4 Twenty-four-hour ambulatory and home blood pressure monitoring**

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

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

717
 718

719 **Basic autonomic function tests**

Recommendations	Class ^a	Level ^b
Valsalva manoeuvre Valsalva manoeuvre should be considered for 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. cough, brass instrument playing, singing and weight lifting. ¹⁴⁴	IIb	C
Deep breathing test Deep breathing test should be considered for 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 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 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

<p>Additional advice and clinical perspectives</p> <ul style="list-style-type: none"> • Whenever possible, reproduction of the trigger situation (e.g. coughing, swallowing, laughing, bass instrument playing, weight lifting) under beat-to-beat non-invasive HR and BP measurement should be performed in patients with suspected situational syncope. • The effect 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 		
<p>ABPM = ambulatory blood pressure monitoring; BP = blood pressure; HBPM = home blood pressure monitoring; HR = heart rate; OH = orthostatic hypotension.</p> <p>^a Class of recommendation.</p> <p>^b Level of evidence.</p>		

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 pretest 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% to 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 period, 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 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

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

749

750 4.2.4.5 External loop recorders

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

755

756 4.2.4.6 Remote (at home) telemetry

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

761

762 4.2.4.7 Implantable loop recorders

763 In a meta-analysis of five randomized controlled trials,¹⁷²⁻¹⁷⁶ 660 patients with unexplained syncope were
764 randomized to a conventional strategy consisting of an external loop recorder, tilt testing, and an
765 electrophysiological study (EPS) or to prolonged monitoring with an ILR. The results showed that
766 implantation of an ILR initially in the work-up provided a 3.7 (95% confidence interval [CI] 2.7–5.0) increased
767 relative probability of a diagnosis compared with the conventional strategy (*Web Data Supplement Table 5*).
768 ILR was more cost-effective than a conventional strategy.^{172,173,177,178}

769 In pooled data from nine studies¹⁷⁹ performed in 506 patients with unexplained syncope at the end of
770 complete negative work-up, a correlation between syncope and ECG was found in 176 patients (35%); of
771 these, 56% had asystole (or bradycardia in a few cases) at the time of the recorded event, 11% had
772 tachycardia, and 33% had no arrhythmia. Presyncope was much less likely to be associated with an
773 arrhythmia than syncope. Similar findings were subsequently observed with ILR use expanded in an early
774 phase of evaluation in patients with recurrent syncope of uncertain origin and in the absence of high-risk
775 criteria and structural heart disease^{176,180-183} and in suspected reflex syncope.¹⁸⁴⁻¹⁸⁶ In particular, an asystolic
776 pause was present during syncope in about 50% of these patients.

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

- 779 • Patients with bundle branch block (BBB) in whom paroxysmal atrioventricular (AV) block is likely despite
780 negative complete EPS: an arrhythmia was observed in 41% of these patients (being paroxysmal AV
781 block in 70%) ILR observation based on pooled data from three studies^{174,187,188} (*Web Data Supplement*
782 *Table 6*).
- 783 • Patients in whom epilepsy was suspected but the treatment has proven ineffective: in pooled data, an
784 attack could have been documented by ILR in 62% of patients, with an arrhythmic cause being
785 responsible in 26%^{137,189-191} (*Web Data Supplement Table 7*).
- 786 • 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 (*Web Data Supplement Table 8*).

- Patients with HCM, arrhythmogenic right ventricular cardiomyopathy, 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 some 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 as 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 a specific diagnosis, it allows exclusion of an arrhythmia as the mechanism of the syncope. The 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 5* and *Web Practical Instructions section 8*.

Electrocardiographic monitoring

RecommendationsRecommendations	Class ^a	Level ^b
Indications		
<i>Immediate in-hospital monitoring</i> (in bed or by telemetry) is indicated in high-risk patients (defined in <i>Table 6</i>).	I	C
<i>Holter monitoring</i> should be considered in patients who have frequent syncope or presyncope (≥ 1 episode per week). ¹⁶¹	IIa	B
<i>External loop recorders</i> 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: ILR is indicated in an early phase of evaluation in patients with recurrent syncope of uncertain origin, absence of high-risk criteria (listed in <i>Table 6</i>), and a high likelihood of recurrence within the battery life of the device. ^{175,176,181-184,202} and <i>Data Supplement Table 5</i>	I	A

ILR is indicated in patients with high-risk criteria (listed in <i>Table 6</i>) 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 and Data Supplement 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 and Data Supplement Table 7}	IIb	B
ILR may be considered in patients with unexplained falls. ^{191-194 and Data Supplement 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 seconds (with 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- <ul style="list-style-type: none"> • Be aware that the pretest 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 for up to 4 years 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) form 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,

820 thus helping to distinguish VVS from PPS. This approach revealed new pathophysiological insights in
821 syncope.⁹ Attaching the camera to the tilt table allows detailed study of the face and head, useful to assess
822 the start and the end of LOC.^{9,205} Video-recording of tilt-induced PPS¹¹⁶ ensures that apparent TLOC occurs
823 while BP and HR are not low; adding an EEG increases the diagnostic probability of PPS even further. The
824 method proved able to show the combined presence of VVS and PPS.¹¹⁷

825

826 *4.2.5.2 Home video recording*

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

834

835 **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}	Ila	C
Adding video recording to tilt testing may be considered in order to increase reliability of clinical observation of induced events. ^{9,116,117,205}	Ilb	C

836 ^a Class of recommendation.

837 ^b Level of evidence.

838

839 **4.2.6 Electrophysiological study**

840 **Indications**

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

849

850 **Diagnostic criteria**

851 *4.2.6.1 Asymptomatic sinus bradycardia – suspected sinus arrest causing syncope*

852 The pretest probability of bradycardia-related syncope is relatively high when there is asymptomatic sinus
853 bradycardia (<50 b.p.m.) or sinoatrial block, usually documented by 12-lead ECG or ECG monitoring. The
854 prognostic value of a prolonged sinus node recovery time (SNRT) is not well defined. An abnormal response

855 is defined as ≥ 1.6 or 2 seconds for SNRT or ≥ 525 ms for corrected SNRT.²¹⁰ One observational study
856 showed a relationship between the presence of prolonged SNRT at EPS and the effect of pacing on
857 symptoms.²¹¹ Another small prospective study showed that a corrected SNRT ≥ 800 ms had an eightfold
858 higher risk of syncope than a SNRT below this value.²¹²

859

860 4.2.6.2 Syncope in bifascicular bundle branch block (impending high-degree atrioventricular block)

861 Patients with bifascicular block and syncope are at higher risk of developing high-degree AV block.²¹³ A
862 prolonged H-V interval ≥ 70 ms or induction of 2nd or 3rd degree AV block by pacing or by pharmacological
863 stress (ajmaline, procainamide, or disopyramide) identifies a group at higher risk of developing AV block. By
864 combining the above-mentioned parts of the electrophysiological protocol, a positive EPS yielded a positive
865 predictive value as high as $\geq 80\%$ to identify patients who will develop AV block in old studies.²¹⁴⁻²¹⁶ This
866 finding has been indirectly confirmed by recent studies that showed a significant reduction in syncopal
867 recurrences in patients with prolonged HV implanted with a pacemaker compared with a control group of
868 untreated patients with a negative EPS¹⁸⁸ or with a control group who received an empiric pacemaker.²¹⁷
869 These results justify an upgrade of the recommendation for EPS-guided therapy (i.e. cardiac pacing) in
870 patients with a positive EPS from class IIa to class I.

871 ***Even if the quality of evidence is moderate, there is strong consensus that a positive EPS***

872 ***indicates that the likely mechanism of syncope is paroxysmal AV block.***

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

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

877

878 4.2.6.3 Suspected tachycardia

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

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

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

892

893

894

895

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, or 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 to manage induction of sustained monomorphic VT 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 to manage the induction of rapid SVT or VT, which reproduces hypotensive or spontaneous symptoms, 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		
<ul style="list-style-type: none"> • 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 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.		

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4.2.7 Endogenous adenosine and other biomarkers

Established cardiac biomarkers such as troponin and B-type natriuretic peptide have been used in distinguishing cardiac from non-cardiac syncope and in identifying 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 in the assessment of 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/ATP provocation test has been performed to demonstrate adenosine sensitivity and paroxysmal cardioinhibitory propensity for selection of appropriate pacemaker candidates.^{4,227,228} The test requires rapid (<2 seconds) injection of a 20-mg bolus of ATP/Adenosine during ECG monitoring. The induction of AV block with ventricular asystole lasting >6 seconds, or the induction of AV block lasting >10 seconds, is considered abnormal. ATP testing was positive in most patients with syncope of unknown origin (especially syncope without prodrome and without structural heart disease⁴ but not in controls, suggesting that paroxysmal AV block could be the cause of unexplained syncope. Although in elderly patients with unexplained syncope and a positive ATP test, cardiac pacing may lead to substantial reduction of syncopal attacks,²²⁹ previous studies showed no correlation between AV block induced by ATP and the electrocardiographic 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 confirming 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, aortic dissection).²³⁷⁻²³⁹ In a literature review, right and left atrial myxoma presented with syncope in less than 20% of cases.²⁴⁰⁻²⁴⁴

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4.2.8.1 Exercise stress echocardiography

Upright or semisupine exercise stress echocardiography to detect provokable 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 <i>during exercise</i> in the standing, sitting, or semi-supine position to detect provokable 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 echocardiogram shows the typical features of these conditions. ²³⁷⁻²⁴⁴	I	C
Additional advice and clinical perspectives <ul style="list-style-type: none"> For patients without suspected cardiac disease after history taking, physical examination, and electrocardiography, the echocardiogram does not provide additional useful information, suggesting that syncope alone is not an indication for echocardiography. Computed tomography or magnetic resonance imaging should be considered in selected patients presenting with syncope of suspected cardiac structural origin when echocardiography is not diagnostic. 		
HCM = hypertrophic cardiomyopathy. ^a Class of recommendation. ^b Level of evidence.		

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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 if some case reports showed 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 node²⁵³ and predicts progression to permanent AV block.^{254,255} A resting ECG frequently shows intraventricular

957 conduction abnormalities,^{253,254} but also cases with a normal resting ECG are described.^{256,257} There are no
958 data supporting an indication for exercise testing in a general population with syncope.

959

960 **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.		

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962 **4.2.10 Coronary angiography**

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

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969 **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.		

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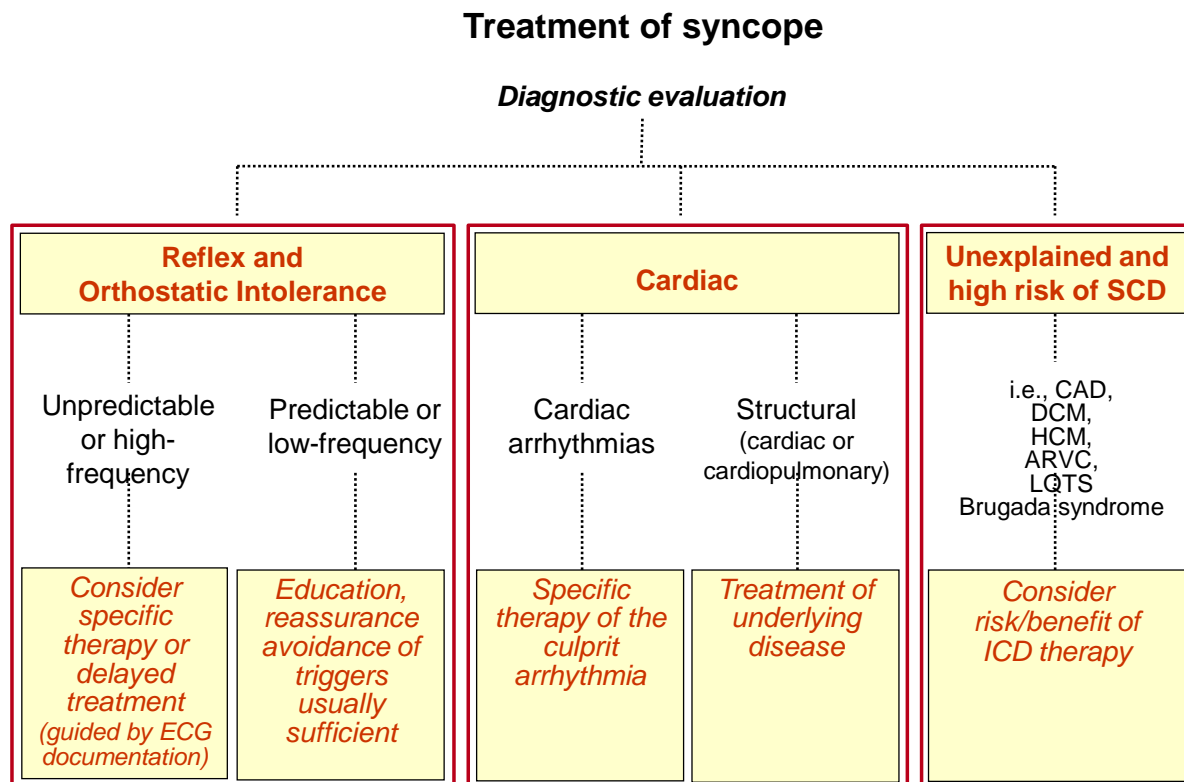
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974 **5. Treatment**

975 **5.1 General principles of treatment of syncope**

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



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

984 The following three general principles should be considered:

- 985
- 986 • The efficacy of therapy aimed at preventing syncope recurrence is largely determined by the mechanism
987 of syncope rather than its aetiology. Bradycardia is a frequent mechanism of syncope. Cardiac pacing is
988 the most powerful therapy of bradycardia but its efficacy is less if hypotension coexists (*Table 9* and *Web*
989 *Data Supplement Table 9*). The treatment of syncope due to a hypotensive reflex or to OH is more
990 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 less than 50% of patients within 1–2 years (*Web Data Supplement Table 10*). The decrease seems to be more evident when there is 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 (*Web Data Supplement 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, and makes the results of observational data on therapy questionable in the absence of a control group.

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

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5.2 Treatment of reflex syncope

Despite its benign course, recurrent and unpredictable reflex syncope may be disabling. The cornerstone of management of these patients is a 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 Instruction 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, 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*.

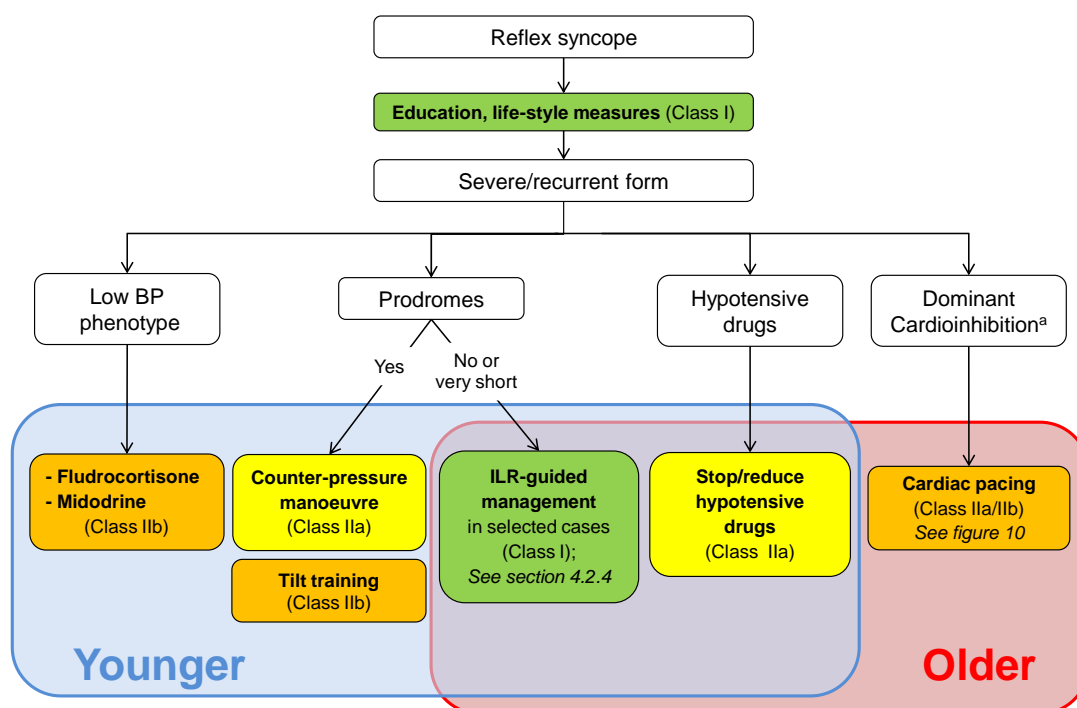


Figure 9 Schematic practical decision pathway for the first-line management of reflex syncope (based on patient's history and tests) according to age, severity of syncope, and clinical forms. *Younger patients* are those age <40 years while *older patients* are >60 years, with an overlap between 40 and 60 years. *Severity* of reflex syncope is defined in the text. The *duration* of prodrome is largely subjective and imprecise. A value of ≤5 seconds distinguishes arrhythmic from reflex syncope⁴⁹; in patients without structural heart disease, a duration >10 seconds 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 age <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 >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 younger than 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.

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 and education regarding awareness and possible avoidance of triggers and situations (dehydration, hot crowded environments), and 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, more than 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, the burden of syncope decreases even more than 70% compared with the preceding period. The effect of education and reassurance is probably the most likely reason for the decrease in syncope (*Web Data Supplement Table 10*). An example of a patient instruction sheet can be found in the *Web Practical Instructions* section 9.1: *ESC 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

Key in prevention of recurrence of syncope is careful avoidance of agents that lower BP, i.e. any antihypertensive agents, nitrates, diuretics, neuroleptic antidepressants or L-dopa antagonists. In a small randomized trial²⁶⁰ 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 twofold risk of syncope versus the control group targeting a systolic BP of 140 mmHg. In a short-term randomized trial²⁶² 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 trial¹²¹ 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

1087 Manoeuvres Trial (PC-Trial),¹²¹ 223 patients aged 38 ± 15 years with recurrent reflex syncope and
1088 recognizable prodromal symptoms were randomized to receive standardized conventional therapy alone or
1089 conventional therapy plus training in PCM. Actuarial recurrence-free survival was better in the PCM group
1090 (log-rank $P = 0.018$), resulting in a relative risk reduction of 39% (95% CI 11–53). No adverse events were
1091 reported. A limitation of this treatment is that it cannot be used in patients with short or absent prodrome and
1092 that PCM are less effective in patients older than 60 years.²⁶⁴ An instruction sheet on how to perform PCM
1093 can be found in the *Web Practical Instructions* section 9.2.

1094 ***There is moderate evidence that PCM is effective in reducing syncopal recurrences in***
1095 ***patients less than 60 years old with long-lasting recognizable prodromal symptoms.***

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1097 **5.2.4 Tilt training**

1098 In highly motivated young patients with recurrent vasovagal symptoms triggered by orthostatic stress, the
1099 prescription of progressively prolonged periods of enforced upright posture (so-called tilt training) has been
1100 proposed to reduce syncope recurrence.²⁶⁵ While some studies suggested modest benefit with outpatient tilt
1101 training,^{266,267} most controlled trials reported no significant effect.²⁶⁸⁻²⁷² Moreover, this treatment is hampered
1102 by the low compliance of patients in continuing the training programme for a long period.

1103 ***There is sufficient evidence from multiple trials that tilt training has little efficacy in reducing***
1104 ***recurrence of syncope in young patients with long-lasting recognizable prodromal symptoms.***
1105 ***Further research is unlikely to have an important impact on our confidence in the estimate.***

1106

1107 **5.2.5 Pharmacological therapy**

1108 Pharmacological therapy may be considered in patients who have recurrent syncope despite education and
1109 lifestyle modifications including training in PCM. Many drugs have been tested in the treatment of reflex
1110 syncope, for the most part with disappointing results. While results have been satisfactory in uncontrolled
1111 trials or short-term controlled trials, several long-term placebo-controlled prospective trials have not shown a
1112 benefit of the active drug over placebo, with some exceptions.

1113

1114 **5.2.5.1 Fludrocortisone**

1115 Fludrocortisone, by increasing renal sodium re-absorption and expanding plasma volume, may counteract
1116 the physiological cascade leading to the orthostatic vasovagal reflex.²⁷³ The mechanism of action can be
1117 compared with that of saline infusion, which has also proved effective in acute tilt-test studies.²⁷⁴ The
1118 Prevention of Syncope Trial (POST) 2²⁷⁵ enrolled 210 young (median age 30 years) patients with low-normal
1119 values of arterial BP and without comorbidities and randomized them to receive fludrocortisone (titrated at a
1120 dosage from 0.05 to 0.2 mg once per day) or placebo. The primary endpoint showed only a marginal non-
1121 significant reduction in syncope in the fludrocortisone group compared with the placebo group (hazard ratio
1122 0.69, 95% CI 0.46–1.03; $P = 0.069$), which became more significant when the analysis was restricted to
1123 patients who achieved 0.2 mg/day dose stabilization at 2 weeks. The clinical benefit of fludrocortisone
1124 therapy was modest: at 12 months 44% of patients in the fludrocortisone arm continued to suffer syncope, a
1125 rate only slightly lower than the 60.5% rate observed in the placebo arm. In the meantime, a similar number
1126 of patients discontinued fludrocortisone therapy owing to side-effects, thus equating the benefit/risk ratio.

1127 Fludrocortisone should not be used in patients with hypertension or heart failure. Fludrocortisone was
1128 ineffective in a small randomized double-blind trial in children.²⁷⁶

1129 ***There is moderate evidence that fludrocortisone may be effective in reducing syncopal***
1130 ***recurrences in young patients with low-normal values of arterial BP and without comorbidities.***
1131 ***Further research is likely to have an important impact on our confidence in the estimate of effect.***
1132

1133 5.2.5.2 Alpha-agonists

1134 As failure to achieve proper vasoconstriction of the peripheral vessels is common in reflex syncope, alpha-
1135 agonist vasoconstrictors (etilefrine and midodrine) have been used. Etilefrine has been studied in a large
1136 randomized placebo-controlled double-blind trial.²⁷⁷ During follow-up, patients treated twice daily with
1137 etilefrine 25 mg or placebo showed no difference in the frequency of syncope or the time to recurrence.
1138 Midodrine (usually 2.5–10 mg, three times daily) has proved effective in small studies but none satisfied the
1139 criteria of a pivotal clinical trial. A recent systematic review of these trials²⁷⁸ showed that the confidence in
1140 estimates was moderate because of imprecision and publication bias. The most frequent side-effects that led
1141 to discontinuation of midodrine were supine hypertension, pilomotor reactions, and urinary problems (urinary
1142 retention, hesitancy, or urgency). The major limitation of midodrine is frequent dosing, limiting long-term
1143 compliance. Overall, these data suggest that chronic pharmacological treatment with alpha agonists alone
1144 may be of little use in reflex syncope and long-term treatment cannot be advised for occasional symptoms.

1145 ***There are contrasting results from multiple trials that alpha-agonists may be effective in***
1146 ***reducing syncopal recurrences in patients with the orthostatic form of VVS. Further research is likely***
1147 ***to have an important impact on our confidence in the estimate.***
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1149 5.2.5.3 Beta-blockers

1150 Beta-blockers have been presumed to lessen the degree of ventricular mechanoreceptor activation owing to
1151 their negative inotropic effect in reflex syncope. This theory has not been supported by the outcome of
1152 clinical trials. Beta-blockers failed to be effective in VVS in two randomized double-blind controlled
1153 trials.^{279,280} A rationale for use of beta-blockers in other forms of neurally mediated syncope is lacking. It
1154 should be emphasized that beta-blockers may enhance bradycardia in CSS.

1155 ***There is sufficient evidence from multiple trials that beta-blockers are not appropriate in***
1156 ***reducing syncopal recurrences. Desirable and undesirable effects are closely balanced.***
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1158 5.2.5.4 Other drugs

1159 Paroxetine, a selective serotonin reuptake inhibitor, was effective in one placebo-controlled trial, which
1160 included highly symptomatic patients from one institution.²⁸¹ This finding has not been confirmed in other
1161 studies and has no experimental support. Conversely, human studies with different subtypes of serotonin-
1162 receptor antagonists demonstrated a decreased tolerance to tilt.^{1,282} In a small randomized trial,
1163 benzodiazepine was as effective as metoprolol.²⁸³ A somatostatin analogue (octreotide)²⁸⁴ was used in a few
1164 patients affected by orthostatic intolerance and its effect cannot be properly evaluated.

1166 5.2.5.5 Emerging new therapies in specific subgroups

1167 *Low adenosine phenotype.* In a series of case reports, theophylline appeared effective in patients with
1168 recurrent sudden onset (pre)syncope who presented with the common biological characteristic of low
1169 circulating adenosine levels.^{285,286} Theophylline is a non-selective adenosine receptor antagonist that is
1170 potentially effective when adenosine is suspected to be involved in the mechanism of syncope. An
1171 inpatient comparison between a period with and a period without theophylline therapy with the support of
1172 prolonged ECG monitoring showed that symptoms disappeared and the number of prolonged asystolic
1173 pauses was impressively reduced from a median of 1.11 per month during 13 months of no treatment to 0
1174 per month during 20 months of theophylline treatment.

1175 *Low norepinephrine phenotype.* A mismatch between sympathetic nerve activity and norepinephrine
1176 spill-over is present in patients with orthostatic VVS.²⁸⁷ Norepinephrine transport inhibitors (reboxetine,
1177 sibutramine) lead to a selective increase in sympathetic tone during stress by inhibiting reuptake of
1178 norepinephrine in sympathetic neuronal synapses. In double-blind, randomized, cross-over fashion,
1179 reboxetine and sibutramine block or attenuate the vasovagal reflex during tilt testing.²⁸⁸ In an open-label
1180 prospective clinical study in seven very symptomatic patients who had not responded to any previous
1181 treatment, sibutramine achieved 94% suppression of syncopal episodes at 6 months.²⁸⁹

1182 *Ganglionic plexus ablation.* Radiofrequency ablation of vagal ganglia located close to the sinus node
1183 and AV node was reported to abolish the vagal efferent output during VVS in some observational studies
1184 and case reports.^{290,291} However, owing to a weak rationale, small populations, weak documentation of
1185 follow-up results, procedural risks, and lack of control groups, the current evidence is insufficient to confirm
1186 the efficacy of vagal ganglia ablation.

1187

1188 **5.2.6 Cardiac pacing**

1189 Permanent pacemaker therapy may be effective if asystole is a dominant feature of reflex syncope.
1190 Establishing a relationship between symptoms and bradycardia should be the goal of the clinical evaluation
1191 of patients with syncope and a normal baseline ECG. The efficacy of pacing depends on the clinical setting.
1192 A comparative table of results in different settings is reported in *Web Data Supplement Table 9*.

1193 *Figure 10* summarizes the recommended indication for pacing.

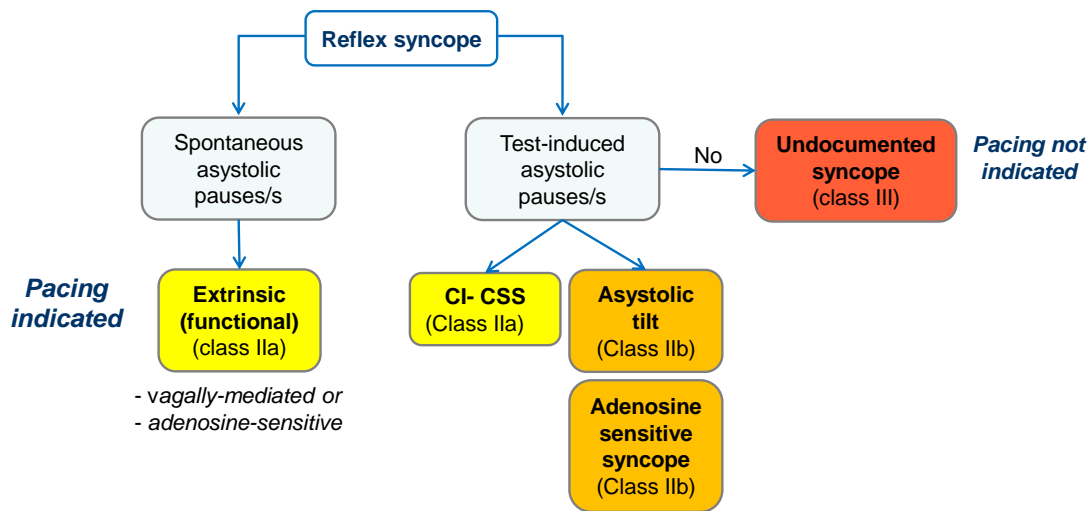


Figure 10 Summary of indications for pacing in patients with reflex syncope. CI-CSS = cardioinhibitory carotid sinus syndrome.

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 -second asystole or ≥ 6 -second 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 used in the ISSUE studies.

1215 5.2.6.2 Evidence from the trials in patients with carotid sinus syndrome

1216 The evidence supporting the benefit of cardiac pacing in patients affected by cardioinhibitory CSS is limited
1217 to a few small controlled trials and retrospective observational studies. In a review²⁹³ including 12 studies for
1218 a total of 601 paced and 305 unpaced patients, the syncopal recurrence rate during follow-up ranged from
1219 0% to 20% with pacing, whereas the recurrence of syncope was always higher in untreated patients, who
1220 showed a rate between 20% and 60%. In a meta-analysis of the three studies²⁹³ with a control group of
1221 untreated patients, syncope recurred in 9% of 85 paced patients and in 38% of 91 controls (relative risk 0.24,
1222 95% CI 0.12–0.48). In a single-centre registry of 169 consecutive patients treated with pacemakers, the
1223 actuarial estimate of syncopal recurrence was 7% at 1 year, 16% at 3 years, and 20% at 5 years.⁹⁰ In the
1224 CSS subgroup of the multicentre SUP 2 study,²⁹² the estimated syncope recurrence rates with pacing were
1225 9% at 1 year, 18% at 2 years, and 20% at 3 years, and were significantly lower than the corresponding rates
1226 observed in untreated controls, which were 21%, 33%, and 43%, respectively. Given the similar outcome of
1227 patients with reflex spontaneous asystolic pauses and those with CSS, this Task Force voted to downgrade
1228 recommendation for pacing in patients with CSS from class I of the 2103 ESC Pacing Guidelines²⁹⁴ to class
1229 IIa.

1230 ***Despite the lack of large RCTs, there is sufficient evidence that dual-chamber cardiac pacing***
1231 ***should be considered to reduce syncopal recurrences in patients affected by dominant***
1232 ***cardioinhibitory CSS.***

1233 Two variables are well-known to hamper the efficacy of pacing therapy in CSS: the mixed forms^{93,98}
1234 (see also *Web Practical Instructions* section 5) and the association with positivity of tilt testing. Patients who
1235 had positive tilt tests have a threefold greater probability of syncope recurrence after dual chamber pacing
1236 than those with negative tilt tests^{293,295}; thus, when tilt-testing is positive, caution must be recommended over
1237 pacemaker implantation.

1238
1239 5.2.6.3 Evidence from trials in patients with tilt-induced vasovagal syncope

1240 Effectiveness of pacing in patients with tilt-induced VVS has been studied in five multicentre randomized
1241 controlled trials.²⁹⁶⁻³⁰⁰ When combining the results of these trials, 318 patients were evaluated; syncope
1242 recurred in 21% of the paced patients and in 44% of unpaced patients ($P < 0.001$). A meta-analysis of all
1243 studies suggested a non-significant 17% reduction in syncope from the double-blind studies, and an 84%
1244 reduction in the studies where the control group did not receive a pacemaker.³⁰¹ In general, pacing was
1245 ineffective in trials that enrolled patients without an asystolic tilt response.^{299,300} All of these studies have
1246 limitations, and a direct comparison is somewhat difficult because of important differences in study design,
1247 largely focused on patient selection. Overall, in typical vasovagal populations, pacing seems to have
1248 marginal efficacy.

1249 The rationale for efficacy of cardiac pacing is that the cardioinhibitory reflex is dominant in some
1250 patients, as there is no role for pacing in preventing vasodilatation and hypotension. In a substudy of the
1251 ISSUE-3 trial,³⁰² an asystolic response during tilt testing predicted a similar asystolic form during
1252 spontaneous ILR-documented syncope, with a positive predictive value of 86%. In the tilt subgroup of the
1253 SUP 2 study,²⁹² among 38 patients with dominant cardioinhibitory reflex (with a mean asystolic pause of $22 \pm$
1254 16 seconds) the estimated rates of syncope recurrence with pacing were 3% at 1 year, 17% at 2 years, and
1255 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 randomized controlled cross-over trial 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 seconds 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 in common a supposed role of adenosine in the genesis of syncope.

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 and 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 trial²²⁷ 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 registry³⁰⁶ showed that dual-chamber pacing is better than the VVI 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 close-loop stimulation both in the acute setting during repeated tilt testing³⁰⁷ 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 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 diagnostic accuracy of tilt testing for syncope diagnosis, emerging evidence supports the use of tilt testing in assessing *hypotensive susceptibility* to reflex hypotension.¹³² Tilt testing 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-analysis³⁰⁹ of individual patient data from four studies performed in patients with asystolic reflex syncope documented by a ILR, the estimated 3-year recurrence rate of syncope was 2% (95% CI $\pm 4\%$) in tilt-negative patients and 33% (95% CI $\pm 20\%$) in tilt-positive patients; a positive tilt test response was the only significant predictor of syncope recurrence with a hazard ratio of 4.3. The patients with hypotensive susceptibility should need measures directed to counteract hypotensive susceptibility in addition to cardiac pacing, e.g. discontinuation/reduction of hypotensive drugs and 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

Pacing for reflex syncope: decision pathway

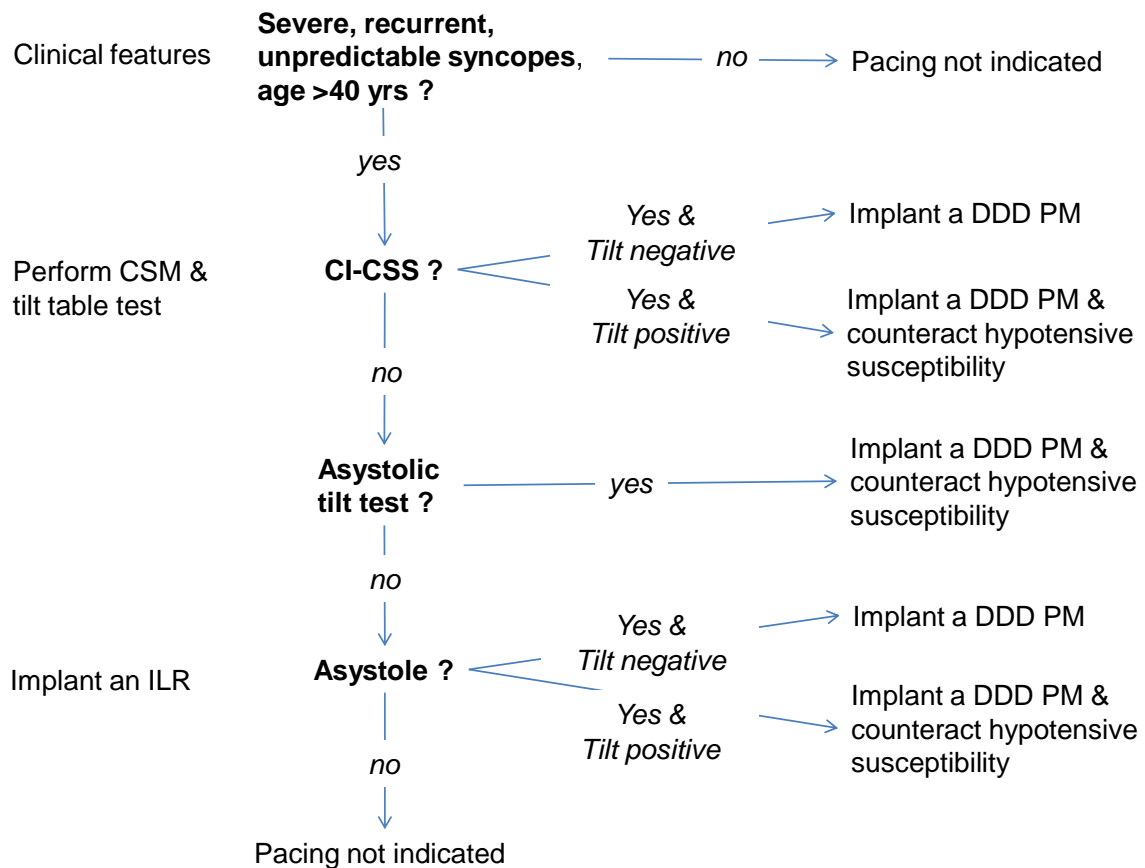


Figure 11 Decision pathway for cardiac pacing in patients with reflex syncope. CI-CSS = cardioinhibitory carotid sinus syndrome; CSM = carotid sinus massage; DDD PM = dual-chamber pacemaker; ILR = implantable loop recorder.

Treatment of reflex syncope

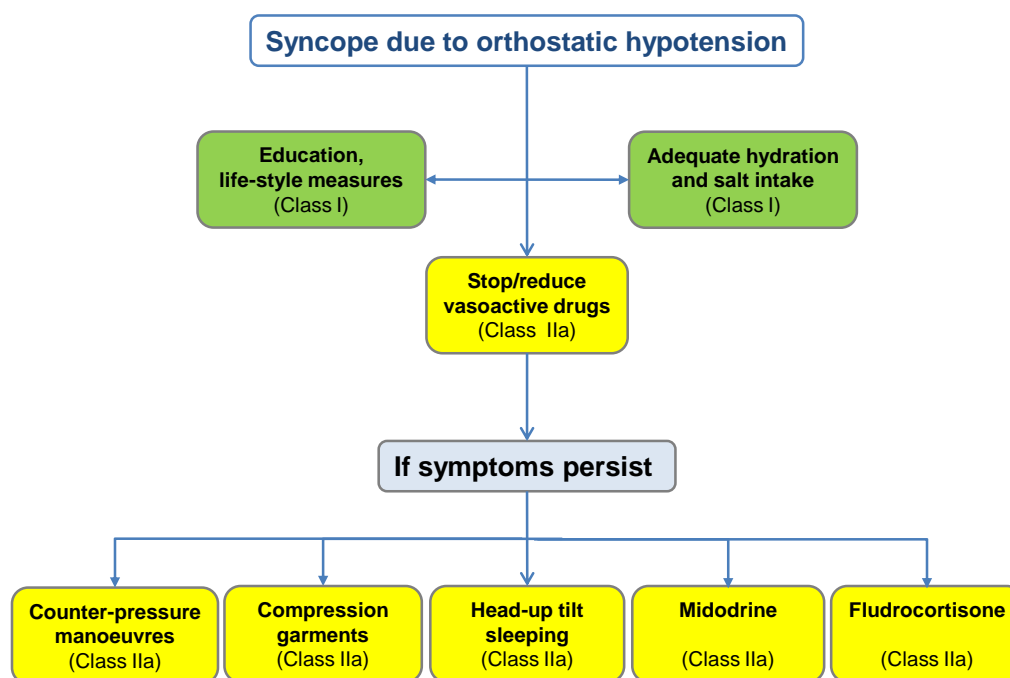
Recommendations	Class ^a	Level ^b
Education and lifestyle modifications Explanation of the diagnosis, provision of reassurance, explanation of risk of recurrence, avoidance of triggers and situations are indicated in all patients. ^{Web Data Supplement Table 10}	I	B
Discontinuation/reduction of hypotensive 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 less than 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 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 seconds or asymptomatic pause/s >6 seconds due to sinus arrest or 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 <ul style="list-style-type: none"> 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 negative tilt test will have a risk of syncope recurrence of syncope 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 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.		

1337
1338
1339
1340

5.3 Treatment of orthostatic hypotension and orthostatic intolerance syndromes

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



1341
1342 **Figure 12** Schematic practical guide for treatment of orthostatic hypotension.
1343

5.3.1 Education and lifestyle measures

1345 Education regarding the nature of the condition in conjunction with lifestyle advice outlined in section 5.2.1
1346 can markedly improve orthostatic symptoms, even though the rise in BP is relatively small (10–15 mmHg);
1347 raising standing BP to just within the autoregulatory zone can make a substantial functional difference.
1348 Ambulatory BP recordings may be helpful in identifying abnormal diurnal patterns. These recordings may
1349 also help identify supine or nocturnal hypertension in treated patients.
1350

5.3.2 Adequate hydration and salt intake

1351 Expansion of extracellular volume is an important goal. In the absence of hypertension, patients should be
1352 instructed to have a sufficient salt and water intake, targeting 2–3 litres of fluids per day and 10 grams of
1353

1354 sodium chloride.³¹⁰ Rapid ingestion of cool water is reported to be effective in combating orthostatic
1355 intolerance and postprandial hypotension.³¹¹
1356

1357 **5.3.3 Discontinuation/reduction of vasoactive drugs**

1358 Several studies that evaluated the association of vasoactive drugs (i.e. any antihypertensive agents, nitrates,
1359 diuretics, neuroleptic antidepressants or L-dopa antagonist) with OH and falls have yielded contrasting
1360 results.³¹² Intensely prescribed antihypertensive therapy, however, can increase the risk of OH. Intensive
1361 antihypertensive treatment can be defined as higher doses of antihypertensive medications, increased
1362 number of antihypertensive drugs, or lowering BP to a target <140/90 mmHg. The total number of BP-
1363 lowering medications³¹³ or the use of three or more antihypertensive drugs may be a significant predictor of
1364 OH.³¹⁴ Angiotensin-converting enzyme inhibitors, angiotensin receptors blockers, and calcium-channel
1365 blockers are less likely to be associated with OH compared with beta-blockers and thiazide diuretics.³¹⁵⁻³¹⁸

1366 ***The principal treatment strategy in drug-induced autonomic failure is eliminating the***
1367 ***offending agent. The quality of evidence is moderate. Longer-term future randomized controlled***
1368 ***studies are likely to have an important impact to determine the net risk–benefit ratio of withdrawal of***
1369 ***culprit medications.***
1370

1371 **5.3.4 Counter-pressure manoeuvres**

1372 PCM such as leg crossing and squatting should be encouraged in patients with warning symptoms who are
1373 able to perform them.³¹⁹
1374

1375 **5.3.5 Abdominal binders and/or support stockings**

1376 Gravitational venous pooling in older patients can be treated with abdominal binders or compression
1377 stockings.^{23,320,321}
1378

1379 **5.3.6 Head-up tilt sleeping**

1380 Sleeping with the head of the bed elevated (10 degrees) prevents nocturnal polyuria, maintains a more
1381 favourable distribution of body fluids, and ameliorates nocturnal hypertension.^{104,322,323}
1382

1383 **5.3.7 Midodrine**

1384 The alpha-agonist, midodrine, is a useful addition to first-line treatment in patients with chronic autonomic
1385 failure. It cannot be regarded as a cure, nor is it helpful in all affected patients but it is very useful in some.
1386 There is no doubt that midodrine increases BP both in the supine and upright posture and ameliorates the
1387 symptoms of OH. Midodrine (2.5–10 mg, three times daily) was shown to be effective in three randomized
1388 placebo-controlled trials.³²⁴⁻³²⁶

1389 ***The desirable effects of midodrine outweigh the undesirable effects. The quality of evidence***
1390 ***is moderate and further research is likely to have an important impact on the estimate of benefit.***
1391

1392 **5.3.8 Fludrocortisone**

1393 Fludrocortisone (0.1–0.3 mg once daily) is a mineralocorticoid that stimulates renal sodium retention and
1394 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, use of walking-sticks, frequent small meals, and 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 United States 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 randomized controlled trials³²⁹⁻³³² with a total of 485 patients. They showed a modest increase in standing systolic BP and symptom benefit of droxidopa over placebo regarding some items of quality of life after 2 weeks of treatment, but its benefit was lost after 8 weeks.³³³ Thus, current evidence is insufficient to confirm the efficacy of droxidopa for long-term use.

Treatment of OH

Recommendations	Class ^a	Level ^b
Explanation of the diagnosis, provision of reassurance, explanation of risk of recurrence, and 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 drugs regimen should be considered. ³¹²⁻³¹⁸	Ila	B
Isometric PCM should be considered. ³¹⁹	Ila	C
Abdominal binders and/or support stockings to reduce venous pooling should be considered. ^{23,320,321}	Ila	B
Head-up tilt sleeping (>10 degrees) to increase fluid volume should be considered. ^{104,322,323}	Ila	C
Midodrine should be considered if symptoms persist. ³²⁴⁻³²⁶	Ila	B
Fludrocortisone should be considered if symptoms persist. ^{322,327,328}	Ila	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 hypertension; PCM = physical counter-pressure manoeuvres.

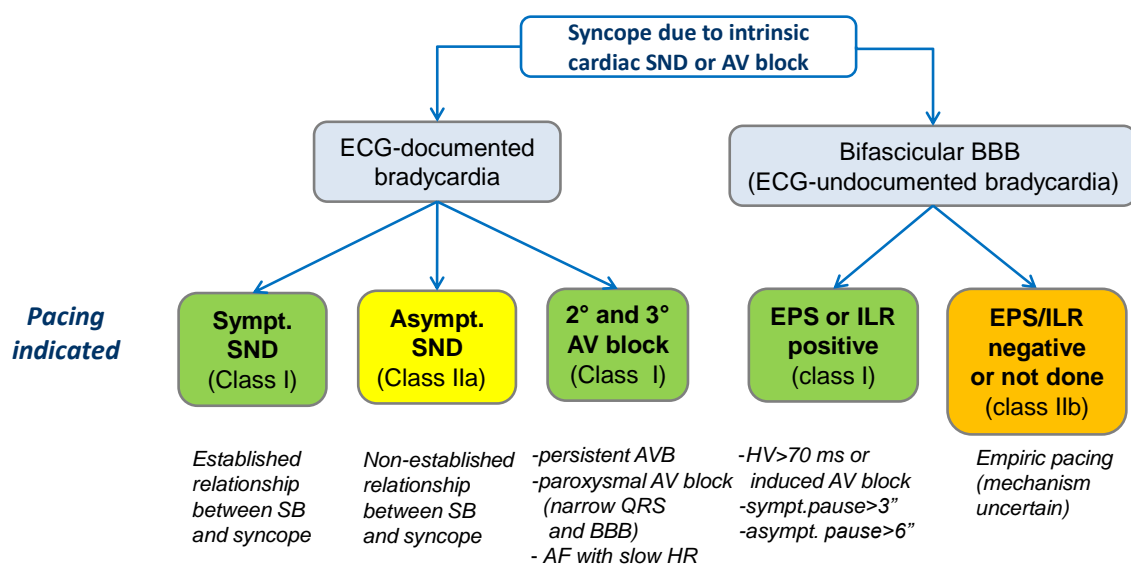
^a Class of recommendation.

^b Level of evidence.

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*.



1425 **Figure 13** Summary of indications for pacing in patients with syncope due to intrinsic cardiac bradycardia.
1426 AF = atrial fibrillation; asympt. = asymptomatic; AV = atrioventricular; BBB = bundle branch block; ECG =
1427 electrocardiogram; EPS = electrophysiological study; HR = heart rate; ILR = implantable loop recorder; SB =
1428 sinus bradycardia; SND = sinus node dysfunction; sympt. = symptomatic.

1429

1430 5.4.1.1 Sinus node disease

1431 In general, cardiac pacemaker therapy is indicated and has proved effective in intrinsic sinus node disease
1432 when intermittent sinus arrest or sinoatrial block has been demonstrated to account for syncope by means of
1433 ECG documentation during spontaneous syncope.³³⁴⁻³³⁸ A frequent situation is that of patients who have
1434 prolonged sinus pause following the termination of tachycardia in the bradycardia–tachycardia syndrome due
1435 to the abnormally prolonged time needed for recovery of automaticity by a diseased sinus node. Permanent
1436 pacing does not affect survival.

1437 ***When the correlation between symptoms and ECG is established, there is general consensus***
1438 ***that cardiac pacing is effective and useful for symptom relief.***

1439 In the absence of the above situations, despite adequate pacing, syncope recurs in approximately
1440 15–28% of patients at 5 years³³⁹⁻³⁴¹ (see *Web Data Supplement Table 9*). This is due to the frequent
1441 association of a vasodepressor reflex mechanism with sinus node disease. In patients with sinus node
1442 disease and syncope, carotid sinus hypersensitivity and a positive response to tilt are present in up to 50% of
1443 patients. Thus, an increased susceptibility to neurally mediated bradycardia/hypotension is often the cause of
1444 syncope.^{135,136} A reflex mechanism of syncope fits well with the unpredictable natural history of syncope
1445 recurrence. Physicians should be aware that effectiveness of therapy is not well documented in such cases.
1446 From a practical perspective, cardiac pacing may be a reasonable solution in patients affected by sinus node
1447 disease, who have the documentation of an asymptomatic ventricular pause >3 seconds (with exceptions for
1448 young trained persons, during sleep and medicated patients), when a competitive diagnosis, i.e.
1449 hypotension, can be ruled out.²⁹⁴ An abnormal SNRT enhances the probability of efficacy of cardiac pacing
1450 (see section 4.2.6.1).²¹⁰⁻²¹²

1451 ***When the correlation between symptoms and ECG is not established, cardiac pacing may be***
1452 ***reasonable in patients with intrinsic sinus node disease, syncope, and documentation of***
1453 ***asymptomatic pause/s.***

1454 Elimination of drugs that may exacerbate or unmask an underlying susceptibility to bradycardia is an
1455 important element in preventing syncope recurrence. Percutaneous cardiac ablative techniques for control of
1456 atrial tachyarrhythmia have become of increasing importance in selected patients with the
1457 bradycardia–tachycardia form of sick sinus syndrome, but are infrequently used primarily for prevention of
1458 syncope.

1459

1460 5.4.1.2 Atrioventricular conduction system disease

1461 Cardiac pacing is the treatment of syncope associated with symptomatic AV block (*Figure 13*). Although
1462 formal randomized controlled trials of pacing in third- or second-degree type 2 AV block have not been
1463 performed, some observational studies suggest that pacing is highly effective in preventing syncope
1464 recurrences when AV block is documented. Langenfeld *et al*³⁴¹ observed a decline in the rate of syncope
1465 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 persistent or intermittent documented AV block (see *Web Data Supplement Table 9*).

1470

1471 5.4.1.3 Bundle branch block and unexplained syncope

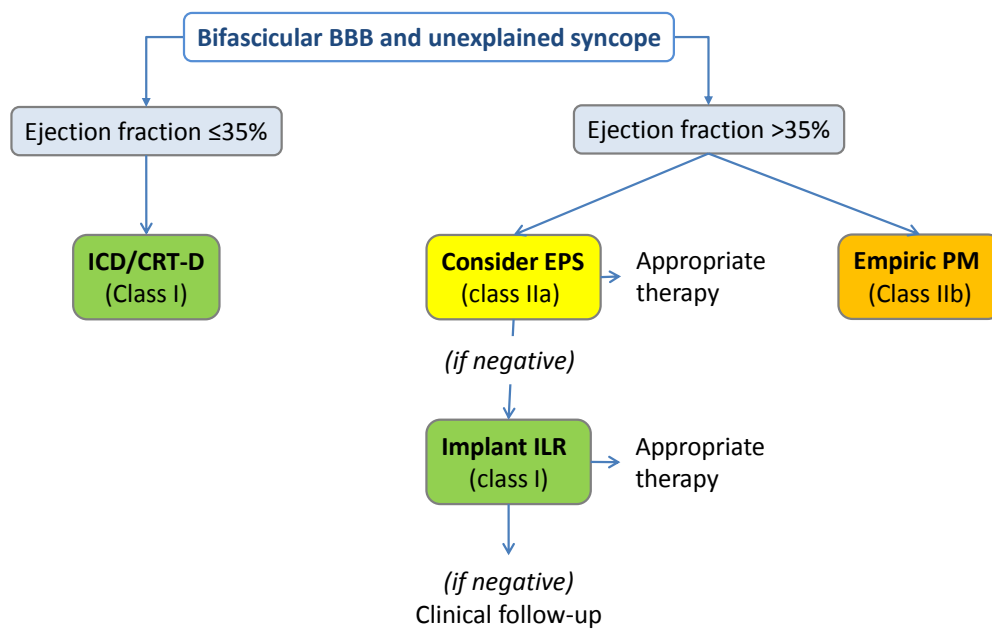
1472 The presence of bifascicular BBB suggests that the cause of syncope may be complete heart block.
1473 Nevertheless, less than half of the patients with bifascicular BBB and syncope will have a final diagnosis of
1474 AV block, a similar percentage will have a final diagnosis of reflex syncope, and, in approximately 15%, the
1475 cause will remain unexplained at the end of a complete work-up.³⁴² In addition, among patients receiving an
1476 ILR, approximately half remained free of syncope for >2 years after the implantation.^{187,188,342,343} Conversely,
1477 implantation of a pacemaker without documentation of AV block (empirical pacing) exposed patients to the
1478 risk of recurrence of syncope in about one-quarter of cases during long-term follow-up and was unnecessary
1479 in another half.^{217,344} Thus, only one in four pacemakers will finally be appropriate. Finally, pacemaker
1480 treatment has not proven to have survival benefit. The above considerations justify a class IIb indication in
1481 the ESC guidelines on pacing.²⁹⁴

1482 To overcome the above problems, ESC guidelines on pacing²⁹⁴ recommend – in patients with LVEF
1483 >35% – a strategy of EPS followed by ILR if the EPS findings are unremarkable. With this strategy, a
1484 pacemaker was implanted in approximately half of the patients and these patients had syncope recurrence
1485 after pacemaker implantation in 0% to 7% of cases^{188,217}; this strategy was safe. However, this Task Force
1486 recognizes that in the “real world”, an empiric pacemaker may be acceptable in selected patients at high risk
1487 of traumatic recurrence (e.g. elderly patients with unpredictable syncopes) and that an individual risk–benefit
1488 evaluation is warranted (*Figure 14*).

1489 ***Even if the quality of evidence is moderate, there is strong consensus that in patients with***
1490 ***bifascicular BBB with a positive EPS or documentation of paroxysmal AV block during prolonged***
1491 ***ECG monitoring, cardiac pacing is highly effective in preventing syncope recurrence. The evidence***
1492 ***of efficacy of empirical pacing strategy is weak and the estimate of benefit uncertain.***

1493 Although syncope is not associated with an increased incidence of sudden death in patients with
1494 preserved cardiac function, a high incidence of total deaths (about one-third sudden) was observed in
1495 patients with BBB and heart failure, previous myocardial infarction, or low ejection fraction.³⁴⁵⁻³⁴⁷ Indeed, the
1496 high total- and sudden mortality seems mainly related to underlying structural heart disease and ventricular
1497 tachyarrhythmias. In this latter situation, syncope is a risk factor rather than the cause of death.²¹⁸
1498 Unfortunately, ventricular programmed stimulation does not seem to correctly identify these patients and the
1499 finding of inducible ventricular arrhythmia (VA) should therefore be interpreted with caution.^{345,346} Therefore,
1500 an implantable cardioverter defibrillator (ICD) or a cardiac resynchronization therapy defibrillator is indicated
1501 in patients with BBB, congestive heart failure, or previous myocardial infarction and depressed systolic
1502 function for prevention of SCD, but may be unable to prevent recurrence of syncope, which is often due to
1503 non-arrhythmic causes such as OH or vasodepressor reflex. The strategy of management of patients with
1504 unexplained syncope and BBB is summarized in the *Figure 14*.

1505



1506
1507

1508 **Figure 14** Therapeutic algorithm for patients presenting with unexplained syncope and BBB. BBB = bundle
1509 branch block; CRT-D = cardiac resynchronization therapy defibrillator; EPS = electrophysiological study; ICD
1510 = implantable cardioverter defibrillator; ILR = implantable loop recorder; PM = pacemaker.

1511

1512 5.4.2 Syncope due to intrinsic cardiac tachyarrhythmias

1513 Current management strategies in patients with syncope due to intrinsic cardiac tachyarrhythmia are
1514 summarized in *Figure 15*.

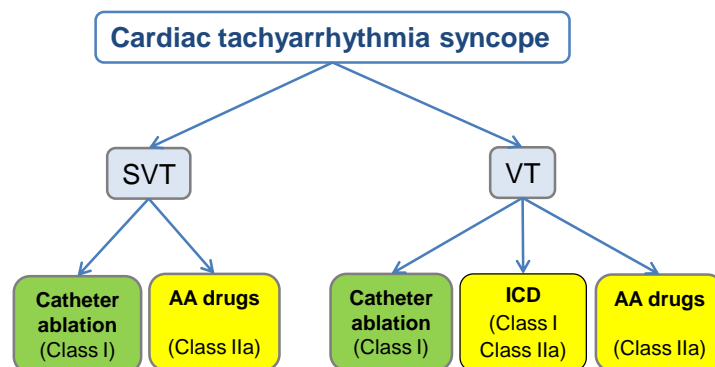


Figure 15 Choice of therapy for patients presenting with syncope due to cardiac tachyarrhythmias as the primary cause. AA = antiarrhythmic; ICD = implantable cardioverter defibrillator; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

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 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 are recommended in patients with syncope due to VT in presence or absence of structural heart disease in order to prevent syncope recurrence (*Figure 15*). A detailed guideline to antiarrhythmic drug usage in patients with VT can be found in 2015 ESC guidelines for VA and prevention of SCD.⁴⁶

1534 An ICD is indicated in patients with syncope and depressed cardiac function, and VT or VF without
 1535 correctable cause. Although in these patients ICD may not prevent syncope recurrence,^{31,348} it is indicated
 1536 to reduce the risk of SCD (refer to 2015 ESC guidelines for VA and prevention of SCD⁴⁶). An ICD is also
 1537 indicated in patients with syncope and previous myocardial infarction who have VT induced during EPS³⁴⁶
 1538 (see section 4.2.6).

1539 In patients with preserved systolic function, the indication for ICD is weaker because trials have not
 1540 addressed this specific issue. However, when VT causes syncope, this Task Force believes that an ICD is
 1541 warranted if catheter ablation and pharmacological therapy has failed or could not be performed (*Figure 15*).

1542

1543

1544 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 correlation between symptoms and ECG.	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 ejection fraction $\leq 35\%$. 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 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 <ul style="list-style-type: none"> The major factors predicting efficacy of pacing in preventing syncope recurrence are an established relationship between symptoms and bradycardia and the absence of associated hypotensive susceptibility (<i>Table 8</i> and <i>Web Data Supplement Table 9</i>). 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 any useful investigation (e.g. CSM, EPS, 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 work-up 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 induction of VT during EPS), catheter ablation should be always attempted when feasible in addition to ICD implantation. <p>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.</p> <p>^a Class of recommendation.</p> <p>^b Level of evidence.</p>		

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, tumours, 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 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 had not yet been documented because of its 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 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 2- to 4-fold increased risk of death^{348,350-353} but varies between specific conditions.³⁵⁴⁻³⁵⁶ Moreover, there are very few studies on ICDs in patients with syncope associated with left ventricular dysfunction,^{31,348} cardiomyopathy, or inheritable arrhythmia syndromes.³⁵⁷ In this guideline, we complement previous ESC guidelines for VA and prevention of SCD⁴⁶ 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 guidelines⁴⁶ 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 work-up. While this strategy may help to prolong life, patients often remain at risk of recurrent syncope, implying the 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 less severe systolic impairment who do not meet the current indication for ICD.³⁵⁸ Data from the 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 the lack of control group, are unable to show a 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.

1599 **ICD 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 for at least 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 <ul style="list-style-type: none">• 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.		

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1603 **5.6.3 Hypertrophic cardiomyopathy**

1604 Unexplained syncope is an independent predictor for SCD and appropriate ICD discharge. In a systematic
1605 review, the average hazard ratio of unexplained syncope (irrespective of definition) was 2.68 (95% CI 0.97–
1606 4.38).³⁶¹ In the largest multicentre study to date (>3600 patients with HCM), syncope was an independent
1607 predictor of the composite of SCD and ICD discharge (hazard ratio 2.05, 95% CI 1.48–2.82).³⁵⁰ A
1608 prophylactic ICD is appropriate in individuals with other features indicative of a high risk of SCD that are
1609 used to estimate the 5-year risk of SCD using the HCM Risk-SCD model²⁴⁵; they include: age, family history
1610 of SCD, maximum left ventricular wall thickness, left atrial diameter, and non-sustained VT.

1611

1612 **ICD indications in patients with unexplained syncope^a and HCM**

Recommendations	Class ^b	Level ^c
It is recommended that the decision for ICD implantation in patients with unexplained syncope ^a is 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 in: http://www.doc2do.com/hcm/webHCM.html		

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 arrhythmogenic right ventricular cardiomyopathy.^{46,351,362,363} The decision to implant an ICD should take into account the other known risk factors for arrhythmic events⁴⁶: frequent non-sustained VT; family history of premature sudden death; extensive right ventricular disease; marked QRS prolongation; late gadolinium enhancement on magnetic resonance imaging (including left ventricular involvement); left ventricular dysfunction; and VT induction during EPS.⁴⁶

ICD indications in patients with unexplained syncope^a and ARVC

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 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 case 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

ICD indications in patients with unexplained syncope^a and LQTS

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: (a) beta-blockers are not effective, not tolerated, or are contraindicated; (b) ICD therapy is contraindicated or refused; or (c) 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 LQTS-3 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.		

5.6.5.2 Brugada syndrome

1637 A history of syncope may increase the risk of arrhythmic events up to two- to threefold compared with that in
 1638 asymptomatic patients. In the FINGER registry (1029 patients), the incidence of arrhythmic events (sustained
 1639 VT or VF, appropriate ICD therapy, or sudden death) in patients with Brugada syndrome was 7.7% per year
 1640 in those with a history of sudden cardiac arrest, 1.9% per year with syncope, and 0.5% per year in
 1641 asymptomatic patients.³⁵³ However, in a second study, the rate of appropriate ICD shocks was similar in
 1642 asymptomatic patients and in those with syncope – a difference possibly explained by patient selection and a
 1643 high rate of non-arrhythmic syncope.³⁵⁵

1644 On balance, this Task Force believes that it is reasonable to consider an ICD in the case of
 1645 unexplained syncope. New studies^{356,365} published after the 2015 ESC guidelines for VA and prevention of
 1646 SCD⁴⁶ showed that non-arrhythmic syncope is frequent in Brugada syndrome and appears to be more
 1647 benign; thus, ICD should be avoided in patients with non-arrhythmic syncope that is established according to
 1648 the definition reported in this section. ILR is increasingly used in doubtful cases to exclude a VA as the cause
 1649 of syncope.^{365,366}

1650 The final decision to implant an ICD in patients with Brugada syndrome and unexplained syncope
 1651 should also take into account other risk factors for arrhythmic events including spontaneous type I Brugada
 1652 ECG pattern, family history of sudden death, VF inducibility with 1 or 2 ventricular premature beats during
 1653 EPS, fractionated QRS, early repolarization in the peripheral leads, increased $T_{peak}-T_{end}$ interval, and long PR
 1654 interval.^{220,367-371} A drug-induced type I ECG pattern has a lower risk of sudden death than a spontaneous
 1655 type 1 response.

1657 ICD 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 I 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.		

1658 1659 5.6.5.3 Other forms

1660 Lacking studies examining unexplained syncope, in other forms of inheritable arrhythmic diseases such as
 1661 catecholaminergic polymorphic VT, early repolarization syndrome, and short QT syndrome, this Task Force
 1662 is unable to give specific recommendations for investigation and treatment of unexplained syncope. For
 1663 further information refer to the 2015 ESC guidelines for VA and prevention of SCD.⁴⁶

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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 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 fibrillation³⁷⁷ may not necessarily be the attributable cause of events.³⁷⁸⁻³⁸⁰

Prescription of polypharmacy, cardiovascular medications, and psychotropic (neuroleptics, antidepressants) and dopaminergic drugs also increase the risk of syncope and falls.³⁸¹⁻³⁸⁵ Conversely, discontinuation or reduction of the 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 not be witnessed in over half of older patients and therefore a collateral history is not available, making 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.

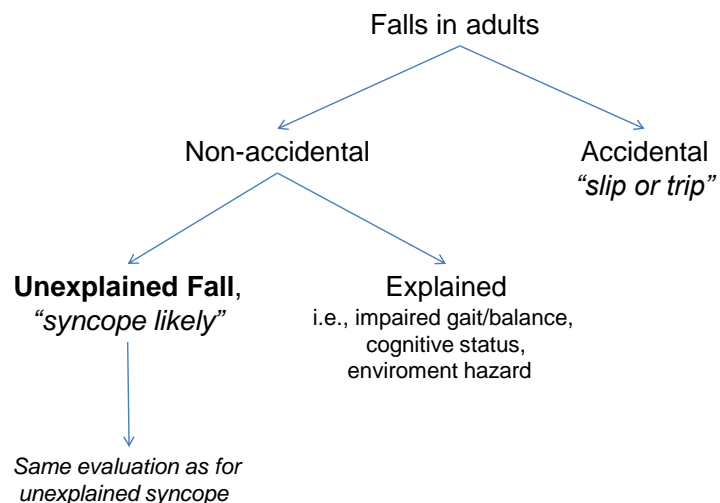


Figure 16 Flow diagram for identifying unexplained falls.

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 lack of 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, polyneuropathies, etc.), are recommended.

Despite the lack of large controlled trials and an overall modest quality of studies, there is strong consensus that 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
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
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}	Ila	B
In patients with unexplained fall, the same assessment as for unexplained syncope should be considered. ^{191,194,387-390}	Ila	C
Additional advice and clinical perspectives <ul style="list-style-type: none"> In some frail elderly patients, the rigour of assessment will depend on compliance with tests and on prognosis. Otherwise, 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 over 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. <p>BP = blood pressure; CSM = carotid sinus massage; TIA = transient ischaemic attack; TLOC = transient loss of consciousness.</p> <p>^a Class of recommendation.</p> <p>^b Level of evidence.</p>		

6.2 Syncope in paediatric patients

6.2.1 Diagnostic evaluation

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

Two specific conditions³⁹⁹ 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 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 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 minutes at 60 or 70 degrees was used and showed a specificity >85%.⁴⁰¹

1733 In young patients, syncope can rarely be the initial manifestation of unusual but life-threatening
1734 conditions such as LQTS, Kearns-Sayre syndrome (external ophthalmoplegia and progressive heart block),
1735 Brugada syndrome, catecholaminergic polymorphic VT, Wolff–Parkinson–White syndrome, right ventricular
1736 arrhythmogenic cardiomyopathy, HCM, pulmonary arterial hypertension, myocarditis, arrhythmia after
1737 repaired congenital heart disease, and anomalous origin of a coronary artery.

1738 Some aspects of the history can suggest a cardiac origin, and should prompt cardiac evaluation:

- 1739 • Family history: premature SCD at age <40 years; familial heart disease;
- 1740 • Known or suspected heart disease;
- 1741 • Event triggers: loud noise, fright, extreme emotional stress;
- 1742 • Syncope during exercise, including swimming;
- 1743 • Syncope without prodromes, while supine or sleeping, or preceded by chest pain or palpitations.

1744

1745 6.2.2. Therapy

1746 The therapeutic approach is the same as in adults. However, it should be stressed that the effectiveness of
1747 pharmacological agents and tilt training for recurrent reflex syncope is undetermined in the absence of well-
1748 designed paediatric trials. Furthermore, even in the presence of VVS with prolonged asystole, pacemakers
1749 should be avoided due to the relatively transient and benign nature of the syndrome.⁴⁰²

1750 In summary, the key points for the evaluation of syncope in paediatrics are as follows:

- 1751 • Syncope in childhood is common, the majority being of reflex origin, with only a minority having a
1752 potentially life-threatening cause;
- 1753 • Discriminating benign from serious causes is made primarily by history, physical examination, and ECG
1754 results;
- 1755 • Children with a history suggesting VVS, a normal ECG, and no family history of arrhythmia should not
1756 undergo further cardiac investigations.
- 1757 • The cornerstone of therapy for young patients with reflex syncope includes education and reassurance.

1758

1759 7. Psychogenic transient loss of consciousness and its evaluation

1760 In psychogenic TLOC there is no gross somatic brain dysfunction, but the attacks fulfil the criteria for TLOC
1761 (see section 3.1). There are two types: PPS and PNES. In PPS movements are absent, so PPS resembles
1762 syncope or longer-lasting LOC, whereas in PNES impressive limb movements mean the attacks resemble
1763 epileptic seizures. PPS and PNES differ pathophysiologically from the TLOC forms they resemble: in PPS,
1764 BP and HR are normal or high rather than low, and the EEG is normal instead of showing the slowing or
1765 flattening typical of syncope; in contrast to epileptic seizures, the EEG in PNES shows no epileptiform brain
1766 activity during an attack.^{9,116}

1767 The frequency of PPS and PNES probably depends on the setting. The rate of PPS varies from 1%
1768 of patients referred to general syncope clinics⁹⁴ to 8% of patients referred to specialist neurological clinics¹¹⁶
1769 but PPS is probably insufficiently recognized.¹⁵⁴

1770

1771 7.1 Diagnosis

1772 7.1.1 Historical criteria for attacks

1773 The presence of a psychological trauma is not a prerequisite for a diagnosis of conversion (Diagnostic and
1774 Statistical Manual of Mental Disorders, Fifth Edition). The diagnosis of PPS rests on positive clues taken
1775 from the history and from documenting normal EEG results, HR, or BP during an attack. History taking in
1776 PPS usually reveals a combination of the following features^{116,154,403}:

- 1777 1. In most cases, the duration of PPS is as short as that in syncope, but a much longer duration is a
1778 useful diagnostic finding: patients may lie immobile on the floor for 15 to 30 minutes.
- 1779 2. The eyes are usually open in epileptic seizures and syncope but are usually closed in psychogenic
1780 TLOC.
- 1781 3. The attack frequency is high, with several attacks occurring over a week or in a day.
- 1782 4. There is usually no recognisable trigger, and no sweating, pallor, or nausea beforehand.
- 1783 5. Injury does not exclude PNES or PPS.

1784 These features should occur together in most attacks. The presence of another pattern of features
1785 suggesting a true syncope type, usually VVS, does not argue against a diagnosis of PPS.

1786

1787 **7.1.2 Documentation of key features during an attack**

1788 The following features are relevant during an attack:

- 1789 • Video recording or clinical observation, including provocation of an attack during tilt testing. Primary
1790 features: sleep-like body position with closed eyes and lack of response to speech or touch, if tested.
1791 Secondary features: subtle signs incompatible with LOC such as eyelid flicker, eyeball movements,
1792 swallowing, intact muscle tone, normal movements absent in true unconsciousness, and resistance to
1793 eye opening.
- 1794 • BP: normal or elevated during TLOC.
- 1795 • EEG: normal waking eye-closed EEG pattern, i.e. usually with alpha activity, during TLOC.

1796 The gold standard for PPS is documenting an attack with home video or with a tilt testing during which BP,
1797 HR and EEG are normal.^{116,204,404} The gold standard for PNES is documenting an attack with video-EEG
1798 monitoring.^{204,404}

1799

1800 *7.1.2.1 Management of psychogenic pseudosyncope*

1801 Announcing a psychological diagnosis to patients may be considered difficult, but is necessary for reasons of
1802 honesty and as the first step of treatment.⁴⁰⁴ It should be done by the somatic specialist who diagnoses
1803 PPS.^{116,404} Important aspects are to assure patients that they are taken seriously and that attacks are as
1804 involuntary as syncope or an epileptic seizure. Acceptance of the diagnosis by patients may be critical for
1805 therapy. In one observational study,⁴⁰⁵ communicating and explaining the diagnosis resulted in an immediate
1806 reduction of attack frequency with 39% of patients being asymptomatic during a mean follow-up period of 4
1807 years. Some advice on how to inform the patient is provided in the *Web Practical Instructions section 10:*
1808 *ESC information sheet for patients affected by PPS.*

1809 Cognitive behavioural therapy is the usual treatment of PNES and PPS, if attacks remain present
1810 after explanation. One pilot randomized treatment trial, conducted in PNES,⁴⁰⁶ showed that psychological
1811 therapy provided more attack reduction than no treatment or treatment with sertraline. There are no trials on
1812 PPS.

1813

1814 **Diagnosis and management of PPS**

Recommendations	Class ^a	Level ^b
Diagnosis		
Recording of spontaneous attacks with a video by eyewitness should be considered for diagnosis of PPS. ^{116,154}	Ila	C
Tilt testing, preferably with concurrent EEG recording and video monitoring may be considered for diagnosis of PPS. ^{116,403,407}	Ilb	C
Management		
Doctors who diagnose PPS should present the diagnosis of PPS to the patients. ^{116,404}	Ila	C
Cognitive behavioural therapy may be considered in the treatment of PPS if attacks persist after explanation.	Ilb	C

1815 EEG = electroencephalogram; PPS = psychogenic pseudosyncope.

1816 ^a Class of recommendation.

1817 ^b Level of evidence.

1818

1819 **8. Neurological causes and mimics of syncope**

1820 This section discusses neurological disorders causing syncope or resembling it, and tests to be performed in
1821 patients with syncope.

1822

1823 **8.1 Clinical conditions**

1824 **8.1.1. Autonomic failure**

1825 Neurological evaluation should be considered in OH due to autonomic failure. Warning signs are early
1826 impotence, disturbed micturition, hyposmia, rapid-eye movement-sleep behaviour disorders,^{408,409}

1827 Parkinsonism, ataxia, cognitive impairment, and sensory deficits. A multidisciplinary approach may be
1828 required in secondary autonomic failure and in drug-induced OH, depending on the underlying disease.

1829

1830 **8.1.2 Epilepsy and ictal asystole**

1831 *Table 10* provides a number of clues that aid differentiation of syncope from epileptic seizures.^{9,50,410,411}

1832 Epilepsy and syncope may evoke one another on rare occasions, resulting in epileptic seizures
1833 triggering syncope as well as syncope triggering an epileptic seizure. The first form concerns *ictal asystole*.
1834 Whereas approximately 90% of all epileptic seizures are accompanied by tachycardia, ictal bradycardia and
1835 asystole occur in 0.3–0.5% of seizures.^{412,413} Bradycardia precedes asystole and AV block may occur,
1836 resembling the ECG pattern of reflex syncope.^{412,414} Epileptic asystole occurs during partial complex
1837 seizures, not during generalized seizures. Epileptic asystole occurs in only a fraction of the seizures of one
1838 person, and then occurs after a variable interval of 5–100 seconds from seizure onset.^{415,416} If asystole lasts
1839 for more than about 8 seconds, syncope ensues.⁴¹⁶ A typical history is for a partial complex seizure to
1840 progress as usual for that patient, and then the patient suddenly falls flaccidly, with or without brief myoclonic
1841 jerking.^{416,417} Ictal bradycardia, asystole, and ictal AV block are likely self-terminating,⁴¹² and are due to vagal
1842 activation brought about by the seizure. Cessation of cortical activity due to syncopal cerebral hypoperfusion

will end the seizure. Therapy requires antiepileptic 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.

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 <i>déjà vu</i> . Rising sensation in the abdomen (epigastric aura) and/or an unusual unpleasant smell
Detailed characteristics of myoclonus	<ul style="list-style-type: none"> • <10, irregular in amplitude, asynchronous, asymmetrical; • Starts after the onset of LOC 	<ul style="list-style-type: none"> • 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.		

8.1.3 Cerebrovascular disorders

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

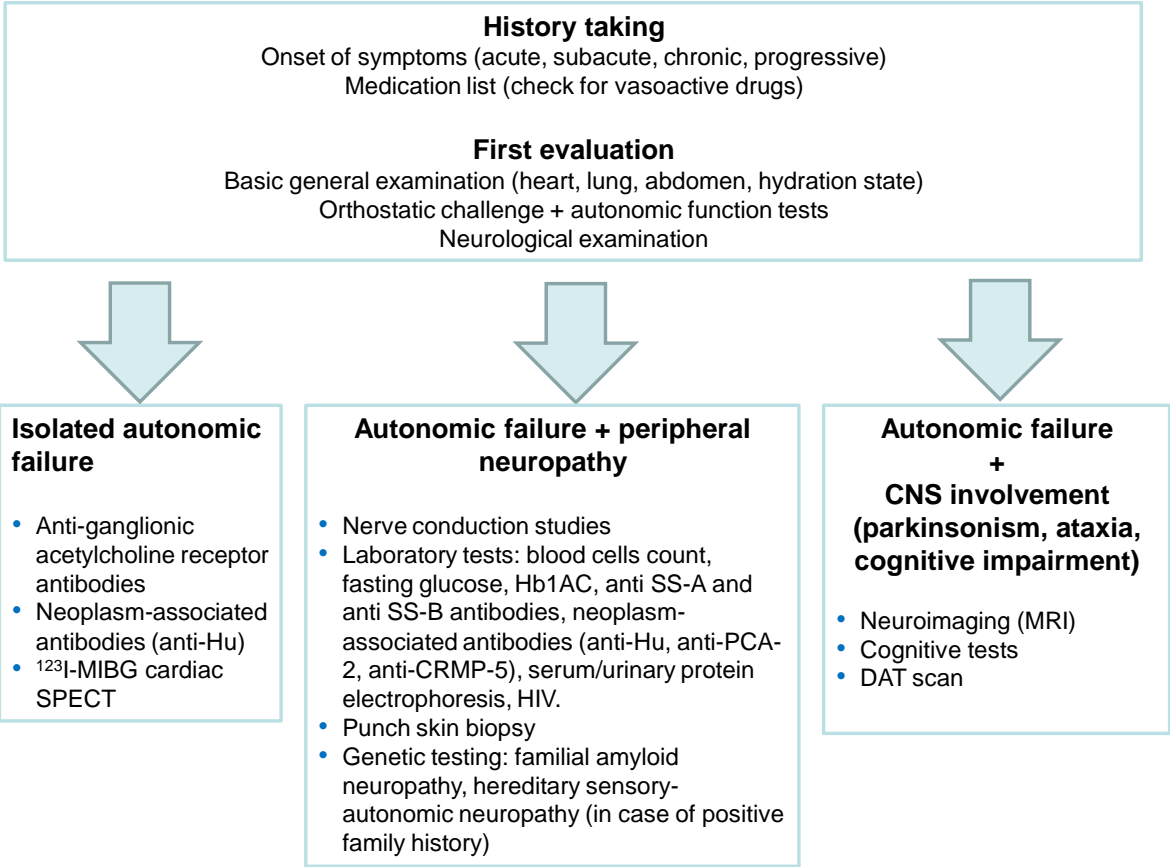
1889 **Neurological evaluation**

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.		

1890

1891 **8.2 Neurological tests**

1892 A schematic comprehensive figure of neurological tests used for autonomic failure is shown in *Figure 17*.



1893

1894 **Figure 17** Diagnostic work-up of cardiovascular autonomic failure (adapted from Fanciulli *et al*⁴²⁹). ¹²³I-MIBG
1895 = ¹²³I-metaiodobenzylguanidine; CNS = central nervous system; CRMP-5 = collapsin response mediator
1896 protein 5; DAT = dopamine active transporter; HbA1c = haemoglobin A1c; HIV = human immunodeficiency
1897 virus; MRI = magnetic resonance imaging; PCA-2 = Purkinje cell cytoplasmic autoantibody type 2; SPECT =
1898 single-photon emission computed tomography; SS-A = Sjogren's syndrome-associated antigen A; SS-B =
1899 Sjogren's syndrome-associated antigen B.

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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 magnetic resonance imaging in uncomplicated syncope should be avoided. Magnetic resonance imaging is recommended if neurological examination points out Parkinsonism, ataxia, or cognitive impairment. In case of contraindication for magnetic resonance imaging, 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 an autoimmune cause. Screening for specific paraneoplastic antibodies is recommended: the most common paraneoplastic antibodies are anti-Hu, 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 receptors antibodies is the serological hallmark of autoimmune autonomic ganglionopathy.^{433,434}

Neurological tests

Recommendations	Class ^a	Level ^b
Brain magnetic resonance imaging 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. ^a Class of recommendation. ^b Level of evidence.		

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9. Organizational aspects

9.1 Syncope (transient loss of consciousness) management unit

Since publication of the 2009 ECS guidelines, the European Heart Rhythm Association (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 interested in establishing a syncope unit in their hospital so that they can meet the standards proposed by ESC, EHRA, and Heart Rhythm Society. The following is the context and evidence for recommendations regarding syncope units (*Table 11*).

Table 11 Key components of a syncope unit

<ul style="list-style-type: none">• The syncope unit should take the lead in service delivery for syncope, and in education and training of healthcare professionals who encounter syncope.
<ul style="list-style-type: none">• 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.
<ul style="list-style-type: none">• 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.
<ul style="list-style-type: none">• 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.
<ul style="list-style-type: none">• Syncope units should employ quality indicators, process indicators, and desirable outcome targets.

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

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-

1953 up, and better education and training of stakeholders. Further research is likely to have an important impact
 1954 on our confidence in the estimate of effect.

1955

1956 **9.1.4 Model of a syncope unit**

1957 The syncope unit should provide minimum core treatments for reflex syncope and OH, and treatments or
 1958 preferential access for cardiac syncope, falls, psychogenic syncope, and epilepsy (*Table 12*). The tests and
 1959 assessments available in the syncope unit are detailed in *Table 13*.

1960

1961 **Table 12 Structure of the syncope unit**

<p>Staffing of a syncope unit is composed of:</p> <ol style="list-style-type: none"> 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 <i>Table 14</i>). 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.
<p>Facility, protocol, and equipment</p> <ol style="list-style-type: none"> 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: <ul style="list-style-type: none"> - 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: <ul style="list-style-type: none"> - 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 upon 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 stands.

9.1.5 Access and referrals to 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 rate, 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 Force⁶³ has developed the following preliminary quality indicators, based on consensus, as 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 advocate, education and training, audit, and research and inter- and intradisciplinary consultations.

9.2.2 Role and skills of 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, external loop recorder), ABPM, ILR monitoring, and subsequent triaging of patient and monitoring response 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 of external and internal loop and Holter monitors and ABPM⁶³ (Table 14).

2006 **Table 14** The role of physician 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	
<p>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.</p> <p>^a Physician need not be in the room, but a physician adequately trained in resuscitation needs to be in the vicinity of the test.</p> <p>^b Current practice limited to a few countries.</p> <p>^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.</p>			

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The clinical nurse specialist should be key in developing and delivering communication strategies and process for the syncope unit for all stakeholders – patients and practitioners – and play a pivotal role in

2011 education and training together with the syncope specialist. The clinical nurse specialist should be involved
2012 in regular audit and collection of data to inform quality indicators. See the video in *Web Practical Instructions*
2013 *section 11*.

2014 ***Although the skill mix of a clinical nurse specialist has not been exposed to rigorous***
2015 ***scientific or economic scrutiny, the consensus is that the clinical nurse specialist should have the***
2016 ***necessary skills to deliver assessment and treatment for syncope and TLOC. Further research is***
2017 ***required to establish the benefits.***

2018

2019 **10. Key messages**

2020 The ESC Task Force has selected 19 simple rules to guide the diagnosis and management of syncope
2021 patients with TLOC according to the 2018 ESC guidelines on syncope:

2022

2023 **Diagnosis: initial evaluation**

2024 1. At the initial evaluation answer the following 4 key questions:

- 2025 • Was the event TLOC?
- 2026 • In case of TLOC, is it of syncopal or non-syncopal origin?
- 2027 • In case of suspected syncope, is there a clear aetiological diagnosis?
- 2028 • Is there evidence to suggest a high risk of cardiovascular events or death?

2029 2. At the evaluation of TLOC in the ED answer the following 3 key questions:

- 2030 • Is there a serious underlying cause that can be identified?
 - 2031 • If the cause is uncertain, what is the risk of a serious outcome?
 - 2032 • Should the patient be admitted to hospital?
- 2033 3. In all patients, perform a complete history taking, physical examination (including standing BP
2034 measurement) and standard ECG.
- 2035 4. Perform immediate ECG monitoring (in bed or telemetry) in high-risk patients when there is a suspicion
2036 of arrhythmic syncope.
- 2037 5. Perform an echocardiogram when there is previous known heart disease or data suggestive of
2038 structural heart disease or syncope secondary to cardiovascular cause.
- 2039 6. Perform CSM in patients >40 years of age with syncope of unknown origin compatible with a reflex
2040 mechanism.
- 2041 7. Perform tilt testing in case there is suspicion of syncope due to reflex or an orthostatic cause.
- 2042 8. Perform blood tests when clinically indicated, e.g. haematocrit and cell blood count when haemorrhage
2043 is suspected, oxygen saturation and blood gas analysis when hypoxic syndromes are suspected,
2044 troponin when cardiac-ischaemia related syncope is suspected, D-dimer when pulmonary embolism is
2045 suspected, etc.

2046

2047 **Diagnosis: subsequent investigations**

2048 9. Perform prolonged ECG monitoring (external or implantable) in patients with recurrent severe
2049 unexplained syncope who:

- 2050 • have clinical or ECG features suggesting arrhythmic syncope; *and*

- 2051 • have a high probability of recurrence of syncope in a reasonable time; *and*
2052 • may benefit a specific therapy if a cause for syncope is found.
- 2053 10. Perform EPS in patients with unexplained syncope and bifascicular BBB (impending high-degree AV
2054 block) or suspected tachycardia.
- 2055 11. Perform an exercise stress test in patients who experience syncope during or shortly after exertion.
- 2056 12. Consider basic autonomic function tests (Valsalva manoeuvre and deep breathing test) and ABPM for
2057 assessment of autonomic function in patients with suspected neurogenic OH.
- 2058 13. Consider video recording (at home or in hospital) of TLOC suspected of non-syncopal nature.
- 2059
- 2060 **Treatment**
- 2061 14. To all patients with reflex syncope and OH, explain the diagnosis, reassure, explain the risk of
2062 recurrence, and give advice on how to avoid triggers and situations. These measures are the
2063 cornerstone of treatment and have a high impact in reducing the recurrence of syncope.
- 2064 15. In patients with *severe forms of reflex syncope*, select one or more of the following additional specific
2065 treatments according to the clinical features:
- 2066 • Midodrine or fludrocortisone in young patients with low BP phenotype;
2067 • Counter-pressure manoeuvres (including tilt training if needed) in young patients with prodromes;
2068 • ILR-guided management strategy in selected patients without or with short prodromes;
2069 • Discontinuation/reduction of hypotensive therapy targeting a systolic BP of 140 mmHg in old
2070 hypertensive patients;
2071 • Pacemaker implantation in old patients with dominant cardioinhibitory forms.
- 2072 16. In patients with *OH*, select one or more of the following additional specific treatments according to
2073 clinical severity:
- 2074 • Education regarding lifestyle manoeuvres;
2075 • Adequate hydration and salt intake;
2076 • Discontinuation/reduction of hypotensive therapy;
2077 • Counter-pressure manoeuvres;
2078 • Abdominal binders and/or support stockings;
2079 • Head-up tilt sleeping;
2080 • Midodrine or fludrocortisone.
- 2081 17. Ensure that all patients with cardiac syncope receive the specific therapy of the culprit arrhythmia and/or
2082 of the underlying disease.
- 2083 18. Balance benefit and harm of an ICD implantation in patients with unexplained syncope at high risk of
2084 SCD (e.g. those affected by left ventricle systolic dysfunction, HCM, arrhythmogenic right ventricular
2085 cardiomyopathy, or inheritable arrhythmogenic disorders). In this situation, *unexplained syncope* is
2086 defined as syncope that does not meet any class I diagnostic criterion defined in the tables of
2087 recommendations of the 2018 ESC guidelines on syncope and is considered a *suspected arrhythmic*
2088 *syncope*.
- 2089 19. Re-evaluate the diagnostic process and consider alternative therapies if the above rules fail or are not
2090 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 – gap between the best available scientific evidence and the need for dissemination of these concepts into clinical practice

There is wide variation in practice of syncope evaluation, and wide variation in 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 recurrences.

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 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 versus conventional management*

Diagnosis – need for new diagnostic tests and devices

BP recording is crucial for the majority of clinical TLOC situations and will add important information for 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 randomized controlled trials have been done 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, and makes the results of observational

2131 data on therapy questionable in the absence of a control group. No therapy can be effective for all patients.
 2132 Any therapy should be assessed in homogeneous subgroups.
 2133 Therefore, there is strong urgent need of randomized controlled clinical trials on the efficacy of:
 2134 4) *Pharmacological therapies targeted to specific subgroups of reflex syncope.*
 2135 5) *Pacemaker therapy targeted to specific subgroups of cardioinhibitory reflex syncope.*
 2136 6) *Pharmacological therapies of OH-mediated syncope.*
 2137 7) *ICD therapy targeted to specific subgroups of patients with unexplained syncope at risk of SCD.*

2139 Treatment – need for new therapies

2140 There is the need to move towards personalized medicine. Improving the knowledge of the biochemical
 2141 mechanisms underlying specific forms of reflex syncope will allow the development of new therapies in such
 2142 specific settings. For example, a low adenosine phenotype and a low norepinephrine phenotype have been
 2143 recently identified.

2144 Therefore, there is a need for:

2145 8) *Randomized clinical trials on the efficacy of theophylline (and other xantine antagonists) for low*
 2146 *adenosine syncope and norepinephrine transport inhibitors for low epinephrine syncope.*

2147 Syncope is a transient phenomenon. The ideal therapy should be that is administered only when needed.

2148 Therefore, there is a need for:

2149 9) *Randomized clinical trials of on-demand administration of specific therapy based on specific sensors*
 2150 *similar to adrenalin injectors in asthma or nasal spray for paroxysmal SVT.*

2151

2152 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 or fear or standing, and is associated with typical progressive prodrome (pallor, sweating, nausea). ^{8,13-17}	I	C
Situational reflex syncope is highly probable if syncope occurs during or immediately after specific triggers, listed in <i>Table 3</i> . ^{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 : <ul style="list-style-type: none"> • Persistent sinus bradycardia <40 b.p.m. or sinus pauses >3 seconds 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

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 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 minutes 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 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
Electrocardiographic 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 and Data Supplement 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 and Data Supplement 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, or 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 to manage induction of sustained monomorphic VT 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 to manage the induction of rapid SVT or VT, which reproduces hypotensive or spontaneous symptoms, 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
Treatment of reflex syncope		
Explanation of the diagnosis, provision of reassurance, explanation of risk of recurrence, avoidance of triggers and situations are indicated in all patients. ^{Web Data Supplement 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, explanation of risk of recurrence, and 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	I	B

symptomatic bradycardia. ^{200,210-212,255,334-338,341}		
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 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 $\leq 35\%$. 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 $\leq 35\%$ after ≥ 3 months of optimal medical therapy who are expected to survive for at least 1 year with good functional status. ⁴⁶	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; BP = blood pressure; b.p.m. = beats per minute; BBB = bundle branch block; 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.

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