



UNIVERSITÀ  
DEGLI STUDI  
FIRENZE

## FLORE

# Repository istituzionale dell'Università degli Studi di Firenze

### **2018 ESC Guidelines for the diagnosis and management of syncope**

Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

*Original Citation:*

2018 ESC Guidelines for the diagnosis and management of syncope / Brignole, Michele\*; Moya, Angel; De Lange, Frederik J; Deharo, Jean-Claude; Elliott, Perry M; Fanciulli, Alessandra; Fedorowski, Artur; Furlan, Raffaello; Kenny, Rose Anne; Martín, Alfonso; Probst, Vincent; Reed, Matthew J; Rice, Ciara P; Sutton, Richard; Ungar, Andrea; Van Dijk, J. Gert. - In: EUROPEAN HEART JOURNAL. - ISSN 0195-668X. - STAMPA. - 39:(2018), pp. 1883-1948. [10.1093/eurheartj/ehy037]

*Availability:*

This version is available at: 2158/1146550 since: 2020-10-05T13:10:39Z

*Published version:*

DOI: 10.1093/eurheartj/ehy037

*Terms of use:*

Open Access

La pubblicazione è resa disponibile sotto le norme e i termini della licenza di deposito, secondo quanto stabilito dalla Policy per l'accesso aperto dell'Università degli Studi di Firenze (<https://www.sba.unifi.it/upload/policy-oa-2016-1.pdf>)

*Publisher copyright claim:*

Conformità alle politiche dell'editore / Compliance to publisher's policies

Questa versione della pubblicazione è conforme a quanto richiesto dalle politiche dell'editore in materia di copyright.

This version of the publication conforms to the publisher's copyright policies.

(Article begins on next page)

1 **ESC Guidelines**

2  
3 **Guidelines for the diagnosis and management of syncope (Version**  
4 **2018)**

5  
6 **The Multidisciplinary Task Force for the Diagnosis and Management of Syncope of the European**  
7 **Society of Cardiology (ESC)**

8  
9 **Developed in collaboration with:**

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

13  
14 **Endorsement to be requested to the following societies:**

15 **European Society of Emergency Medicine (EuSEM)**  
16 **European Federation of Internal Medicine (EFIM)**  
17 **European Union Geriatric Medicine Society (EUGMS)**  
18 **European Neurological Society (ENS)**  
19 **European Federation of Autonomic Societies (EFAS)**

20  
21 **Authors/Task Force Members: Michele Brignole (Chairperson) (Italy); Angel Moya (Co-chairperson)**  
22 **(Spain); Jean-Claude Deharo (France); Frederik de Lange (the Netherlands); Perry Elliott, (UK); Artur**  
23 **Fedorowski (Sweden); Alessandra Fanciulli (Austria); Raffaello Furlan (Italy); Rose Anne Kenny**  
24 **(Ireland); Alfonso Martin (Spain); Vincent Probst (France); Matthew Reed (UK); Ciara Rice (Ireland);**  
25 **Richard Sutton (Monaco); Andrea Ungar (Italy); Gert van Dijk (the Netherlands)**

26  
27 **Key words:** syncope, transient loss of consciousness  
28  
29

30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71  
72  
73  
74  
75  
76  
77  
78  
79  
80  
81  
82  
83  
84

## Table of Contents

<b>1. Preamble</b>	<b>6</b>
<b>2. Introduction</b>	<b>6</b>
<b>3. Definitions, classification and pathophysiology</b>	<b>9</b>
<b>3.1 Definitions</b>	<b>9</b>
<b>3.2 Classification and pathophysiology of syncope and transient loss of consciousness</b>	<b>11</b>
<b>3.2.1 Syncope</b>	<b>11</b>
<b>3.2.2 Non-syncope forms of (real or apparent) transient loss of consciousness</b>	<b>14</b>
<b>4. Diagnostic evaluation and management according to risk stratification</b>	<b>15</b>
<b>4.1 Initial evaluation</b>	<b>15</b>
<b>4.1.1. Diagnosis of syncope</b>	<b>16</b>
<b>4.1.2 Management of syncope in the emergency department based on risk stratification</b>	<b>19</b>
<b>4.2 Diagnostic tests</b>	<b>26</b>
<b>4.2.1 Carotid sinus massage</b>	<b>26</b>
<b>4.2.2 Orthostatic challenge</b>	<b>27</b>
4.2.2.1 Active standing	27
4.2.2.2 Tilt testing	29
<b>4.2.3 Basic autonomic function tests</b>	<b>32</b>
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
<b>4.2.4 Electrocardiographic monitoring (non-invasive and invasive)</b>	<b>34</b>
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
<b>4.2.5 Video recording in suspected syncope</b>	<b>37</b>
4.2.5.1 In-hospital video recording	37
4.2.5.2 Home video recording	38
<b>4.2.6 Electrophysiological study</b>	<b>38</b>
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
<b>4.2.7 Endogenous adenosine and other biomarkers</b>	<b>41</b>
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
<b>4.2.8 Echocardiography</b>	<b>41</b>
4.2.8.1 Exercise stress echocardiography	42
<b>4.2.9 Exercise stress testing</b>	<b>42</b>
<b>4.2.10 Coronary angiography</b>	<b>43</b>
<b>5. Treatment</b>	<b>444</b>
<b>5.1 General principles of treatment of syncope</b>	<b>444</b>
<b>5.2 Treatment of reflex syncope</b>	<b>45</b>
<b>5.2.1 Education and lifestyle modifications</b>	<b>47</b>
<b>5.2.2 Discontinuation/reduction of hypotensive therapy</b>	<b>47</b>
<b>5.2.3 Physical counter-pressure manoeuvres</b>	<b>47</b>
<b>5.2.4 Tilt training</b>	<b>48</b>
<b>5.2.5 Pharmacological therapy</b>	<b>48</b>
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	<b>5.2.6 Cardiac pacing .....</b>	<b>50</b>
90	5.2.6.1 Evidence from trials in suspected or certain reflex syncope and electrocardiogram-documented asystole .....	51
91	.....	51
92	5.2.6.2 Evidence from the trials in patients with carotid sinus syndrome .....	52
93	5.2.6.3 Evidence from trials in patients with tilt-induced vasovagal syncope .....	52
94	5.2.6.4 Evidence from trials in patients with adenosine-sensitive syncope .....	53
95	5.2.6.5 Choice of pacing mode.....	54
96	5.2.6.6 Selection of patients for pacing and proposed algorithm.....	54
97	<b>5.3 Treatment of orthostatic hypotension and orthostatic intolerance syndromes .....</b>	<b>57</b>
98	<b>5.3.1 Education and lifestyle measures.....</b>	<b>57</b>
99	<b>5.3.2 Adequate hydration and salt intake.....</b>	<b>57</b>
100	<b>5.3.3 Discontinuation/reduction of vasoactive drugs .....</b>	<b>58</b>
101	<b>5.3.4 Counter-pressure manoeuvres .....</b>	<b>58</b>
102	<b>5.3.5 Abdominal binders and/or support stockings.....</b>	<b>58</b>
103	<b>5.3.6 Head-up tilt sleeping .....</b>	<b>58</b>
104	<b>5.3.7 Midodrine.....</b>	<b>58</b>
105	<b>5.3.8 Fludrocortisone .....</b>	<b>58</b>
106	<b>5.3.9 Additional therapies .....</b>	<b>59</b>
107	<b>5.3.10 Emerging new pharmacological therapy in specific subgroups.....</b>	<b>59</b>
108	<b>5.4 Cardiac arrhythmias as the primary cause .....</b>	<b>60</b>
109	<b>5.4.1 Syncope due to intrinsic sinoatrial or atrioventricular conduction system disease .....</b>	<b>60</b>
110	5.4.1.1 Sinus node disease.....	61
111	5.4.1.2 Atrioventricular conduction system disease .....	61
112	5.4.1.3 Bundle branch block and unexplained syncope .....	62
113	<b>5.4.2 Syncope due to intrinsic cardiac tachyarrhythmias .....</b>	<b>63</b>
114	5.4.2.1 Paroxysmal supraventricular tachycardia.....	64
115	5.4.2.2 Paroxysmal ventricular tachycardia.....	64
116	<b>5.5 Treatment of syncope secondary to structural cardiac, cardiopulmonary, and great vessel disease.....</b>	<b>66</b>
117	<b>5.6 Treatment of unexplained syncope in patients at high risk of sudden cardiac death .....</b>	<b>67</b>
118	<b>5.6.1 Definition .....</b>	<b>67</b>
119	<b>5.6.2 Left ventricular systolic dysfunction .....</b>	<b>67</b>
120	<b>5.6.3 Hypertrophic cardiomyopathy .....</b>	<b>68</b>
121	<b>5.6.4 Arrhythmogenic right ventricular cardiomyopathy .....</b>	<b>69</b>
122	<b>5.6.5 Patients with inheritable arrhythmogenic disorders .....</b>	<b>70</b>
123	5.6.5.1 Long QT syndrome .....	70
124	5.6.5.2 Brugada syndrome.....	70
125	5.6.5.3 Other forms .....	71
126	<b>6. Special issues .....</b>	<b>72</b>
127	<b>6.1 Syncope in patients with comorbidity and frailty .....</b>	<b>72</b>
128	<b>6.1.1 Comorbidity and polypharmacy.....</b>	<b>72</b>
129	<b>6.1.2 Falls.....</b>	<b>72</b>
130	<b>6.1.3 Cognitive assessment and physical performance tests .....</b>	<b>73</b>
131	<b>6.2 Syncope in paediatric patients.....</b>	<b>74</b>
132	<b>6.2.1 Diagnostic evaluation.....</b>	<b>74</b>
133	<b>6.2.2. Therapy.....</b>	<b>75</b>
134	<b>7. Psychogenic transient loss of consciousness and its evaluation .....</b>	<b>75</b>
135	<b>7.1 Diagnosis.....</b>	<b>75</b>
136	<b>7.1.1 Historical criteria for attacks .....</b>	<b>75</b>
137	<b>7.1.2 Documentation of key features during an attack .....</b>	<b>76</b>
138	7.1.2.1 Management of psychogenic pseudosyncope .....	76
139	.....	76

140	<b>8. Neurological causes and mimics of syncope.....</b>	<b>77</b>
141	<b>8.1 Clinical conditions.....</b>	<b>77</b>
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	<b>8.2 Neurological tests.....</b>	<b>80</b>
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	<b>9. Organizational aspects .....</b>	<b>82</b>
154	<b>9.1 Syncope (transient loss of consciousness) management unit .....</b>	<b>82</b>
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	<b>9.2 The clinical nurse specialist in the syncope unit.....</b>	<b>85</b>
162	9.2.1 Definition .....	85
163	9.2.2 Role and skills of clinical nurse specialist .....	85
164	<b>10. Key messages .....</b>	<b>87</b>
165	<b>11. Gaps in evidence and areas for future research .....</b>	<b>89</b>
166	<b>12. “What to do” and “what not to do” messages from the guidelines .....</b>	<b>90</b>
167	<b>13. References.....</b>	<b>93</b>
168		
169		

170	<b>Abbreviations and Acronyms</b>	
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		

222 **1. Preamble**

223 **TO BE INSERTED**

224

225 **Table 1** Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
<b>Class I</b>	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
<b>Class II</b>	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
<b>Class III</b>	Evidence or general agreement that the given treatment or procedure is not useful/effective; and in some cases may be harmful.	Is not recommended

©ESC 2017

226

227

228 **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.

229

230

231

**2. Introduction**

232

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.

234

235

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).

237

238

239

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

240

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

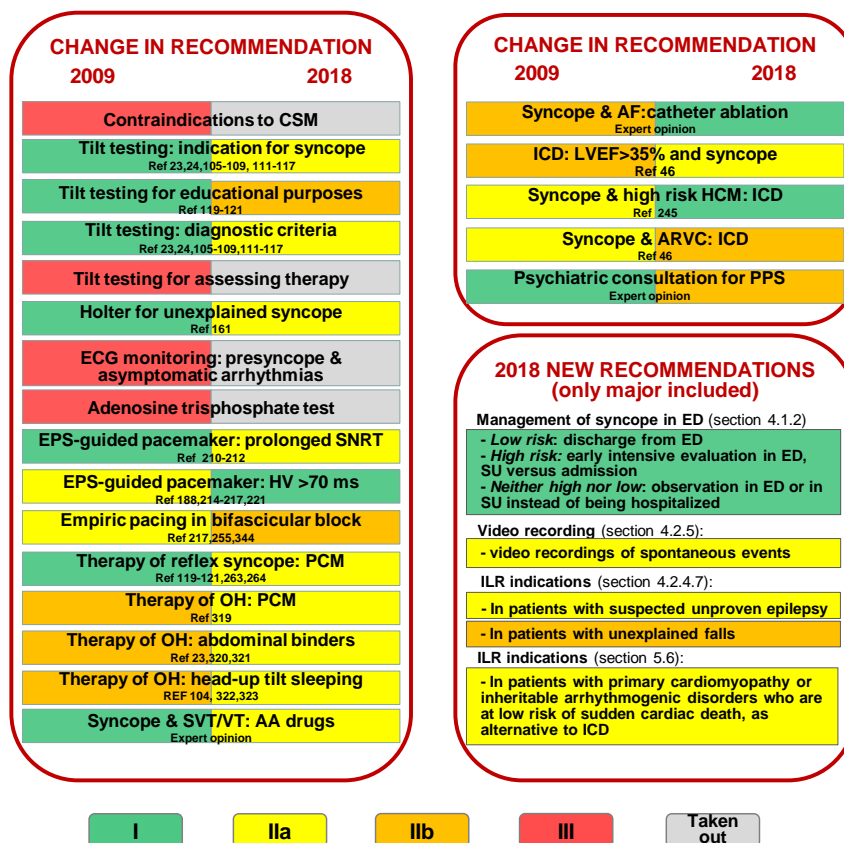
## 259 **2.1 What is new in the 2018 version?**

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*.

262

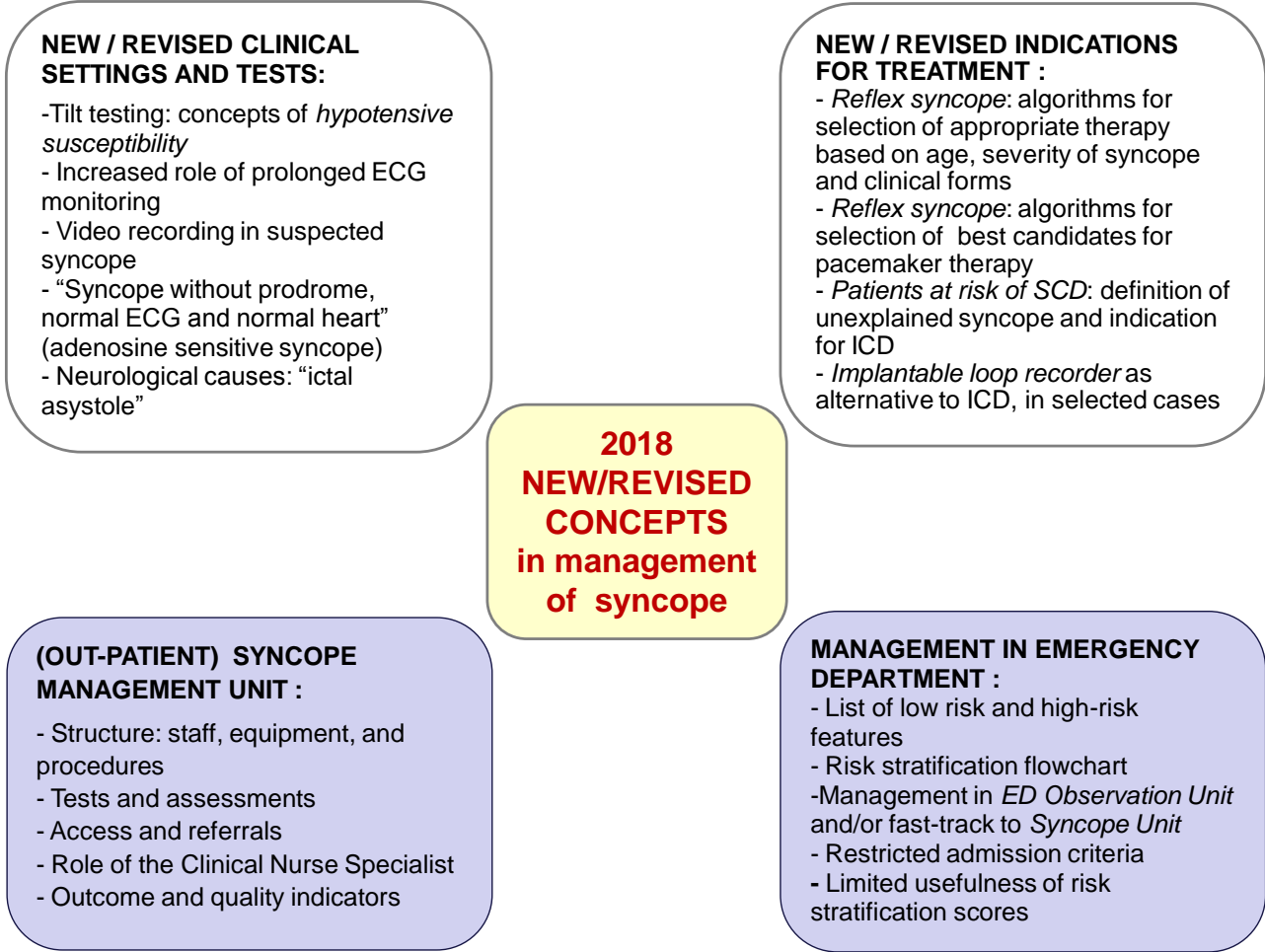
263





264  
265  
266  
267  
268  
269  
270  
271  
272  
273

**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.



274  
275  
276  
277  
278  
279  
280  
281  
282  
283  
284  
285  
286  
287  
288  
289

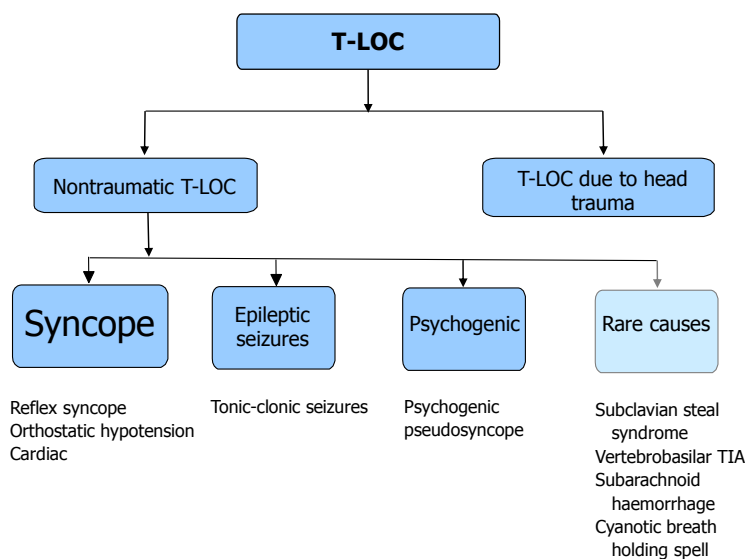
**Central illustration** New/revised concepts in the management of syncope. ECG = electrocardiogram; ED = emergency department; ICD = implantable cardioverter defibrillator; SCD = sudden cardiac death.

**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  
 294 **Figure 2** Syncope in the context of TLOC. Non-traumatic TLOC is classified into one of four groupings:  
 295 syncope, epileptic seizures, psychogenic TLOC, and a miscellaneous group of rare causes. This order  
 296 represents their rate of occurrence. Combinations occur; e.g. non-traumatic TLOC causes can cause falls  
 297 with concussion, in which case TLOC is both traumatic and non-traumatic. TIA = transient ischaemic attack;  
 298 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**

<b>Reflex (neurally mediated) syncope</b> Vasovagal: <ul style="list-style-type: none"><li>- orthostatic VVS: standing, less common sitting</li><li>- emotional: fear, pain (somatic or visceral), instrumentation, blood phobia</li></ul> Situational: <ul style="list-style-type: none"><li>- micturition</li><li>- gastrointestinal stimulation (swallow, defaecation)</li><li>- cough, sneeze</li><li>- post-exercise</li><li>- others (e.g. laughing, brass instrument playing)</li></ul> Carotid sinus syndrome Non-classical forms (without prodromes and/or without apparent triggers and/or atypical presentation)
<b>Syncope due to OH</b> <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"><li>- e.g. vasodilators, diuretics, phenothiazine, antidepressants</li></ul> Volume depletion: <ul style="list-style-type: none"><li>- haemorrhage, diarrhoea, vomiting, etc.</li></ul> Primary autonomic failure (neurogenic OH): <ul style="list-style-type: none"><li>- pure autonomic failure, multiple system atrophy, Parkinson’s disease, dementia with Lewy bodies</li></ul> Secondary autonomic failure (neurogenic OH): <ul style="list-style-type: none"><li>- diabetes, amyloidosis, spinal cord injuries, auto-immune autonomic neuropathy, paraneoplastic autonomic neuropathy, kidney failure</li></ul>
<b>Cardiac syncope</b> 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.<sup>1,2</sup> "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.<sup>3</sup> At present, this group also contains syncope associated with low adenosine plasma levels<sup>4,5</sup>
- 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.<sup>6,7</sup> Syndromes of orthostatic intolerance that may cause syncope are presented in *Web Practical Instruction section 2*.

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

326  
327 The pathophysiological classification centres on a fall in systemic blood pressure (BP) with a decrease in  
328 global cerebral blood flow as the defining characteristic of syncope. *Figure 3* shows low BP and global  
329 cerebral hypoperfusion as the central final common pathway of syncope. A sudden cessation of cerebral  
330 blood flow for as short as 6–8 seconds can cause complete LOC. A systolic BP of 50–60 mmHg at heart  
331 level, i.e. 30–45 mmHg at brain level in the upright position, will cause LOC.<sup>8,9</sup>

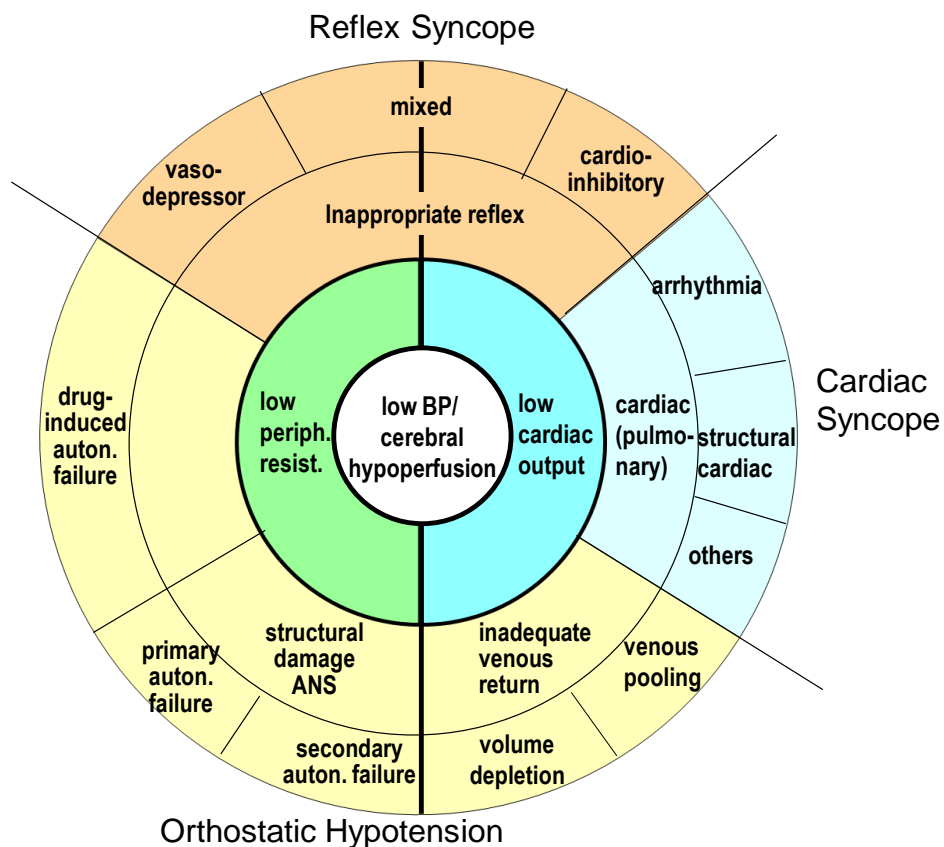
332 Systemic BP is the product of cardiac output and total peripheral resistance; a fall in either can  
333 cause syncope. However, in syncope, often both mechanisms act together to a varying degree.

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.<sup>10</sup> So-called “pallid breath-holding spells” in children do not constitute a primary respiratory  
 371 problem, but are cardioinhibitory reflex syncope.<sup>11</sup>

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

<b>hypoxia, hyperventilation with hypocapnia</b>	
<b>Intoxication</b>	Duration much longer than in TLOC; consciousness may be impaired instead of lost
<b>Cardiac arrest</b>	LOC yet no spontaneous recovery
<b>Coma</b>	Duration much longer than TLOC

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

378

## 379 **4. Diagnostic evaluation and management according to risk stratification**

### 380 **4.1 Initial evaluation**

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

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

389

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

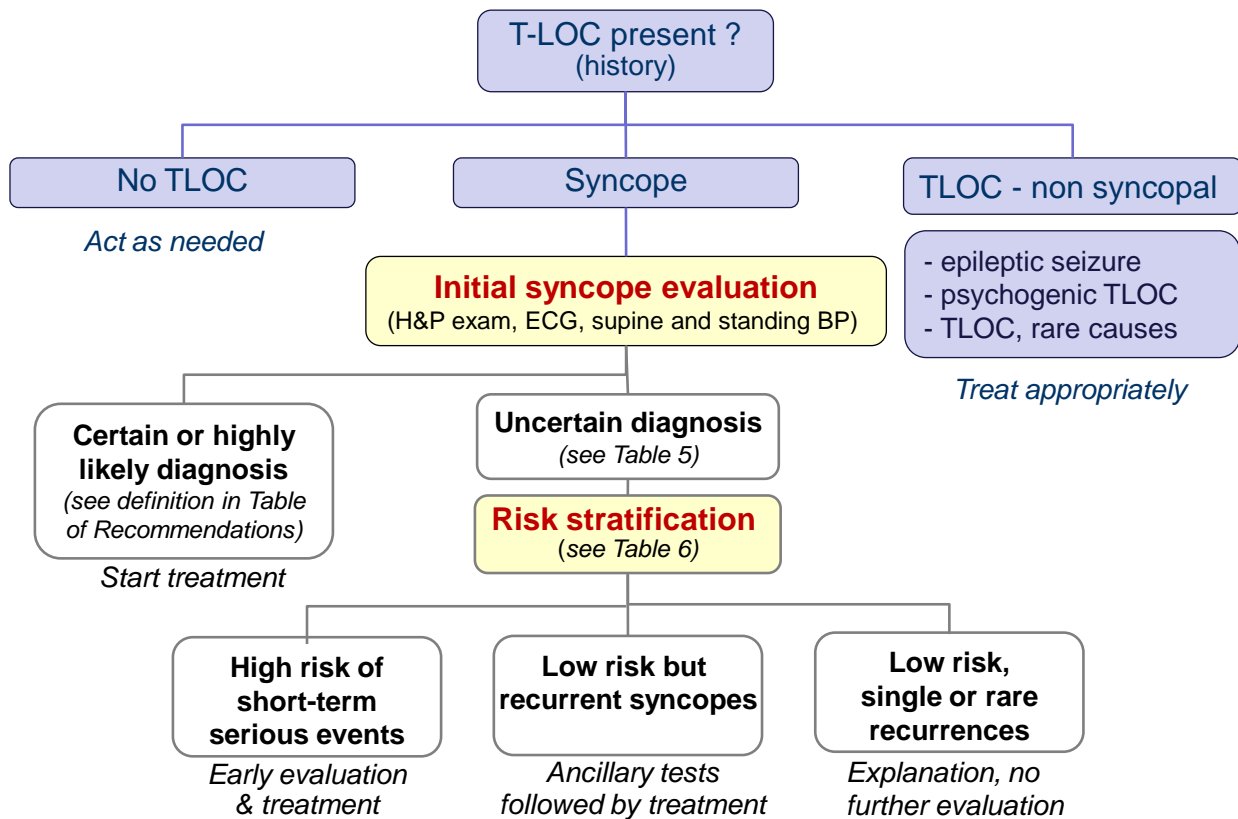
393 TLOC is probably syncope when: a) there are signs and symptoms specific for reflex syncope,  
394 syncope due to OH, or cardiac syncope, and; b) signs and symptoms specific for other forms of TLOC (head  
395 trauma, epileptic seizures, psychogenic TLOC, rare causes) are absent. Practical instructions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

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



## Presentation of patient with probable TLOC

(may include ambulance or referral data)



401  
402 **Figure 4** Flow diagram for initial evaluation and risk stratification of patients with syncope. BP = blood  
403 pressure; ECG = electrocardiogram; H&P exam = history and physical examination; TLOC = transient loss of  
404 consciousness.

405  
406

### 407 4.1.1. Diagnosis of syncope

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

- 410
- 411 • Careful history taking concerning present and previous attacks, as well as eyewitness accounts, in person or through a telephone interview;
  - 412 • Physical examination, including supine and standing BP measurements; and
  - 413 • Electrocardiogram (ECG).
- 414

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

- 416
- 417 • Immediate ECG monitoring when there is a suspicion of arrhythmic syncope;
  - 418 • Echocardiogram when there is previous known heart disease or data suggestive of structural heart disease or syncope secondary to cardiovascular cause;

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

424 ***Even if there is no independent gold/reference standard to diagnose syncope, there is strong***  
 425 ***consensus that the initial evaluation may lead to certain or highly likely diagnosis when the***  
 426 ***diagnostic criteria listed in the table of recommendations are met.***  
 427

428 **Diagnostic criteria with initial evaluation**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Reflex syncope and OH</b>		
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). <sup>8,13-17</sup>	<b>I</b>	<b>C</b>
2. Situational reflex syncope is highly probable if syncope occurs during or immediately after specific triggers, listed in <i>Table 3</i> . <sup>8,13-17</sup>	<b>I</b>	<b>C</b>
3. Syncope due to OH is confirmed when syncope occurs while standing and there is concomitant significant OH. <sup>18-24</sup>	<b>I</b>	<b>C</b>
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> ).	<b>Ila</b>	<b>C</b>
<b>Cardiac syncope</b>		
5. Arrhythmic syncope is highly probable when the ECG shows <sup>25-39</sup> : <ul style="list-style-type: none"> <li>• Persistent sinus bradycardia &lt;40 b.p.m. or sinus pauses &gt;3 seconds in awake state and in absence of physical training</li> <li>• Mobitz II second- and third-degree AV block</li> <li>• Alternating left and right BBB</li> <li>• VT or rapid paroxysmal SVT</li> <li>• Non-sustained episodes of polymorphic VT and long or short QT interval</li> <li>• Pacemaker or ICD malfunction with cardiac pauses.</li> </ul>	<b>I</b>	<b>C</b>
6. Cardiac-ischaemia-related syncope is confirmed when syncope presents with evidence of acute myocardial ischaemia with or without myocardial infarction. <sup>25-39</sup>	<b>I</b>	<b>C</b>
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.	<b>I</b>	<b>C</b>

### 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.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

429

430

431

432

433

434

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  $\geq 0.12$  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

435

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

439

#### 440 **4.1.2 Management of syncope in the emergency department based on risk stratification**

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

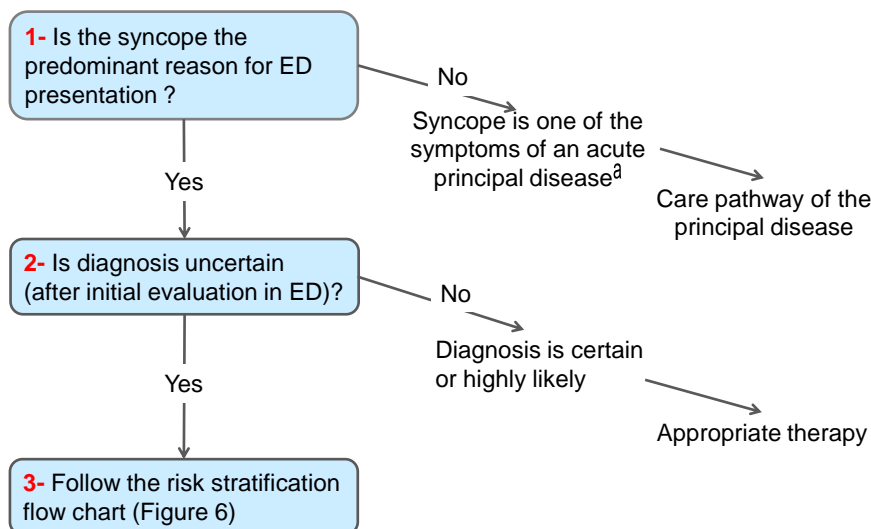
443 1: Is there a serious underlying cause that can be identified?

444 2: What is the risk of a serious outcome?

445 3: Should the patient be admitted to hospital?

446

447 *Figure 5* shows a flowchart for the management and risk stratification of patients referred to the ED for TLOC  
 448 suspected to be syncope (modified from Casagrande *et al*<sup>40</sup>).



449  
450  
451  
452  
453  
454  
455

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

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

456  
457  
458  
459  
460  
461  
462  
463  
464

**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.<sup>41,42</sup> It is the acute underlying disease that most frequently determines short-term adverse events rather than the syncope itself.<sup>43</sup> 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.<sup>44</sup> 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.

465  
466  
467

**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.

468  
469  
470  
471  
472

Risk stratification is important, for two reasons:

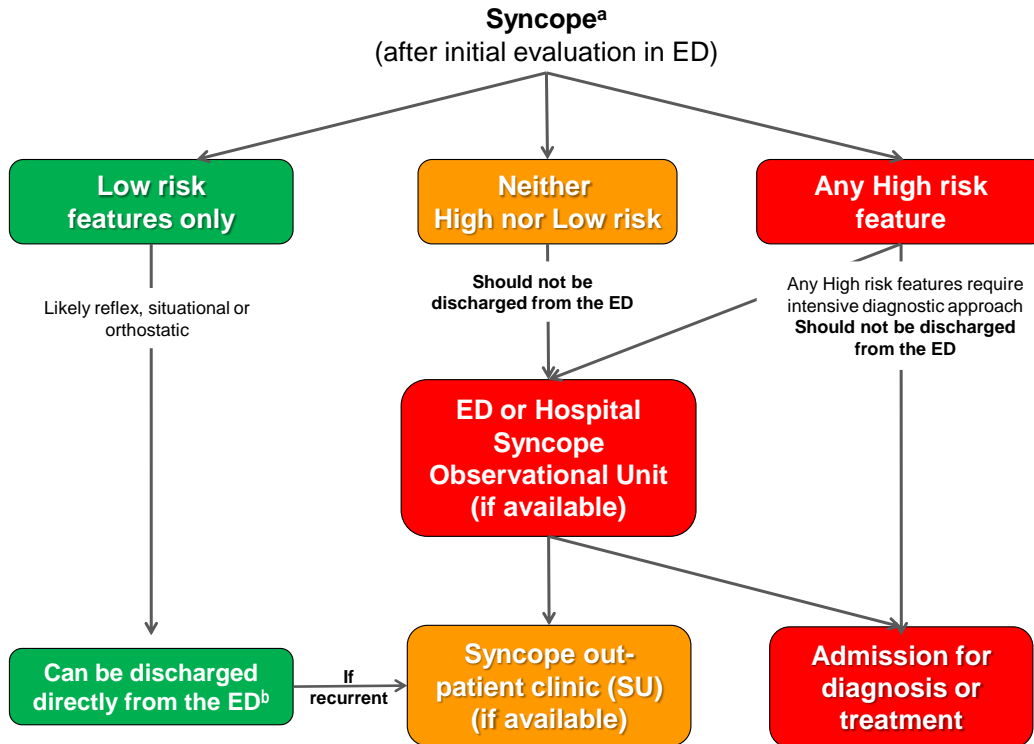
1. To recognize patients with a likely **low**-risk condition able to be discharged with adequate patient education;
2. To recognize patients with a likely **high**-risk cardiovascular condition requiring urgent investigation. This may require admission.

473 High-risk patients are more likely to have cardiac syncope. Structural heart disease<sup>25-27,31,35,36,45</sup> and primary  
 474 electrical disease<sup>46</sup> 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.<sup>47</sup>  
 476 OH is associated with a twofold higher risk of death owing to the severity of comorbidities compared with the  
 477 general population.<sup>48</sup>  
 478

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

	<p>14. Slow AF (&lt;40 b.p.m.)</p> <p>12. Persistent sinus bradycardia (&lt;40 b.p.m.), or repetitive sinoatrial block or sinus pauses &gt;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<sup>44,56</sup></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 &gt;460 ms in repeated 12-lead ECGs indicating LQTS<sup>46</sup></p> <p><b>Minor</b> (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.)<sup>56</sup></p> <p>22. Paroxysmal SVT or atrial fibrillation.<sup>50</sup></p> <p>23. Pre-excited QRS complex</p> <p>24. Short QTc interval (<math>\leq 340</math> ms)<sup>46</sup></p> <p>25. Atypical Brugada patterns<sup>46</sup></p> <p>26. Negative T waves in right precordial leads, epsilon waves suggestive of ARVC<sup>46</sup></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><sup>a</sup> 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.<sup>61</sup></p>	



481

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

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

487 Patients with high-risk features. These patients should be classified as HIGH RISK; they require an intensive  
 488 diagnostic approach and may need urgent treatment and admission. These patients should be monitored  
 489 (although it is unclear for how long this should be, most studies suggesting up to 6 hours in the ED and up to  
 490 24 hours in hospital) in a setting where resuscitation can be performed in case of deterioration.<sup>40,62</sup>

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

495 <sup>a</sup>Recent studies have suggested that outcomes in patients presenting with presyncope are similar to those  
 496 presenting with syncope.<sup>66-68</sup>

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

499

500

501

502



503 **Management of syncope in the ED**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
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. <sup>27,35,36,49-54,58,62,69</sup>	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. <sup>26,27,35,36,44-46,50,55-57,59,60,70-76</sup>	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. <sup>40,63-65,77</sup>	I	B
Risk stratification scores may be considered for risk stratification in the ED. <sup>78-86</sup>	IIb	B
<p><b>Additional advice and clinical perspectives</b></p> <ul style="list-style-type: none"> <li>• In the ED, presyncope should be managed with the same accuracy as syncope as it carries the same prognosis.<sup>66-68</sup></li> <li>• 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.</li> <li>• 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.</li> <li>• 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.</li> <li>• To reduce inappropriate admissions, patients who have a cardiac device and syncope should undergo prompt device interrogation.</li> <li>• Risk stratification scores perform no better than good clinician judgement and should not be used alone to perform risk stratification in the ED.</li> </ul>		

504 ED = emergency department; OH = orthostatic hypotension.

505 <sup>a</sup> Class of recommendation.

506 <sup>b</sup> 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.<sup>87</sup> 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.<sup>80</sup>

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,<sup>40</sup> 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%.<sup>77</sup> 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.<sup>77</sup>

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
<p><b>High-risk features AND:</b></p> <ul style="list-style-type: none"> <li>• Stable, known structural heart disease</li> <li>• Severe chronic disease</li> <li>• Syncope during exertion</li> <li>• Syncope while supine or sitting</li> <li>• Syncope without prodrome</li> <li>• Palpitations at the time of syncope</li> <li>• Inadequate sinus bradycardia or sinoatrial block</li> <li>• Suspected device malfunction or inappropriate intervention</li> <li>• Pre-excited QRS complex</li> <li>• SVT or paroxysmal atrial fibrillation</li> <li>• ECG suggesting an inheritable arrhythmogenic disorders</li> <li>• ECG suggesting ARVC</li> </ul>	<p><b>High-risk features AND:</b></p> <ul style="list-style-type: none"> <li>• Any potentially severe coexisting disease that requires admission</li> <li>• Injury caused by syncope</li> <li>• 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.</li> <li>• Need for treatment of syncope</li> </ul>
<p>ARVC = arrhythmogenic right ventricular cardiomyopathy; ECG = electrocardiogram; ED = emergency department; SVT = supraventricular tachycardia.</p>	

527

528

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*).<sup>26,34-36,44,88</sup> 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.<sup>70,78-85</sup> Syncope clinical decision rules perform no better than clinician judgment at  
 534 predicting short-term serious outcomes.<sup>86</sup> 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*,<sup>58</sup> particularly in the long term.<sup>56</sup>

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

541  
542

## 543 **4.2 Diagnostic tests**

### 544 **4.2.1 Carotid sinus massage**

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

558 The main complications of CSM are neurological. When pooling the data from four studies<sup>90,95-97</sup> in  
559 which 8720 patients were analysed, TIAs or strokes were observed in 21 (0.24%).

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

568

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

575  
576  
577

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Indications</b> CSM is indicated in patients >40 years of age with syncope of unknown origin compatible with a reflex mechanism. <sup>92-94</sup>	I	B
<b>Diagnostic criteria</b> 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. <sup>89,90,92,93,98-102</sup>	I	B
<b>Additional advice and clinical perspectives</b> <ul style="list-style-type: none"> <li>History of syncope and its reproduction by CSM defines CSS; positive CSM without a history of syncope defines carotid sinus hypersensitivity.<sup>89,90,92,93</sup> 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.</li> <li>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.<sup>90</sup></li> <li>Albeit neurological complications are very rare,<sup>90,95-97</sup> 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 &gt;70%.</li> </ul>		

579 BP = blood pressure; CSM = carotid sinus massage; CSS = carotid sinus syndrome; TIA = transient  
 580 ischaemic attack.

581 <sup>a</sup> Class of recommendation.

582 <sup>b</sup> Level of evidence.

583

#### 584 4.2.2 Orthostatic challenge

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

589 Currently, there are three methods for assessing the response to change in posture from supine to  
 590 erect<sup>20,103,104</sup>: active standing (see section 4.2.2.1), head-up tilt (see section 4.2.2.2), and 24-hour ambulatory  
 591 BP monitoring (ABPM) (see section 4.2.3.4).

592

##### 593 4.2.2.1 Active standing

#### 594 **Indications**

595 This test is used to diagnose different types of orthostatic intolerance (see *Web Practical Instructions – Web*  
 596 *Table 1*). A sphygmomanometer is adequate for routine clinical testing for classical OH and delayed OH  
 597 because of its ubiquity and simplicity. Automatic arm-cuff devices, which are programmed to repeat and  
 598 confirm measurements when discrepant values are recorded, are a disadvantage due to the rapidly falling  
 599 BP during OH. With a sphygmomanometer, more than four measurements per minute cannot be obtained

600 without venous obstruction in the arm. When more frequent readings are required, as for initial OH,  
 601 continuous beat-to-beat non-invasive BP measurement is needed.<sup>20,103,104</sup>

602  
 603 **Diagnostic criteria**

604 Abnormal BP fall is defined as a progressive and sustained fall in systolic BP from baseline value  $\geq 20$  mmHg  
 605 or diastolic BP  $\geq 10$  mmHg or a decrease in systolic BP to  $< 90$  mmHg. This definition of OH differs from the  
 606 2011 consensus<sup>6</sup> in adding the 90 mmHg threshold. This Task Force believes that an absolute threshold of  
 607 90 mmHg of systolic BP is useful especially in patients with a supine BP  $< 110$  mmHg. An isolated diastolic  
 608 BP drop is very rare and its clinical relevance for OH diagnosis is limited. Orthostatic heart rate (HR)  
 609 increase is blunted or absent (usually not  $> 10$  beats per minute [b.p.m.]) in patients with neurogenic OH, but  
 610 increases or even exaggerates with anaemia or hypovolemia. The probability that syncope and orthostatic  
 611 complaints are due to OH can be assessed using the information given in *Table 8*.

612  
 613 **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	<b>Syncope is due to OH (class I)</b>	<b>Syncope is likely due to OH (class IIa)</b>
	Asymptomatic abnormal BP fall	<b>Syncope is likely due to OH (class IIa)</b>	<b>Syncope may be due to OH (class IIb)</b>
	No abnormal BP drop	<b>Unproven</b>	<b>Unproven</b>

614 BP = blood pressure; OH = orthostatic hypotension.

615  
 616 **Active standing**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Indications</b> Intermittent determination by sphygmomanometer of BP and HR while supine and during active standing for 3 minutes are indicated at initial syncope evaluation. <sup>20,103,104</sup>	<b>I</b>	<b>C</b>
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. <sup>20,103,104</sup>	<b>IIb</b>	<b>C</b>

<b>Diagnostic criteria</b> Syncope due to OH is confirmed when there is a fall in systolic BP from baseline value $\geq 20$ mmHg or diastolic BP $\geq 10$ mmHg or a decrease in systolic BP to $< 90$ mmHg that reproduces spontaneous symptoms. <sup>6,20,103,104</sup>	<b>I</b>	<b>C</b>
Syncope due to OH should be considered likely when there is an asymptomatic fall in systolic BP from baseline value $\geq 20$ mmHg or diastolic BP $\geq 10$ mmHg or a decrease in systolic BP to $< 90$ mmHg and symptoms (from history) are consistent with OH. <sup>6,20,103,104</sup>	<b>IIa</b>	<b>C</b>
Syncope due to OH should be considered likely when there is a symptomatic fall in systolic BP from baseline value $\geq 20$ mmHg or diastolic BP $\geq 10$ mmHg or a decrease in systolic BP to $< 90$ mmHg and not all of the features (from history) are suggestive of OH. <sup>6,20,103,104</sup>	<b>IIa</b>	<b>C</b>
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. <sup>6,20,103,104</sup>	<b>IIa</b>	<b>C</b>
Syncope due to OH may be considered possible when there is an asymptomatic fall in systolic BP from baseline value $\geq 20$ mmHg or diastolic BP $\geq 10$ mmHg or a decrease in systolic BP to $< 90$ mmHg and symptoms (from history) are less consistent with OH. <sup>6,20,103,104</sup>	<b>IIb</b>	<b>C</b>

617 BP = blood pressure; b.p.m. = beats per minute; OH = orthostatic hypotension; HR = heart rate; POTS =  
618 postural orthostatic tachycardia syndrome.

619 <sup>a</sup> Class of recommendation.

620 <sup>b</sup> Level of evidence.

621

#### 622 4.2.2.2 Tilt testing

623 Since its introduction in 1986,<sup>105</sup> many protocols have been reported with variations in the initial  
624 stabilization phase, duration, tilt angle, type of support, and pharmacological provocation. The most  
625 commonly used are the trinitroglycerin (TNG) test using 300–400  $\mu\text{g}$  of sublingual TNG after a 20-minute  
626 unmedicated phase,<sup>106,107</sup> and the low-dose intravenous isoproterenol test, which uses incremental doses to  
627 increase average HR by about 20–25% over baseline (usually  $\leq 3$   $\mu\text{g}/\text{min}$ ).<sup>108,109</sup> In a recent systematic  
628 literature review,<sup>110</sup> the overall positivity rate in patients with syncope was 66% for the TNG protocol and  
629 61% for the isoproterenol protocol; the respective positivity rate in subjects without syncope (controls)  
630 ranged from 11% to 14%; the test differentiated patients with syncope from controls with an odds ratio of 12.  
631 Methodology and classification of responses are described in the *Web Practical Instructions section 6.*  
632 Adding video recording to a tilt table permits review of clinical signs in relation to BP and HR objectively and  
633 repeatedly, helps to assess the relative contribution of bradycardia and hypotension to syncope (see section  
634 5.2.6.3 and explanatory video in *Web Practical Instruction section 6.3.15*) and to distinguish between VVS  
635 and PPS (see section 4.2.5).

636 The clinical situation corresponding to tilt-induced syncope is that which is triggered by prolonged  
637 standing. The test should be considered: 1) to confirm a diagnosis of reflex syncope in patients in whom this  
638 diagnosis was suspected but not confirmed by initial evaluation<sup>105-109,111</sup>; 2) for the assessment of autonomic  
639 failure especially for the reproduction of delayed OH (which could not be detected by active standing

640 because of its delayed onset)<sup>23,24,112,113</sup> and postural orthostatic tachycardia syndrome (POTS).<sup>114</sup> Tilt testing  
641 may be helpful in separating syncope from PPS.<sup>115-117</sup>

642 Tilt testing has limited value in assessing treatment efficacy.<sup>118</sup> 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).<sup>119-121</sup>

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.*

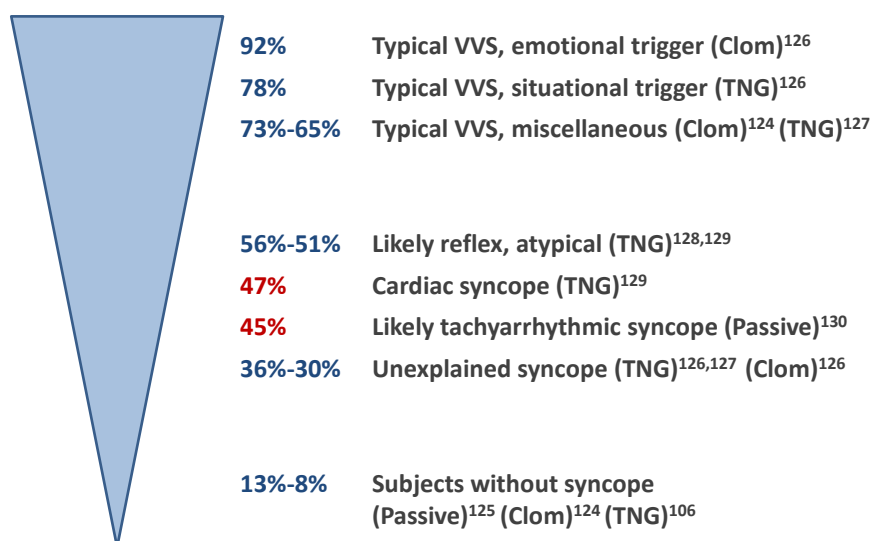
649

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

651 Some studies<sup>122,123</sup> 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.<sup>122,123</sup>

655 Tilt testing has an acceptable sensitivity<sup>124</sup> and specificity<sup>106,124,125</sup> 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,<sup>106,124-128</sup> in 30–36% with unexplained syncope  
660 after full investigation,<sup>124,129</sup> and in 45–47% with true cardiac arrhythmic syncope.<sup>130,131</sup> 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.<sup>132</sup> 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.<sup>130,131</sup> Similarly, multifactorial mechanisms are  
666 likely in other types of cardiac syncope, e.g. aortic stenosis,<sup>133</sup> hypertrophic cardiomyopathy (HCM),<sup>134</sup> and  
667 sick sinus syndrome.<sup>135,136</sup> 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



671  
672 **Figure 7** Rates of tilt testing positivity in different clinical conditions. These studies used the Westminster  
673 protocol for passive tilt,<sup>125</sup> the Italian protocol for TNG tilt,<sup>106</sup> and the clomipramine protocol,<sup>124</sup> for a total of  
674 1453 syncope patients and 407 controls without syncope. Studies using other tilt protocols, e.g. isoproterenol  
675 challenge, were not included. Clom = clomipramine; TNG = trinitroglycerin; VVS = vasovagal syncope.

### 676 677 Tilt testing

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Indications</b>		
Tilt testing should be considered in patients with suspected reflex syncope, OH, POTS, or PPS. <sup>23,24,105-109,111-117</sup>	<b>Ila</b>	<b>B</b>
Tilt testing may be considered to educate patients to recognize symptoms and learn physical manoeuvres. <sup>119-121</sup>	<b>IIb</b>	<b>B</b>
<b>Diagnostic criteria</b>		
Reflex syncope, OH, POTS, or PPS should be considered likely if tilt testing reproduces symptoms along with the characteristic circulatory pattern of these conditions. <sup>23,24,105-109,111-117</sup>	<b>Ila</b>	<b>B</b>
<b>Additional advice and clinical perspectives</b>		
<ul style="list-style-type: none"> <li>• A negative tilt-table response does not exclude a diagnosis of reflex syncope.</li> <li>• 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</li> </ul>		



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.<sup>122,123</sup>
- Tilt testing may be helpful in separating syncope with abnormal movements from epilepsy.<sup>137</sup>
- Tilt testing may have value in distinguishing syncope from falls.<sup>23</sup>
- 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.<sup>116,117</sup> 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.<sup>118</sup>

EEG = electroencephalogram; OH = orthostatic hypotension; POTS = postural orthostatic tachycardia syndrome; PPS = psychogenic pseudosyncope; VVS = vasovagal syncope.

<sup>a</sup> Class of recommendation.

<sup>b</sup> Level of evidence.

678

679

### 4.2.3 Basic autonomic function tests

680

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

681

682

#### 4.2.3.1 Valsalva manoeuvre

683

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.<sup>138-143</sup> 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.<sup>144</sup>

688

689

690

691

#### 4.2.3.2 Deep breathing

692

The methodology of the deep breathing test is described in the *Web Practical Instructions section 7.1.2*.

693

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  $\geq 15$  b.p.m. in healthy individuals aged  $>50$  years.<sup>145</sup> There is strong consensus that blunted or abolished variation is suggestive of parasympathetic dysfunction.<sup>142,143,146,147</sup>

694

695

#### 4.2.3.3 Other autonomic function tests

696

Further tests to evaluate cardiovascular sympathetic function include calculation of the 30:15 ratio, cold

700

701 pressure test, sustained hand grip, and mental arithmetic. There is weak evidence that these tests may be  
 702 useful.<sup>13,142,143,147</sup>

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.<sup>148</sup> 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<sup>140,148-151</sup> (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.<sup>152</sup> There is weak evidence that ABPM may also detect the degree  
 712 of OH in daily life better than single office BP measurements.<sup>153</sup>

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.<sup>154</sup>

717  
 718

719 **Basic autonomic function tests**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Valsalva manoeuvre</b> Valsalva manoeuvre should be considered for assessment of autonomic function in patients with suspected neurogenic OH. <sup>138-143</sup>	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. <sup>144</sup>	IIb	C
<b>Deep breathing test</b> Deep breathing test should be considered for assessment of autonomic function in patients with suspected neurogenic OH. <sup>142,143,146,147</sup>	IIa	B
<b>Other autonomic function tests</b> 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. <sup>13,142,143,147</sup>	IIb	C
<b>ABPM</b> ABPM is recommended to detect nocturnal hypertension in patients with autonomic failure. <sup>140,148-151</sup>	I	B
ABPM should be considered to detect and monitor degree of OH and supine hypertension in daily life in patients with autonomic failure. <sup>152,153</sup>	IIa	C
ABPM and HBPM may be considered to detect whether BP is abnormally low during episodes suggestive of orthostatic intolerance.	IIb	C

<p><b>Additional advice and clinical perspectives</b></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• The effect of age and sex should be considered when interpreting autonomic function tests.<sup>145,155-157</sup></li> <li>• 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.<sup>147</sup></li> </ul>		
<p>ABPM = ambulatory blood pressure monitoring; BP = blood pressure; HBPM = home blood pressure monitoring; HR = heart rate; OH = orthostatic hypotension.</p> <p><sup>a</sup> Class of recommendation.</p> <p><sup>b</sup> Level of evidence.</p>		

720

721 **4.2.4 Electrocardiographic monitoring (non-invasive and invasive)**

722

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

726

727 *4.2.4.1 In-hospital monitoring*

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

732

733 *4.2.4.2 Holter monitoring*

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

740

741 *4.2.4.3 Prospective external event recorders*

742 Event recorders are external devices applied by the patient when symptoms occur. Whereas these recorders  
743 can be useful in the investigation of palpitations,<sup>163</sup> they have a marginal role in the evaluation of syncope.

744

745 *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.<sup>164,165</sup> 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.<sup>162</sup> External loop  
752 recorders can be useful in patients with relatively frequent syncope episodes.<sup>166-168</sup> 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.<sup>166</sup>

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.<sup>169-171</sup>

761

#### 762 4.2.4.7 Implantable loop recorders

763 In a meta-analysis of five randomized controlled trials,<sup>172-176</sup> 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.<sup>172,173,177,178</sup>

769 In pooled data from nine studies<sup>179</sup> 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<sup>176,180-183</sup> and in suspected reflex syncope.<sup>184-186</sup> 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<sup>174,187,188</sup> (*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%<sup>137,189-191</sup> (*Web Data Supplement Table 7*).
- 786 • Patients with unexplained falls: in pooled data, an attack could have been documented by ILR in 70% of

787 patients, with an arrhythmic cause being responsible in 14%<sup>191-194</sup> (*Web Data Supplement Table 8*).  
 788 • Patients with HCM, arrhythmogenic right ventricular cardiomyopathy, or primary electrical diseases (see  
 789 section 5.4).

790  
 791 **4.2.4.8 Diagnostic criteria**

792 The gold standard for the diagnosis of arrhythmic syncope is when there is a correlation between the  
 793 symptoms and an ECG recording.<sup>195,196</sup> The presence of some asymptomatic significant arrhythmias –  
 794 defined as prolonged asystole (≥3 s), rapid supraventricular tachycardias (SVTs) (i.e. >160 b.p.m. for >32  
 795 beats), or ventricular tachycardias (VTs) – has been considered by several authors as a diagnostic  
 796 finding.<sup>185,188,197-199</sup> On the other hand, although the absence of documentation of an arrhythmia during a  
 797 syncopal episode cannot be considered a specific diagnosis, it allows exclusion of an arrhythmia as the  
 798 mechanism of the syncope. The most evidence in support of the above diagnostic criteria is indirectly based  
 799 on the benefit of specific therapies guided by ECG monitoring in preventing syncopal recurrences.<sup>172,184-  
 800 186,188,200</sup>

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

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

811  
 812 **Electrocardiographic monitoring**

RecommendationsRecommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Indications</b>		
<i>Immediate in-hospital monitoring</i> (in bed or by telemetry) is indicated in high-risk patients (defined in <i>Table 6</i> ).	<b>I</b>	<b>C</b>
<i>Holter monitoring</i> should be considered in patients who have frequent syncope or presyncope (≥1 episode per week). <sup>161</sup>	<b>Ila</b>	<b>B</b>
<i>External loop recorders</i> should be considered, early after the index event, in patients who have an inter-symptom interval ≤4 weeks. <sup>162,166,168,201</sup>	<b>Ila</b>	<b>B</b>
<b>ILR:</b> ILR is indicated in an early phase of evaluation in patients with recurrent syncope of uncertain origin, absence of high-risk criteria (listed in <i>Table 6</i> ), and a high likelihood of recurrence within the battery life of the device. <sup>175,176,181-184,202</sup> and <i>Data Supplement Table 5</i>	<b>I</b>	<b>A</b>

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. <sup>174,180,187,188,195</sup> and <i>Data Supplement Tables 5 and 6</i>	<b>I</b>	<b>A</b>
ILR should be considered in patients with suspected or certain reflex syncope presenting with frequent or severe syncopal episodes. <sup>184-186</sup>	<b>IIa</b>	<b>B</b>
ILR may be considered in patients in whom epilepsy was suspected but the treatment has proven ineffective. <sup>137,189-191</sup> and <i>Data Supplement Table 7</i>	<b>IIb</b>	<b>B</b>
ILR may be considered in patients with unexplained falls. <sup>191-194</sup> and <i>Data Supplement Table 8</i>	<b>IIb</b>	<b>B</b>
<b>Diagnostic criteria</b>		
Arrhythmic syncope is confirmed when a correlation between syncope and an arrhythmia (bradyarrhythmia or tachyarrhythmia) is detected. <sup>172,184-186,188,200</sup>	<b>I</b>	<b>B</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. <sup>185,188,197-199</sup>	<b>IIa</b>	<b>C</b>
<b>Additional advice and clinical perspectives-</b>		
<ul style="list-style-type: none"> <li>• 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.<sup>158-160,183</sup></li> <li>• Exclude patients with a clear indication for ICD, pacemaker, or other treatments independent of a definite diagnosis of the cause of syncope.</li> <li>• 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.<sup>203</sup></li> <li>• 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.<sup>199</sup></li> <li>• The absence of arrhythmia during syncope excludes arrhythmic syncope</li> </ul>		
AV = atrioventricular; ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; SVT = supraventricular tachycardia; VT = ventricular tachycardia.		
<sup>a</sup> Class of recommendation.		
<sup>b</sup> Level of evidence.		

813

814

## 815 4.2.5 Video recording in suspected syncope

### 816 4.2.5.1 In-hospital video recording

817 For PNES, a video-electroencephalogram (EEG) form the highest level of diagnostic probability.<sup>204</sup> For  
818 syncope and PPS, video can play a similar, probably underused, role (see section 7). Adding video recording  
819 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.<sup>9</sup> 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.<sup>9,205</sup> Video-recording of tilt-induced PPS<sup>116</sup> 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.<sup>117</sup>

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.<sup>206,207</sup> 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.<sup>206</sup> Home video records allow  
 833 complex events such as syncope-induced epileptic seizures to be diagnosed.<sup>208</sup>

834

835 **Video recording in suspected syncope**

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

836 <sup>a</sup> Class of recommendation.

837 <sup>b</sup> 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,<sup>209</sup> 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.<sup>71</sup> 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  $\geq 1.6$  or 2 seconds for SNRT or  $\geq 525$  ms for corrected SNRT.<sup>210</sup> One observational study  
856 showed a relationship between the presence of prolonged SNRT at EPS and the effect of pacing on  
857 symptoms.<sup>211</sup> Another small prospective study showed that a corrected SNRT  $\geq 800$  ms had an eightfold  
858 higher risk of syncope than a SNRT below this value.<sup>212</sup>

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.<sup>213</sup> A  
862 prolonged H-V interval  $\geq 70$  ms or induction of 2<sup>nd</sup> or 3<sup>rd</sup> 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.<sup>214-216</sup> 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 EPS<sup>188</sup> or with a control group who received an empiric pacemaker.<sup>217</sup>  
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.<sup>187</sup> 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.<sup>213</sup>

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,<sup>218</sup> whereas  
884 the induction of ventricular fibrillation (VF) is considered a non-specific finding.<sup>37</sup> The absence of induction of  
885 ventricular arrhythmias identifies a group at lower risk of arrhythmic syncope.<sup>219</sup>

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,<sup>220</sup> 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 <sup>a</sup>	Level <sup>b</sup>
<b>Indications</b>		
In patients with syncope and previous myocardial infarction or other scar-related conditions, EPS is indicated when syncope remains unexplained after non-invasive evaluation. <sup>218</sup>	I	B
In patients with syncope and bifascicular BBB, EPS should be considered when syncope remains unexplained after non-invasive evaluation. <sup>188,214-217,221</sup>	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. <sup>210-212</sup>	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
<b>EPS-guided therapy</b>		
In patients with unexplained syncope and bifascicular BBB, a pacemaker is indicated in the presence of either a baseline H-V interval of $\geq 70$ ms, or second- or third-degree His-Purkinje block during incremental atrial pacing, or with pharmacological challenge. <sup>188,214-217,221</sup>	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. <sup>46</sup>	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. <sup>46,222</sup>	I	C
In patients with syncope and asymptomatic sinus bradycardia, a pacemaker should be considered if a prolonged corrected SNRT is present. <sup>210-212</sup>	IIa	B
<b>Additional advice and clinical perspectives</b>		
<ul style="list-style-type: none"> <li>• 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.</li> <li>• The induction of polymorphic VT or VF in patients with ischaemic or DCM cannot be considered a diagnostic finding of the cause of syncope.</li> <li>• EPS is generally not useful in patients with syncope, normal ECG, no heart disease, and no palpitations</li> </ul>		
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.		
<sup>a</sup> Class of recommendation.		
<sup>b</sup> Level of evidence.		

897

## 898 **4.2.7 Endogenous adenosine and other biomarkers**

899 Established cardiac biomarkers such as troponin and B-type natriuretic peptide have been used in  
900 distinguishing cardiac from non-cardiac syncope and in identifying structural heart disease.<sup>223-225</sup>

901

### 902 *4.2.7.1 Adenosine (triphosphate) test and plasma concentration*

903 The purinergic signalling system, including adenosine and its receptors, has been proposed in the  
904 assessment of unexplained syncope without prodrome.<sup>4,226</sup> A low plasma-adenosine level is associated with  
905 paroxysmal AV block or CSS, whereas a high level is seen in those with a hypotensive/vasodepressive  
906 tendency and VVS. In parallel, the adenosine/ATP provocation test has been performed to demonstrate  
907 adenosine sensitivity and paroxysmal cardioinhibitory propensity for selection of appropriate pacemaker  
908 candidates.<sup>4,227,228</sup> The test requires rapid (<2 seconds) injection of a 20-mg bolus of ATP/Adenosine during  
909 ECG monitoring. The induction of AV block with ventricular asystole lasting >6 seconds, or the induction of  
910 AV block lasting >10 seconds, is considered abnormal. ATP testing was positive in most patients with  
911 syncope of unknown origin (especially syncope without prodrome and without structural heart disease<sup>4</sup> but  
912 not in controls, suggesting that paroxysmal AV block could be the cause of unexplained syncope. Although  
913 in elderly patients with unexplained syncope and a positive ATP test, cardiac pacing may lead to substantial  
914 reduction of syncopal attacks,<sup>229</sup> previous studies showed no correlation between AV block induced by ATP  
915 and the electrocardiographic findings (documented by ILR) during spontaneous syncope.<sup>122,123,227</sup> Thus, the  
916 low predictive value of the test does not support its routine use in selecting patients for cardiac pacing, but  
917 rather its positivity suggests confirming the suspicion of asystolic syncope by means of prolonged ECG  
918 monitoring. The role of endogenous adenosine release in triggering a special form of asystolic syncope (so-  
919 called adenosine-sensitive syncope) remains under investigation.

920

### 921 *4.2.7.2 Cardiovascular biomarkers*

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

926

### 927 *4.2.7.3 Immunological biomarkers*

928 Autoantibodies against adrenergic receptors in OH and POTS have been reported, but further studies are  
929 needed.<sup>232-234</sup>

930

## 931 **4.2.8 Echocardiography**

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

937

938  
939  
940  
941  
942  
943  
944  
945  
946

#### 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  $\geq 50$  mmHg is usually considered to be the threshold at which left ventricular outflow tract obstruction becomes haemodynamically important.<sup>245-249</sup>

### Echocardiography

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Indications</b> Echocardiography is indicated for diagnosis and risk stratification in patients with suspected structural heart disease. <sup>235,236</sup>	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. <sup>245-249</sup>	I	B
<b>Diagnostic criteria</b> 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. <sup>237-244</sup>	I	C
<b>Additional advice and clinical perspectives</b>		
<ul style="list-style-type: none"> <li>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.</li> <li>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.</li> </ul>		
HCM = hypertrophic cardiomyopathy. <sup>a</sup> Class of recommendation. <sup>b</sup> Level of evidence.		

947  
948  
949  
950  
951  
952  
953  
954  
955  
956

### 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.<sup>250-252</sup> Tachycardia-related exercise-induced second- and third-degree AV block has been shown to be located distal to the AV node<sup>253</sup> and predicts progression to permanent AV block.<sup>254,255</sup> A resting ECG frequently shows intraventricular

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

959

960 **Exercise testing**

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

961

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.<sup>258</sup> 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.

968

969 **Coronary angiography**

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

970

971

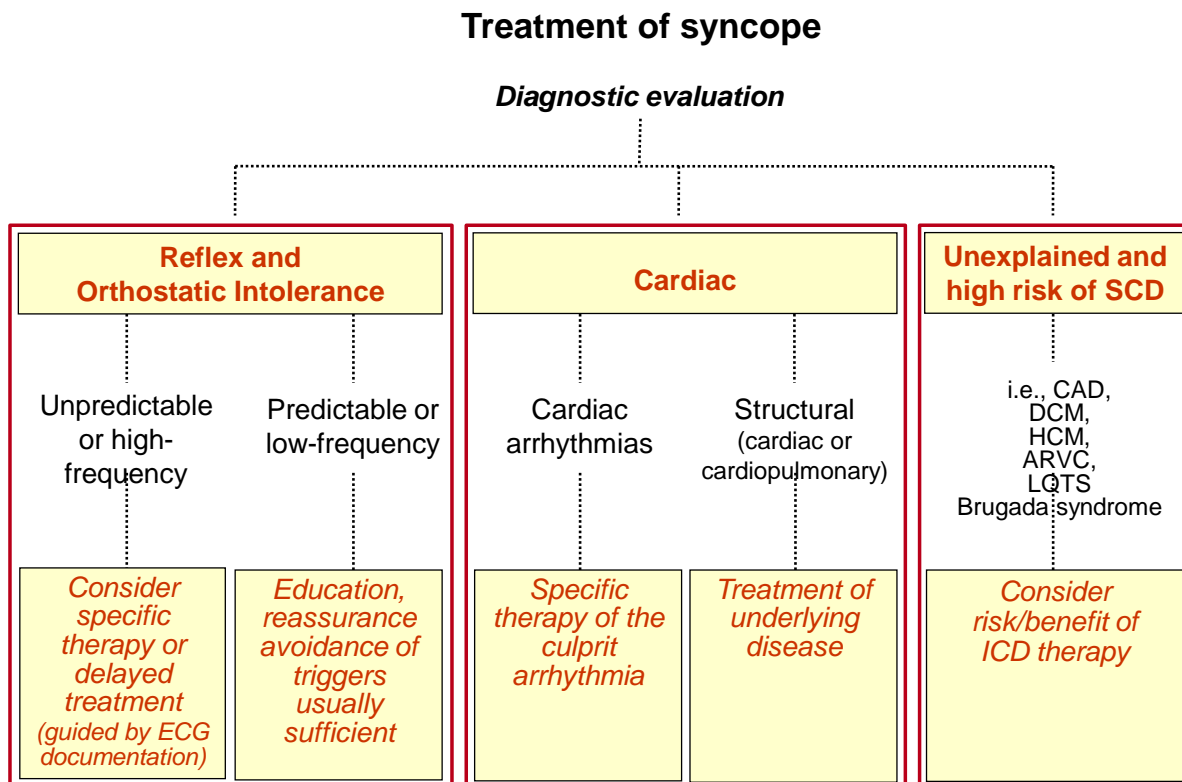
972

973

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.  
983

984  
985 The following three general principles should be considered:

- 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.

- 991 • Often, therapy to prevent recurrence differs from that for the underlying disease. The management of  
992 patients at high risk of SCD requires careful assessment of the individual patient's risk (see section 5.5).
- 993 • Syncopal recurrences often decrease spontaneously after medical assessment even in the absence of a  
994 specific therapy; in general syncope recurs in less than 50% of patients within 1–2 years (*Web Data  
995 Supplement Table 10*). The decrease seems to be more evident when there is lack of a clear anatomical  
996 substrate for syncope such as in the case of reflex syncope and unexplained syncope. The reason for this  
997 decrease is not known. Several potential clinical, statistical, and psychological explanations have been  
998 provided and all probably play a role (*Web Data Supplement Table 10*). Whatever the reason, the  
999 possibility of spontaneous improvement has major practical importance for treatment that can be  
1000 postponed in low-risk conditions. The consequence of the spontaneous decrease is that any therapy for  
1001 syncope prevention appears to be more effective than it actually is, and makes the results of  
1002 observational data on therapy questionable in the absence of a control group.

1003  
1004 **Table 9 Expected syncope recurrence rates with a permanent pacemaker in different clinical settings**  
1005 (for more details see *Web Data Supplement Table 9*).

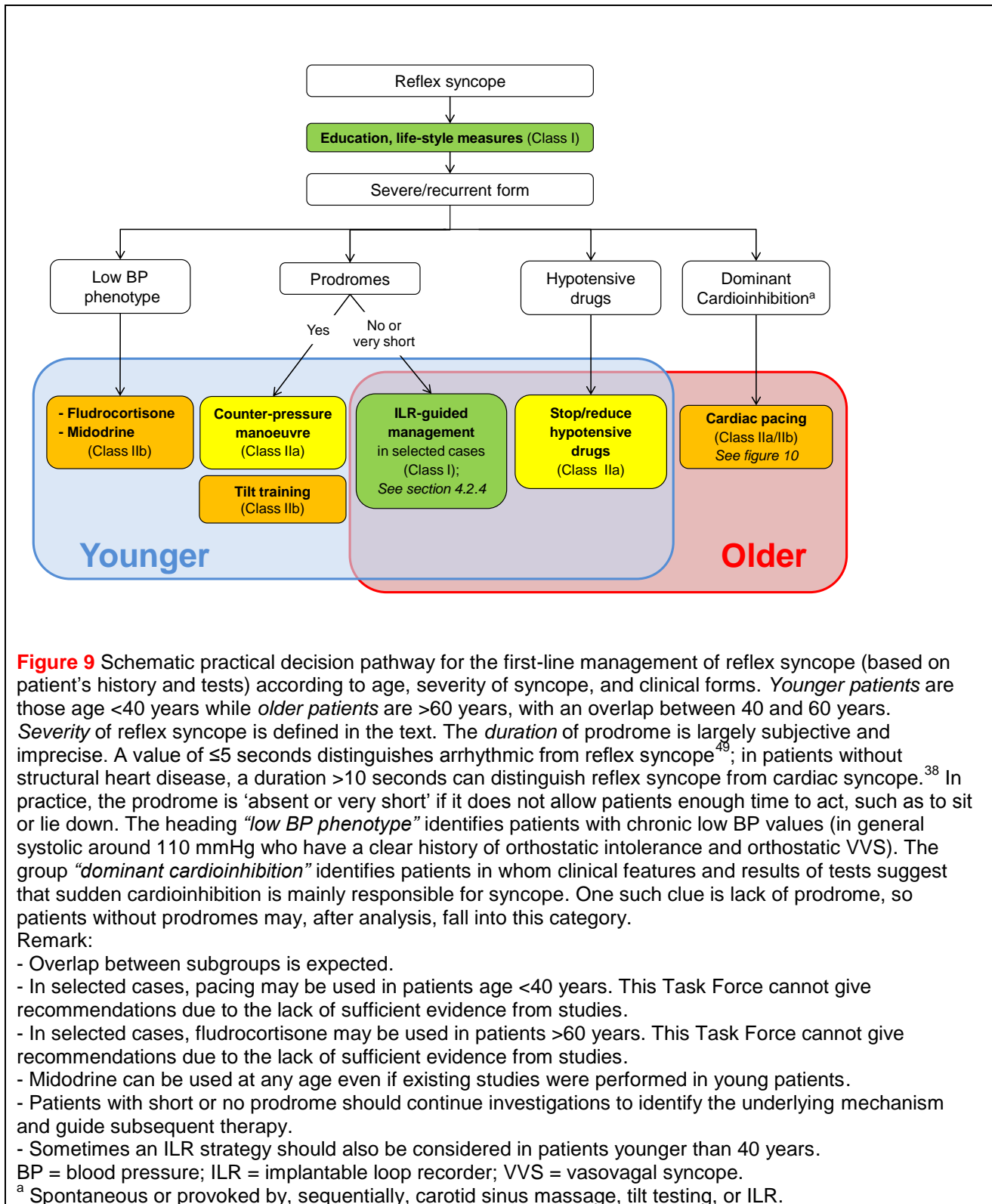
Clinical setting	Expected 2-year syncope recurrence rate with cardiac pacing
Syncope due to established bradycardia and absence of hypotensive mechanism	High efficacy ( $\leq 5\%$ recurrence rate)
Syncope due to established bradycardia and associated hypotensive mechanism	Moderate efficacy (5–25% recurrence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

1006

## 1007 5.2 Treatment of reflex syncope

1008 Despite its benign course, recurrent and unpredictable reflex syncope may be disabling. The cornerstone of  
1009 management of these patients is a non-pharmacological treatment, including education, lifestyle  
1010 modification, and reassurance regarding the benign nature of the condition.

1011 Additional treatment may be necessary in patients with *severe forms* as defined in *Web Practical  
1012 Instruction section 2.3* in particular: when very frequent syncope alters quality of life; when recurrent  
1013 syncope without – or with a very short – prodrome exposes the patient to a risk of trauma; and when  
1014 syncope occurs during a high-risk activity (e.g. driving, machine operation, flying, competitive athletics, etc.).  
1015 Only 14% of the highly selected population with reflex syncope who are referred to specialized syncope  
1016 units may need such additional treatment.<sup>186</sup> In general, no therapy is appropriate for every form of reflex  
1017 syncope. The most important discriminant for the choice of therapy is age. A decision pathway for the  
1018 selection of a specific therapy according to age, severity of syncope, and clinical forms is summarized in  
1019 *Figure 9*.



1020  
1021  
1022  
1023  
1024  
1025  
1026  
1027  
1028  
1029  
1030  
1031  
1032  
1033  
1034  
1035  
1036  
1037  
1038  
1039  
1040  
1041  
1042  
1043  
1044  
1045

### 1046 **5.2.1 Education and lifestyle modifications**

1047 Education and lifestyle modifications have not been evaluated in randomized studies, but there is a  
1048 consensus for implementing them as first-line therapy in all cases. These comprise reassurance about the  
1049 benign nature of the disease and education regarding awareness and possible avoidance of triggers and  
1050 situations (dehydration, hot crowded environments), and early recognition of prodromal symptoms in order  
1051 to sit or lie down and activate counter-pressure manoeuvres without delay. If possible, triggers should be  
1052 addressed directly, such as cough suppression in cough syncope, micturition in the sitting position, etc.  
1053 Increased intake of oral fluids is also advised. Salt supplementation at a dose of 120 mmol/day of sodium  
1054 chloride has been proposed.<sup>259</sup> In general, more than 50% of patients with recurrent syncopal episodes in  
1055 the 1 or 2 years before evaluation do not have syncopal recurrences in the following 1 or 2 years and, in  
1056 those with recurrences, the burden of syncope decreases even more than 70% compared with the  
1057 preceding period. The effect of education and reassurance is probably the most likely reason for the  
1058 decrease in syncope (*Web Data Supplement Table 10*). An example of a patient instruction sheet can be  
1059 found in the *Web Practical Instructions section 9.1: ESC information sheet for patients affected by reflex*  
1060 *syncope*..

1061 ***Despite the lack of controlled studies, there is strong consensus that education and lifestyle***  
1062 ***modifications have a high impact in reducing recurrence of syncope.***

### 1064 **5.2.2 Discontinuation/reduction of hypotensive therapy**

1065 Key in prevention of recurrence of syncope is careful avoidance of agents that lower BP, i.e. any  
1066 antihypertensive agents, nitrates, diuretics, neuroleptic antidepressants or L-dopa antagonists. In a small  
1067 randomized trial<sup>260</sup> performed in 58 patients (mean age 74 ± 11 years) affected by vasodepressor reflex  
1068 syncope diagnosed by tilt testing or CSM who were taking on average 2.5 hypotensive drugs,  
1069 discontinuation or reduction of the vasoactive therapy caused a reduction of the rate of the primary combined  
1070 endpoint of syncope, presyncope, and adverse events from 50% to 19% (hazard ratio 0.37) compared with a  
1071 control group who continued hypotensive therapy during a follow-up of 9 months. In the Systolic Blood  
1072 Pressure Intervention Trial,<sup>261</sup> patients at high cardiovascular risk who were already using antihypertensive  
1073 drugs targeting a systolic BP of 120 mmHg had an approximately twofold risk of syncope versus the control  
1074 group targeting a systolic BP of 140 mmHg. In a short-term randomized trial<sup>262</sup> conducted in 32 patients  
1075 affected by CSS, withdrawal of vasodilator therapy reduced the magnitude of the vasodepressor reflex  
1076 induced by CSM.

1077 ***There is moderate evidence that discontinuation/reduction of hypotensive therapy targeting a***  
1078 ***systolic BP of 140 mmHg should be effective in reducing syncopal recurrences in patients with***  
1079 ***hypotensive susceptibility. Further research is likely to have an important impact on our confidence***  
1080 ***in the estimate.***

### 1082 **5.2.3 Physical counter-pressure manoeuvres**

1083 Isometric muscle contractions increase cardiac output and arterial BP during the phase of impending reflex  
1084 syncope. Three clinical studies<sup>119,120,263</sup> and one prospective multicentre randomized trial<sup>121</sup> assessed the  
1085 effectiveness of physical counter-pressure manoeuvres (PCM) of the legs or arms and showed that they  
1086 allowed the patient to avoid or delay losing consciousness in most cases. In the Physical Counterpressure



1087 Manoeuvres Trial (PC-Trial),<sup>121</sup> 223 patients aged  $38 \pm 15$  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.<sup>264</sup> 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.***  
1096

#### 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.<sup>265</sup> While some studies suggested modest benefit with outpatient tilt  
1101 training,<sup>266,267</sup> most controlled trials reported no significant effect.<sup>268-272</sup> 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.

##### 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.<sup>273</sup> The mechanism of action can be  
1117 compared with that of saline infusion, which has also proved effective in acute tilt-test studies.<sup>274</sup> The  
1118 Prevention of Syncope Trial (POST) 2<sup>275</sup> 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.<sup>276</sup>

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.<sup>277</sup> 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 trials<sup>278</sup> 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.***  
1148

#### 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.<sup>279,280</sup> 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.***  
1157

#### 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.<sup>281</sup> 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.<sup>1,282</sup> In a small randomized trial,  
1163 benzodiazepine was as effective as metoprolol.<sup>283</sup> A somatostatin analogue (octreotide)<sup>284</sup> was used in a few  
1164 patients affected by orthostatic intolerance and its effect cannot be properly evaluated.

#### 1165 5.2.5.5 Emerging new therapies in specific subgroups

1166

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.<sup>285,286</sup> 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.<sup>287</sup> 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.<sup>288</sup> 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.<sup>289</sup>

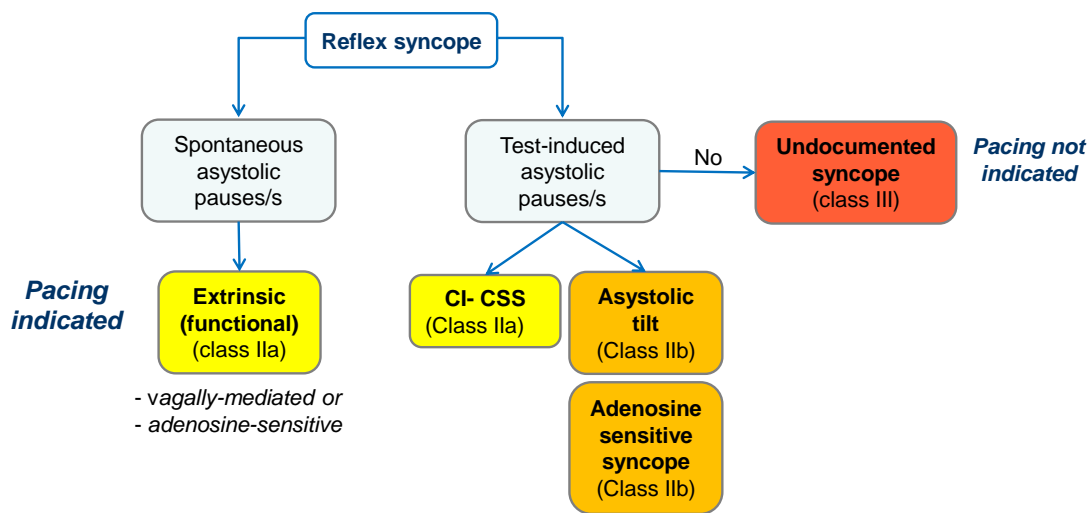
1182 *Ganglionic plexus ablation.* Radiofrequency ablation of vagal ganglia located close to the sinus node  
1183 and AV node was reported to abolish the vagal efferent output during VVS in some observational studies  
1184 and case reports.<sup>290,291</sup> However, owing to a weak rationale, small 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.



1194

1195

1196

1197

1198

1199

1200

1201

1202

1203

1204

1205

1206

1207

1208

1209

1210

1211

1212

1213

1214

**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%<sup>184</sup> and 83%,<sup>200</sup> but did not prevent all syncopal events. In the randomized double-blind Third International Study on Syncope of Uncertain Etiology (ISSUE)-3 trial,<sup>185</sup> 77 patients who had documentation, by means of ILR, of syncope with  $\geq 3$ -second asystole or  $\geq 6$ -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,<sup>292</sup> 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  $\geq 40$  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 review<sup>293</sup> including 12 studies for  
1218 a total of 601 paced and 305 unpaced patients, the syncope 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 studies<sup>293</sup> 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 syncope recurrence was 7% at 1 year, 16% at 3 years, and 20% at 5 years.<sup>90</sup> In the  
1224 CSS subgroup of the multicentre SUP 2 study,<sup>292</sup> 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 Guidelines<sup>294</sup> 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 syncope 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<sup>93,98</sup>  
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<sup>293,295</sup>; 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.<sup>296-300</sup> 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.<sup>301</sup> In general, pacing was  
1245 ineffective in trials that enrolled patients without an asystolic tilt response.<sup>299,300</sup> 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,<sup>302</sup> 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,<sup>292</sup> 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

1256 controls and were similar to those observed in patients with CSS or with ECG-documented asystole. In a  
1257 recent multicentre randomized controlled cross-over trial performed in 46 patients aged >40 years, affected  
1258 by severely recurrent (>5 episodes during life) cardioinhibitory VVS,<sup>303</sup> during 24-month follow-up, syncope  
1259 recurred in 4 (9%) patients treated with a dual-chamber pacemaker with closed loop stimulation compared  
1260 with 21 (46%) patients who had received a sham pacemaker programmed off ( $P = 0.0001$ ).

1261 Adding video recording to tilt testing, Saal *et al*<sup>205</sup> recently showed, in patients with asystole, that  
1262 asystole occurred 3 seconds before syncope or later in one-third of patients, in whom cardioinhibition was  
1263 too late to have primarily caused syncope; in the other two-thirds of asystolic tilt responses, the cause must  
1264 have been mainly cardioinhibition or a combination of cardioinhibition and vasodepression.

1265 The clinical presentation is probably as important as tilt-test positivity when selecting patients who  
1266 can benefit from cardiac pacing. The SUP 2 study population was characterized by higher mean age, history  
1267 of recurrent syncope beginning in middle or older age, and frequent injuries, probably due to presentation  
1268 without warning.<sup>292</sup>

1269 ***Owing to the contrasting results of the randomized trials, the estimated benefit of dual-***  
1270 ***chamber pacing in cardioinhibitory tilt-positive patients is weak. Divergence of opinion exists among***  
1271 ***experts. Further research is very likely to have an important impact on recommendations.***  
1272 ***Conversely, there is strong consensus that pacing cannot be offered to patients with non-***  
1273 ***cardioinhibitory tilt-positive response and further tests (e.g. ILR) are warranted to document the***  
1274 ***mechanism of the spontaneous reflex.***

1275  
1276

#### 1277 5.2.6.4 Evidence from trials in patients with adenosine-sensitive syncope

1278 Under this term, classified as a non-classical form of reflex syncope in *Table 3*, different clinical conditions  
1279 are included, which have in common a supposed role of adenosine in the genesis of syncope.

1280 A new clinical entity, called idiopathic AV block, has recently been described in patients with a long  
1281 history of syncope and in whom paroxysmal AV block could be recorded at the time of syncope recurrence.<sup>5</sup>  
1282 These patients had an otherwise normal heart and no sign of conduction disease on ECG and EPS; they  
1283 had very low plasma adenosine levels and a high induction rate of transient complete heart block during  
1284 exogenous injections of adenosine. No syncope recurrence was observed after permanent cardiac pacing  
1285 over very long periods of follow-up and there was no permanent AV block.

1286 Similarly, the entity of “low adenosine syncope” has recently been described in patients who have  
1287 an otherwise unexplained syncope with sudden onset without prodrome and a normal heart and normal  
1288 ECG.<sup>4</sup> The clinical, laboratory, and biological features of these patients are similar to those observed in  
1289 patients affected by idiopathic paroxysmal AV block. Unlike in VVS, tilt testing is usually negative.<sup>4,226</sup> No  
1290 syncope recurrence was observed after permanent cardiac pacing in 10 patients who had ECG  
1291 documentation of asystolic pause due to sinus arrest or AV block.<sup>286</sup>

1292 In a small multicentre trial<sup>227</sup> performed in 80 highly selected elderly patients with unexplained  
1293 unpredictable syncope who had a positive response to intravenous injection of a bolus of 20 mg of ATP,  
1294 dual-chamber cardiac pacing significantly reduced the 2-year syncope recurrence rate from 69% in the  
1295 control group to 23% in the active group.

1296 ***There is weak evidence that dual-chamber cardiac pacing may be useful in reducing***  
1297 ***recurrences of syncope in patients with the clinical features of adenosine-sensitive syncope. The***  
1298 ***documentation of possible bradyarrhythmia in spontaneous syncope remains the preferred eligibility***  
1299 ***criterion for pacing.***

1300

#### 1301 *5.2.6.5 Choice of pacing mode*

1302 In CSS, a few small controlled studies<sup>304,305</sup> and one registry<sup>306</sup> showed that dual-chamber pacing is better  
1303 than the VVI mode in counteracting BP fall during CSM and in preventing symptom recurrences. Even if the  
1304 quality of evidence is weak, dual-chamber pacing is widely preferred in clinical practice.

1305 In patients with VVS, dual-chamber pacing was used mostly with a rate-drop response feature that  
1306 instituted rapid dual-chamber pacing if the device detected a rapid decrease in HR. A comparison between  
1307 dual-chamber closed-loop stimulation and conventional dual-chamber pacing has been performed by means  
1308 of a crossover design in two small studies; these studies showed fewer syncope recurrences with close-loop  
1309 stimulation both in the acute setting during repeated tilt testing<sup>307</sup> and during 18-month clinical follow-up.<sup>308</sup>

1310

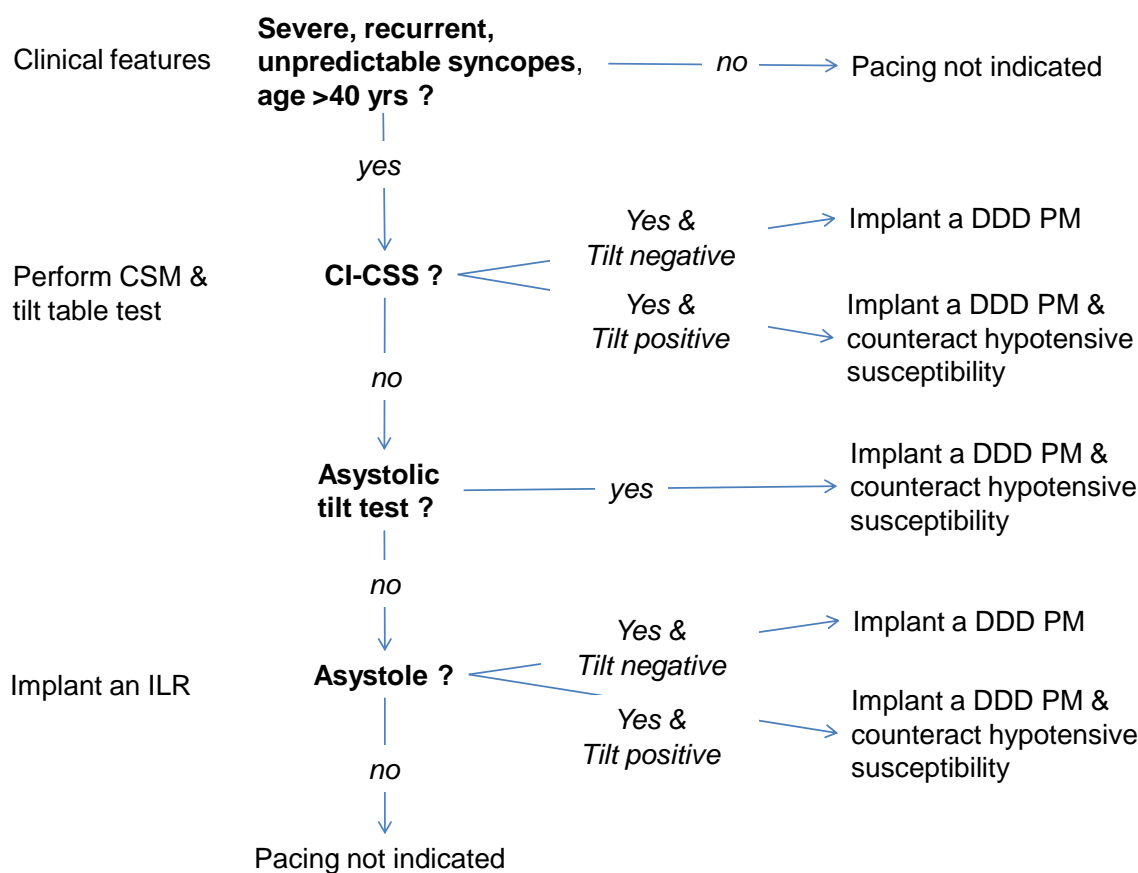
#### 1311 *5.2.6.6 Selection of patients for pacing and proposed algorithm*

1312 The fact that pacing is effective does not mean it is always necessary. In patients with reflex syncope,  
1313 cardiac pacing should be the last choice and should only be considered in highly selected patients, i.e. those  
1314  $\geq 40$  years of age (mostly  $>60$  years), affected by severe forms of reflex syncope with frequent recurrences  
1315 associated with a high risk of injury, often due to the lack of prodrome.<sup>186</sup> While there is growing scepticism  
1316 over diagnostic accuracy of tilt testing for syncope diagnosis, emerging evidence supports the use of tilt  
1317 testing in assessing *hypotensive susceptibility* to reflex hypotension.<sup>132</sup> Tilt testing may be considered to  
1318 identify patients with an associated hypotensive response who would be less likely to respond to permanent  
1319 cardiac pacing (see section 4.2.2.2). In a meta-analysis<sup>309</sup> of individual patient data from four studies  
1320 performed in patients with asystolic reflex syncope documented by a ILR, the estimated 3-year recurrence  
1321 rate of syncope was 2% (95% CI  $\pm$  4%) in tilt-negative patients and 33% (95% CI  $\pm$  20%) in tilt-positive  
1322 patients; a positive tilt test response was the only significant predictor of syncope recurrence with a hazard  
1323 ratio of 4.3. The patients with hypotensive susceptibility should need measures directed to counteract  
1324 hypotensive susceptibility in addition to cardiac pacing, e.g. discontinuation/reduction of hypotensive drugs  
1325 and administration of fludrocortisone or midodrine.

1326 The algorithm shown in *Figure 11* has recently been prospectively validated in a multicentre  
1327 pragmatic study, which showed a low recurrence rate of syncope with pacing of 9% at 1 year and 15% at 2  
1328 years, significantly lower than the 22% and 37%, respectively, observed in unpaced controls.<sup>186</sup>

1329

## Pacing for reflex syncope: decision pathway



1330

1331

1332 **Figure 11** Decision pathway for cardiac pacing in patients with reflex syncope. CI-CSS = cardioinhibitory  
 1333 carotid sinus syndrome; CSM = carotid sinus massage; DDD PM = dual-chamber pacemaker; ILR =  
 1334 implantable loop recorder.

1335

1336

### Treatment of reflex syncope

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Education and lifestyle modifications</b> Explanation of the diagnosis, provision of reassurance, explanation of risk of recurrence, avoidance of triggers and situations are indicated in all patients. <small>Web Data Supplement Table 10</small>	<b>I</b>	<b>B</b>
<b>Discontinuation/reduction of hypotensive therapy</b> Modification or discontinuation of hypotensive drug regimen should be considered in patients with vasodepressor syncope, if possible. <small>260-262</small>	<b>IIa</b>	<b>B</b>
<b>Physical manoeuvres</b> Isometric PCM should be considered in patients with prodromes who are less than 60 years of age. <small>119-121,263,264</small>	<b>IIa</b>	<b>B</b>



Tilt training may be considered for the education of young patients. <sup>265-272</sup>	<b>IIb</b>	<b>B</b>
<b>Pharmacological therapy</b>		
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. <sup>275</sup>	<b>IIb</b>	<b>B</b>
Midodrine may be considered in patients with the orthostatic form of VVS. <sup>278</sup>	<b>IIb</b>	<b>B</b>
Beta-adrenergic blocking drugs are not indicated. <sup>279,280</sup>	<b>III</b>	<b>A</b>
<b>Cardiac pacing</b>		
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. <sup>184,185,200,292</sup>	<b>IIa</b>	<b>B</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. <sup>90,292,293</sup>	<b>IIa</b>	<b>B</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. <sup>292,297,298,303</sup>	<b>IIb</b>	<b>B</b>
Cardiac pacing may be considered to reduce syncope recurrences in patients with the clinical features of adenosine-sensitive syncope. <sup>5,227,286</sup>	<b>IIb</b>	<b>B</b>
Cardiac pacing is not indicated in the absence of a documented cardioinhibitory reflex. <sup>299,300</sup>	<b>III</b>	<b>B</b>

#### **Additional advice and clinical perspectives**

- In general, no therapy can completely prevent syncope recurrence during long-term follow-up. A decrease of the syncope burden is a reasonable goal of therapy.
- The fact that pacing may be effective does not mean that it is also always necessary. It must be emphasized that the decision to implant a pacemaker needs to be made in the clinical context of a benign condition that frequently affects young patients. Thus, cardiac pacing should be limited to a highly selected small proportion of patients affected by severe reflex syncope. Patients suitable for cardiac pacing are older with a history of recurrent syncope beginning in middle or older age and with frequent injuries, probably due to presentation without warning. Syncope recurrence is still expected to occur despite cardiac pacing in a minority of patients.
- Tilt test response is the strongest predictor of pacemaker efficacy.<sup>309</sup> 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.

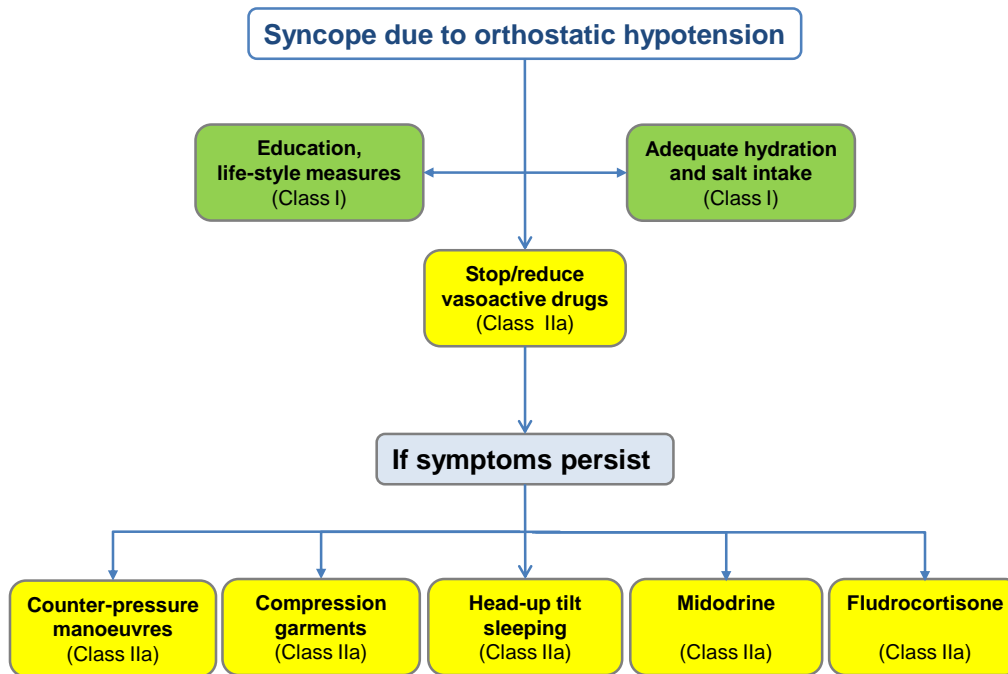
<sup>a</sup> Class of recommendation.

<sup>b</sup> 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

1344  
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  
1352 Expansion of extracellular volume is an important goal. In the absence of hypertension, patients should be  
1353 instructed to have a sufficient salt and water intake, targeting 2–3 litres of fluids per day and 10 grams of

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

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.<sup>312</sup> 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 medications<sup>313</sup> or the use of three or more antihypertensive drugs may be a significant predictor of  
1364 OH.<sup>314</sup> 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.<sup>315-318</sup>

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.<sup>319</sup>

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.<sup>23,320,321</sup>

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.<sup>104,322,323</sup>

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.<sup>324-326</sup>

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.<sup>327</sup> The evidence in favour of fludrocortisone is from two small observational studies (in

1395 combination with head-up sleeping) and one double-blind trial in 60 patients; the observational studies  
 1396 showed haemodynamic benefit and, in the trial, treated patients were less symptomatic with higher  
 1397 BP.<sup>322,327,328</sup>

1398 ***The desirable effects of fludrocortisone outweigh the undesirable effects. The quality of***  
 1399 ***evidence is moderate and further research is likely to have an important impact on the estimate of***  
 1400 ***benefit.***

1401  
 1402 **5.3.9 Additional therapies**

1403 Additional and less frequently used treatments, alone or in combination, include desmopressin in patients  
 1404 with nocturnal polyuria, octreotide in postprandial hypotension, erythropoietin in anaemia, pyridostigmine,  
 1405 use of walking-sticks, frequent small meals, and judicious exercise of leg and abdominal muscles, especially  
 1406 swimming. Their efficacy is less established.<sup>104</sup>

1407  
 1408 **5.3.10 Emerging new pharmacological therapy in specific subgroups**

1409 Droxidopa, a precursor of norepinephrine, is a centrally and peripherally acting alpha/beta agonist approved  
 1410 by the United States Food and Drug Administration for the treatment of symptomatic neurogenic OH.  
 1411 Droxidopa has recently been investigated for the treatment of neurogenic OH in four short-term randomized  
 1412 controlled trials<sup>329-332</sup> with a total of 485 patients. They showed a modest increase in standing systolic BP and  
 1413 symptom benefit of droxidopa over placebo regarding some items of quality of life after 2 weeks of treatment,  
 1414 but its benefit was lost after 8 weeks.<sup>333</sup> Thus, current evidence is insufficient to confirm the efficacy of  
 1415 droxidopa for long-term use.

1416  
 1417 **Treatment of OH**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
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. <sup>310,311</sup>	I	C
Modification or discontinuation of hypotensive drugs regimen should be considered. <sup>312-318</sup>	IIa	B
Isometric PCM should be considered. <sup>319</sup>	IIa	C
Abdominal binders and/or support stockings to reduce venous pooling should be considered. <sup>23,320,321</sup>	IIa	B
Head-up tilt sleeping (>10 degrees) to increase fluid volume should be considered. <sup>104,322,323</sup>	IIa	C
Midodrine should be considered if symptoms persist. <sup>324-326</sup>	IIa	B
Fludrocortisone should be considered if symptoms persist. <sup>322,327,328</sup>	IIa	C

**Additional advice and clinical perspectives**

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

BP = blood pressure; OH = orthostatic hypertension; PCM = physical counter-pressure manoeuvres.

<sup>a</sup> Class of recommendation.

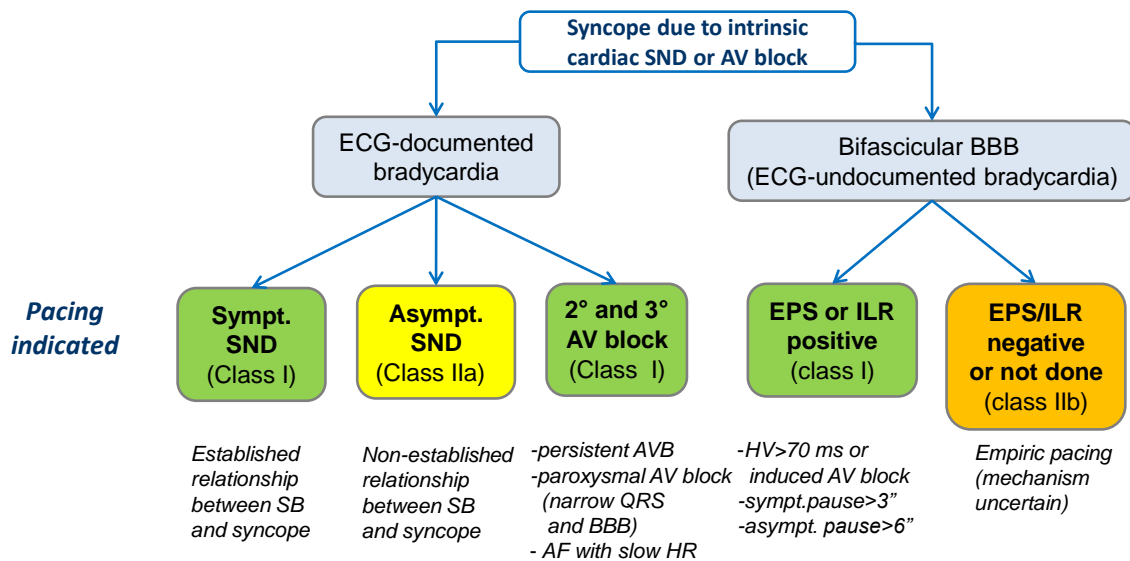
<sup>b</sup> Level of evidence.

1418  
1419  
1420  
1421  
1422  
1423

**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*.



1424

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.<sup>334-338</sup> 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 years<sup>339-341</sup> (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.<sup>135,136</sup> 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.<sup>294</sup> An abnormal SNRT enhances the probability of efficacy of cardiac pacing  
1450 (see section 4.2.6.1).<sup>210-212</sup>

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*<sup>341</sup> 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

1466 the subgroup with syncope before pacemaker implantation. More recently, Sud *et al*<sup>200</sup> reported no syncope  
1467 recurrence, and Aste *et al*<sup>255</sup> reported a recurrence of 1% at 5 years after pacemaker implantation among 73  
1468 patients with documented persistent or intermittent documented AV block (see *Web Data Supplement Table*  
1469 *9*).

1470

#### 1471 *5.4.1.3 Bundle branch block and unexplained syncope*

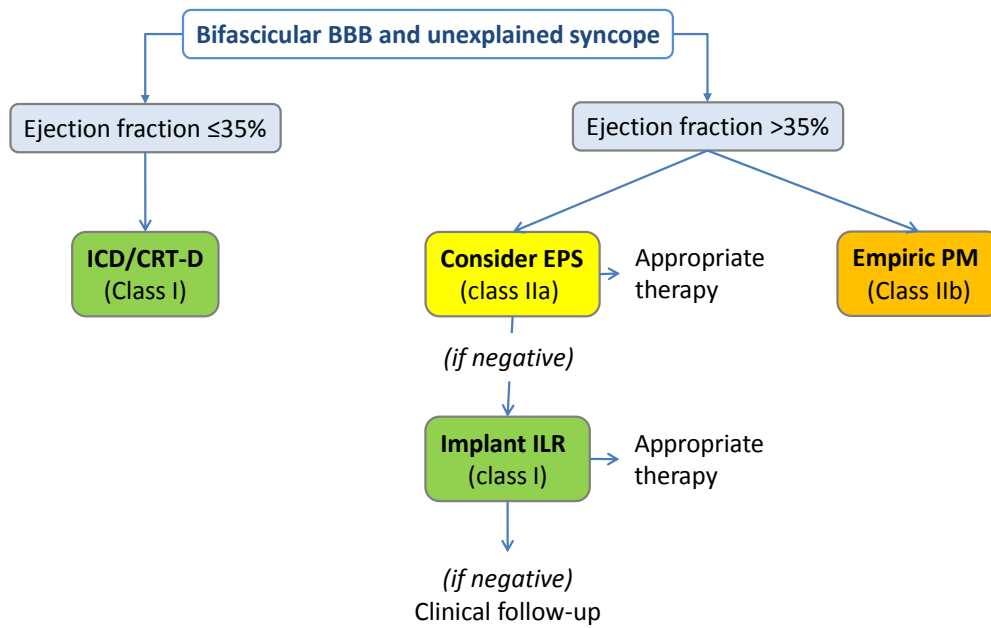
1472 The presence of bifascicular BBB suggests that the cause of syncope may be complete heart block.  
1473 Nevertheless, less than half of the patients with bifascicular BBB and syncope will have a final diagnosis of  
1474 AV block, a similar percentage will have a final diagnosis of reflex syncope, and, in approximately 15%, the  
1475 cause will remain unexplained at the end of a complete work-up.<sup>342</sup> In addition, among patients receiving an  
1476 ILR, approximately half remained free of syncope for >2 years after the implantation.<sup>187,188,342,343</sup> 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.<sup>217,344</sup> 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.<sup>294</sup>

1482 To overcome the above problems, ESC guidelines on pacing<sup>294</sup> 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<sup>188,217</sup>; 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.<sup>345-347</sup> 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.<sup>218</sup>  
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.<sup>345,346</sup> 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

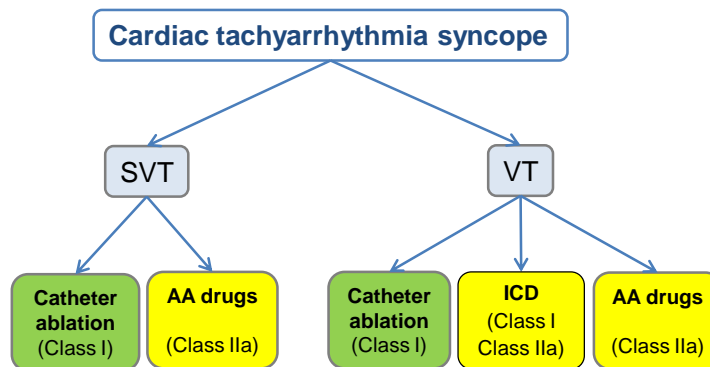
1508 **Figure 14** Therapeutic algorithm for patients presenting with unexplained syncope and BBB. BBB = bundle  
1509 branch block; CRT-D = cardiac resynchronization therapy defibrillator; EPS = electrophysiological study; ICD  
1510 = implantable cardioverter defibrillator; ILR = implantable loop recorder;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





1515  
 1516 **Figure 15** Choice of therapy for patients presenting with syncope due to cardiac tachyarrhythmias as the  
 1517 primary cause. AA = antiarrhythmic; ICD = implantable cardioverter defibrillator; SVT = supraventricular  
 1518 tachycardia; VT = ventricular tachycardia.

1519  
 1520 *5.4.2.1 Paroxysmal supraventricular tachycardia*

1521 In patients with paroxysmal AV nodal re-entrant tachycardia, AV re-entrant tachycardia, typical atrial flutter,  
 1522 and ectopic tachycardia associated with syncope, catheter ablation is the first-choice treatment. In these  
 1523 patients, the role of drug therapy is limited to being a bridge to ablation or when ablation has failed. In  
 1524 patients with syncope associated with atrial fibrillation or atypical left atrial flutter, the decision should be  
 1525 individualized.

1526  
 1527 *5.4.2.2 Paroxysmal ventricular tachycardia*

1528 Syncope due to torsade de pointes is not uncommon and is, in its acquired form, the result of drugs that  
 1529 prolong the QT interval. Treatment is the immediate discontinuation of the suspected drug.

1530 Catheter ablation or drug therapy are recommended in patients with syncope due to VT in presence  
 1531 or absence of structural heart disease in order to prevent syncope recurrence (*Figure 15*). A detailed  
 1532 guideline to antiarrhythmic drug usage in patients with VT can be found in 2015 ESC guidelines for VA and  
 1533 prevention of SCD.<sup>46</sup>

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,<sup>31,348</sup> it is indicated  
 1536 to reduce the risk of SCD (refer to 2015 ESC guidelines for VA and prevention of SCD<sup>46</sup>). An ICD is also  
 1537 indicated in patients with syncope and previous myocardial infarction who have VT induced during EPS<sup>346</sup>  
 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 <sup>a</sup>	Level <sup>b</sup>
<b>Bradycardia (intrinsic)</b>		
Cardiac pacing is indicated when there is an established relationship between syncope and symptomatic bradycardia due to:		
• Sick sinus syndrome. <sup>210-212,334-338</sup>	I	B
• Intrinsic AV block. <sup>200,255,341</sup>	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. <sup>135,136,210-212,339,340</sup>	IIa	C
Cardiac pacing is not indicated in patients when there are reversible causes for bradycardia.	III	C
<b>Bifascicular BBB</b>		
Cardiac pacing is indicated in patients with syncope, BBB, and a positive EPS or ILR-documented AV block. <sup>188,217</sup>	I	B
Cardiac pacing may be considered in patients with unexplained syncope and bifascicular BBB. <sup>217,255,344</sup>	IIb	B
<b>Tachycardia</b>		
Catheter ablation is indicated in patients with syncope due to SVT or VT in order to prevent syncope recurrence. <sup>46</sup>	I	B
An ICD is indicated in patients with syncope due to VT and ejection fraction $\leq 35\%$ . <sup>46</sup>	I	A
An ICD is indicated in patients with syncope and previous myocardial infarction who have VT induced during EPS. <sup>218</sup>	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. <sup>46</sup>	IIa	C

Antiarrhythmic drug therapy, including rate-control drugs, should be considered in patients with syncope due to SVT or VT.	<b>IIa</b>	<b>C</b>
<p><b>Additional advice and clinical perspectives</b></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Pacing is not indicated in unexplained syncope without evidence of any conduction disturbance.</li> <li>• 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.</li> <li>• 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.</li> <li>• When indicated, ICD prevents SCD but it may be unable to prevent syncope due to VT recurrence.<sup>31,348</sup> 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.</li> </ul>		
<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><sup>a</sup> Class of recommendation.</p> <p><sup>b</sup> Level of evidence.</p>		

1545

1546

1547

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

1548

1549

1550

1551

1552

1553

1554

1555

1556

1557

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.

1558 ***Even in the absence of specific trials, there is strong consensus that with syncope secondary***  
1559 ***to structural cardiac disease, the goal of treatment is not only to prevent syncopal recurrence, but to***  
1560 ***treat the underlying disease and decrease the risk of death.***  
1561

## 1562 **5.6 Treatment of unexplained syncope in patients at high risk of sudden cardiac death**

1563 The underlying clinical situation is that of a patient being evaluated for ICD implantation because they are  
1564 affected by syncope/s supposedly due to transient self-terminating ventricular tachyarrhythmias (fast VT or  
1565 VF), which had not yet been documented because of its short duration.<sup>349</sup> Syncope due to documented  
1566 VT/VF is outside the scope of this section; please refer to section 5.4.2. General guidance may be sought in  
1567 the 2015 ESC guidelines for VA and prevention of SCD.<sup>46</sup>  
1568

### 1569 **5.6.1 Definition**

1570 In general, a history of syncope in patients with structural heart disease or inheritable arrhythmia syndromes  
1571 is associated with a 2- to 4-fold increased risk of death<sup>348,350-353</sup> but varies between specific conditions.<sup>354-</sup>  
1572 <sup>356</sup> Moreover, there are very few studies on ICDs in patients with syncope associated with left ventricular  
1573 dysfunction,<sup>31,348</sup> cardiomyopathy, or inheritable arrhythmia syndromes.<sup>357</sup> In this guideline, we complement  
1574 previous ESC guidelines for VA and prevention of SCD<sup>46</sup> by providing a precise definition of unexplained  
1575 syncope and making recommendations for its investigation and management in different clinical settings.

- 1576 • For this section, *unexplained syncope* is defined as syncope that does not meet any class I diagnostic  
1577 criterion defined in the tables of recommendations in section 4. In the presence of clinical features  
1578 described in this section, unexplained syncope is considered a *suspected arrhythmic syncope*.

1579  
1580 When the mechanism of syncope is non-arrhythmic, the management of patients at high risk of SCD is the  
1581 same as for patients without syncope.  
1582

### 1583 **5.6.2 Left ventricular systolic dysfunction**

1584 The benefit of an ICD to reduce the risk of death is established. Thus, patients with unexplained syncope  
1585 who have an established ICD indication per current guidelines<sup>46</sup> must receive an ICD before and  
1586 independently of the evaluation of the mechanism of syncope, even if the mechanism of syncope is unknown  
1587 or uncertain at the end of a complete work-up. While this strategy may help to prolong life, patients often  
1588 remain at risk of recurrent syncope, implying the need for precise identification of the mechanism of syncope  
1589 and specific treatment when possible.

1590 Few data exist concerning the prevalence and the prognostic implications of unexplained syncope in  
1591 unselected patients with left ventricular dysfunction or non-ischaemic dilated cardiomyopathy with less  
1592 severe systolic impairment who do not meet the current indication for ICD.<sup>358</sup> Data from the observational  
1593 studies in selected cohorts show a high rate of occurrence of ventricular arrhythmias, ICD discharge, and  
1594 death in patients with a history of unexplained syncope but, owing to the lack of control group, are unable to  
1595 show a benefit of an ICD.<sup>27,28,359,360</sup> This Task Force believes that an ICD should be considered in patients  
1596 with unexplained syncope with systolic impairment but without a current indication for ICD to reduce the risk  
1597 of sudden death.  
1598

1599

**ICD indications in patients with unexplained syncope<sup>a</sup> and left ventricular systolic dysfunction**

Recommendations	Class <sup>b</sup>	Level <sup>c</sup>
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. <sup>46</sup>	<b>I</b>	<b>A</b>
An ICD should be considered in patients with unexplained syncope <sup>a</sup> with systolic impairment but without a current indication for ICD to reduce the risk of sudden death. <sup>27,28,359,360</sup>	<b>IIa</b>	<b>C</b>
Instead of an ICD, an ILR may be considered in patients with recurrent episodes of unexplained syncope <sup>a</sup> with systolic impairment but without a current indication for ICD.	<b>IIb</b>	<b>C</b>
<p><b>Additional advice and clinical perspectives</b></p> <ul style="list-style-type: none"> <li>The presence of syncope increases mortality regardless of its cause.<sup>348</sup> Thus, syncope is a risk factor for life-threatening events.</li> <li>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.</li> </ul>		
<p>ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SCD = sudden cardiac death.</p> <p><sup>a</sup> 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.</p> <p><sup>b</sup> Class of recommendation.</p> <p><sup>c</sup> Level of evidence.</p>		

1600

1601

1602

**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).<sup>361</sup> 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).<sup>350</sup> 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 model<sup>245</sup>; 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<sup>a</sup> and HCM**

Recommendations	Class <sup>b</sup>	Level <sup>c</sup>
It is recommended that the decision for ICD implantation in patients with unexplained syncope <sup>a</sup> is made according to the ESC HCM Risk-SCD score. <sup>d 245</sup>	<b>I</b>	<b>B</b>
Instead of an ICD, an ILR should be considered in patients with recurrent episodes of unexplained syncope <sup>a</sup> who are at low risk of SCD according to the HCM Risk-SCD score. <sup>d 245</sup>	<b>IIa</b>	<b>C</b>
<p><b>Additional advice and clinical perspectives</b></p> <p>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.</p> <p>ESC = European Society of Cardiology; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; SCD = sudden cardiac death.</p> <p><sup>a</sup> 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.</p> <p><sup>b</sup> Class of recommendation.</p> <p><sup>c</sup> Level of evidence.</p> <p><sup>d</sup> A web-based calculator of the HCM risk score can be found in: <a href="http://www.doc2do.com/hcm/webHCM.html">http://www.doc2do.com/hcm/webHCM.html</a></p>		

1613

1614

#### 5.6.4 Arrhythmogenic right ventricular cardiomyopathy

1615

Although limited and diverse, current data suggest that unexplained syncope is a marker of arrhythmic risk in patients with arrhythmogenic right ventricular cardiomyopathy.<sup>46,351,362,363</sup> The decision to implant an ICD should take into account the other known risk factors for arrhythmic events<sup>46</sup>: 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.<sup>46</sup>

1616

1617

1618

1619

1620

1621

1622

#### ICD indications in patients with unexplained syncope<sup>a</sup> and ARVC

Recommendations	Class <sup>b</sup>	Level <sup>c</sup>
ICD implantation may be considered in patients with ARVC and a history of unexplained syncope. <sup>a 46</sup>	<b>IIb</b>	<b>C</b>
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.	<b>IIa</b>	<b>C</b>
<p>ARVC = arrhythmogenic right ventricular cardiomyopathy; ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; SCD = sudden cardiac death.</p> <p><sup>a</sup> 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</p>		

section, unexplained syncope is considered a risk factor for ventricular tachyarrhythmias.

<sup>b</sup> Class of recommendation.

<sup>c</sup> Level of evidence.

1623

1624 **5.6.5 Patients with inheritable arrhythmogenic disorders**

1625 *5.6.5.1 Long QT syndrome*

1626 Syncopal events in long QT syndrome (LQTS) are associated with an increased risk of subsequent cardiac  
 1627 arrest. The annual rate of SCD in patients with untreated LQTS is around 0.9% overall and 5% for those with  
 1628 syncope.<sup>352,364</sup> Beta-blocker therapy substantially reduces the risk of syncope and SCD but presentation with  
 1629 cardiac arrest and recurrent syncope during beta-blocker therapy is associated with the same risk of fatal  
 1630 events as in untreated patients.<sup>46</sup> For this reason, ICD treatment should be considered in patients with LQTS  
 1631 and recurrent unexplained syncope despite beta-blocker therapy, especially in case of good treatment  
 1632 compliance, in the absence of precipitating factors, and in LQT2 and LQT3 syndromes. Left cardiac  
 1633 sympathetic denervation should also be considered in this situation, particularly in LQT1.<sup>46</sup>

1634

1635

**ICD indications in patients with unexplained syncope<sup>a</sup> and LQTS**

Recommendations	Class <sup>b</sup>	Level <sup>c</sup>
ICD implantation in addition to beta-blockers should be considered in LQTS patients who experience unexplained syncope <sup>a</sup> while receiving an adequate dose of beta-blockers. <sup>46</sup>	<b>Ila</b>	<b>B</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. <sup>46</sup>	<b>Ila</b>	<b>C</b>
Instead of an ICD, an ILR should be considered in patients with recurrent episodes of unexplained syncope <sup>a</sup> who are at low risk of SCD based on a multiparametric analysis that takes into account the other known risk factors for SCD.	<b>Ila</b>	<b>C</b>

**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.

<sup>a</sup> 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.

<sup>b</sup> Class of recommendation.

<sup>c</sup> Level of evidence.

1636

*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.<sup>353</sup> 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.<sup>355</sup>

1644 On balance, this Task Force believes that it is reasonable to consider an ICD in the case of  
 1645 unexplained syncope. New studies<sup>356,365</sup> published after the 2015 ESC guidelines for VA and prevention of  
 1646 SCD<sup>46</sup> 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.<sup>365,366</sup>

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.<sup>220,367-371</sup> 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<sup>a</sup> and Brugada syndrome**

Recommendations	Class <sup>b</sup>	Level <sup>c</sup>
ICD implantation should be considered in patients with a spontaneous diagnostic type I ECG pattern and a history of unexplained syncope. <sup>a 46,353,355,365,366</sup>	<b>IIa</b>	<b>C</b>
Instead of an ICD, an ILR should be considered in patients with recurrent episodes of unexplained syncope <sup>a</sup> who are at low risk of SCD based on a multiparametric analysis that takes into account the other known risk factors for SCD.	<b>IIa</b>	<b>C</b>
ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; SCD = sudden cardiac death. <sup>a</sup> 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. <sup>b</sup> Class of recommendation. <sup>c</sup> 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.<sup>46</sup>



1664

## 1665 **6. Special issues**

### 1666 **6.1 Syncope in patients with comorbidity and frailty**

1667 The approach to the assessment and management of an older patient with syncope is similar to that of other  
1668 age groups; however, there are a number of additional features pertinent to age-related comorbidity and  
1669 frailty that warrant special attention.<sup>372-374</sup>

1670

#### 1671 **6.1.1 Comorbidity and polypharmacy**

1672 Comorbidity influences diagnosis of syncope and management decisions.<sup>33,375</sup> Older patients frequently have  
1673 abnormal findings on more than one investigation and may have more than one possible cause of  
1674 syncope.<sup>372,374,376</sup> Conversely, coincidental findings of cardiovascular diagnoses such as aortic stenosis or  
1675 atrial fibrillation<sup>377</sup> may not necessarily be the attributable cause of events.<sup>378-380</sup>

1676 Prescription of polypharmacy, cardiovascular medications, and psychotropic (neuroleptics,  
1677 antidepressants) and dopaminergic drugs also increase the risk of syncope and falls.<sup>381-385</sup> Conversely,  
1678 discontinuation or reduction of the hypotensive therapy reduces such risk.<sup>260</sup> Negative dromotropic and  
1679 chronotropic medications should be carefully evaluated in older patients presenting with syncope or falls.

1680 Focal neurological events can occasionally occur due to hypotension and syncope even in patients  
1681 without significant carotid artery stenosis (so called “*hypotensive TIA*”). Although these neurological events  
1682 occur in only 6% of patients with recurrent syncope, their misdiagnosis is particularly important because they  
1683 may lead to a lowering of BP with antihypertensive medications (e.g. if focal neurology is mistakenly  
1684 attributed to vascular pathology rather than hypotension) and to a further increase of the risk of syncope and  
1685 neurologic events.<sup>386</sup>

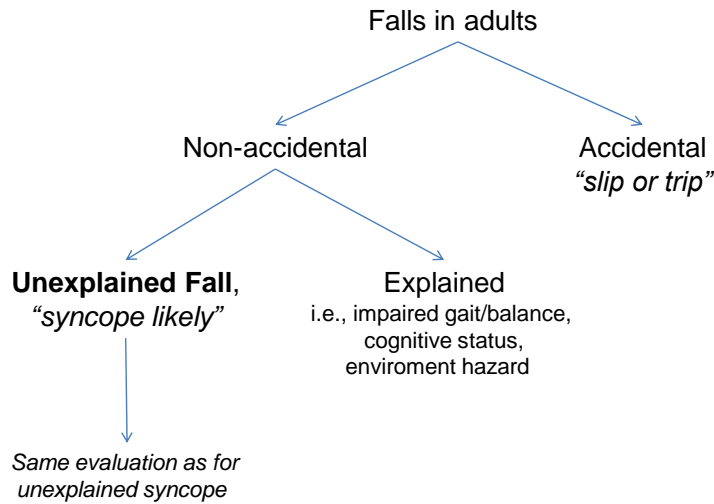
1686 ***Despite the lack of large controlled trials and an overall modest quality of studies, there is***  
1687 ***strong consensus that reduction or discontinuation of hypotensive drugs and psychotropic drugs***  
1688 ***clearly outweighs the undesirable effects (e.g. complications of high BP). Further research is likely to***  
1689 ***have an important impact on our confidence in the estimate of effect).***

1690

#### 1691 **6.1.2 Falls**

1692 Syncopal events may not be witnessed in over half of older patients and therefore a collateral history is not  
1693 available, making discrimination between falls and syncope challenging.<sup>387</sup> If unwitnessed falls are not due to  
1694 mechanical slips or trips (i.e. are unexplained or non-accidental), it is likely that the patient experienced a  
1695 syncopal event and displayed lack of awareness for LOC (*Figure 16*).<sup>388,389</sup> Management of falls in such  
1696 circumstances is the same as that for syncope.<sup>191,194,390</sup>

1697 ***Despite the lack of controlled trials and an overall modest quality of studies, there is strong***  
1698 ***consensus that the management of unexplained falls should be the same as that for unexplained***  
1699 ***syncope.***



1700  
1701 **Figure 16** Flow diagram for identifying unexplained falls.  
1702

1703 **6.1.3 Cognitive assessment and physical performance tests**

1704 Age-related memory impairment or more established forms of cognitive impairment are frequently associated  
1705 with poor recall and therefore lack of accurate history of events. In such circumstances, details of prodromal  
1706 symptoms, whether or not LOC occurred, and symptoms after the event may be unreliable.<sup>373,389,391-394</sup>

1707 Cognitive assessment to inform the accuracy of historical data, and general physical assessment to identify  
1708 comorbid disorders that influence diagnosis and response to treatments (such as Parkinson’s disease, gait  
1709 and balance abnormalities, previous stroke, polyneuropathies, etc.), are recommended.

1710 ***Despite the lack of large controlled trials and an overall modest quality of studies, there is***  
1711 ***strong consensus that assessment of older patients with syncope or unexplained falls may require***  
1712 ***cognitive assessment and physical performance tests in addition to syncope evaluation. Further***  
1713 ***research is likely to have an important impact on our confidence in the estimate of effect.***

1714  
1715 **Syncope in patients with comorbidity and frailty**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
A multifactorial evaluation and intervention is recommended in older patients because more than one possible cause for syncope and unexplained fall may be present. <sup>33,372-374,376-380</sup>	I	B
Cognitive assessment and physical performance tests are indicated in older patients with syncope or unexplained fall. <sup>373,389,391-394</sup>	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. <sup>260,381-385</sup>	<b>Ila</b>	<b>B</b>
In patients with unexplained fall, the same assessment as for unexplained syncope should be considered. <sup>191,194,387-390</sup>	<b>Ila</b>	<b>C</b>
<p><b>Additional advice and clinical perspectives</b></p> <ul style="list-style-type: none"> <li>• 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.<sup>393,395</sup></li> <li>• Orthostatic BP measurements, CSM, and tilt testing are well tolerated, even in the frail elderly with cognitive impairment.<sup>96,396,397</sup></li> <li>• 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.<sup>388,389</sup></li> <li>• 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.<sup>398</sup> Such failure of systolic BP to stabilize is a risk factor for subsequent falls and syncope.</li> <li>• In the absence of a witness account, the differential diagnosis between falls, epilepsy, TIA, and syncope may be difficult.</li> </ul> <p>BP = blood pressure; CSM = carotid sinus massage; TIA = transient ischaemic attack; TLOC = transient loss of consciousness.</p> <p><sup>a</sup> Class of recommendation.</p> <p><sup>b</sup> Level of evidence.</p>		

1716

## 1717 6.2 Syncope in paediatric patients

### 1718 6.2.1 Diagnostic evaluation

1719 Diagnostic evaluation in paediatric patients is similar to that in adults.

1720 Two specific conditions<sup>399</sup> occur in early childhood:

- 1721 • Infantile reflex syncopal attacks (also called pallid breath-holding spells or reflex anoxic seizures),  
1722 elicited by a brief unpleasant stimulus, caused by vagally mediated cardiac inhibition.
- 1723 • Cyanotic breath-holding spells, characterized by stopping breathing during crying, leading to cyanosis  
1724 and usually TLOC.

1725

1726 Careful taking of personal and family history and a standard ECG are most important methods of  
1727 distinguishing benign reflex syncope (also including reflex anoxic seizure or breath-holding spells) from other  
1728 causes. If the family history is positive, genetic causes of electrical disease of the heart should be considered  
1729 first. Some children with reflex syncope also have a positive family history.<sup>400</sup> Tilt testing seems to have high  
1730 false-negative and false-positive rates and should be used with caution for primary identification of reflex  
1731 syncope. Since tilt protocols commonly used in adults may lack specificity in teenagers, in one study, a  
1732 shorter tilt-test duration of 10 minutes at 60 or 70 degrees was used and showed a specificity >85%.<sup>401</sup>

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.<sup>402</sup>

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.<sup>9,116</sup>

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 clinics<sup>94</sup> to 8% of patients referred to specialist neurological clinics<sup>116</sup>  
1769 but PPS is probably insufficiently recognized.<sup>154</sup>

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<sup>116,154,403</sup>:

- 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.<sup>116,204,404</sup> The gold standard for PNES is documenting an attack with video-EEG  
1798 monitoring.<sup>204,404</sup>  
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.<sup>404</sup> It should be done by the somatic specialist who diagnoses  
1803 PPS.<sup>116,404</sup> 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,<sup>405</sup> 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,<sup>406</sup> 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 <sup>a</sup>	Level <sup>b</sup>
<b>Diagnosis</b>		
Recording of spontaneous attacks with a video by eyewitness should be considered for diagnosis of PPS. <sup>116,154</sup>	<b>Ila</b>	<b>C</b>
Tilt testing, preferably with concurrent EEG recording and video monitoring may be considered for diagnosis of PPS. <sup>116,403,407</sup>	<b>Ilb</b>	<b>C</b>
<b>Management</b>		
Doctors who diagnose PPS should present the diagnosis of PPS to the patients. <sup>116,404</sup>	<b>Ila</b>	<b>C</b>
Cognitive behavioural therapy may be considered in the treatment of PPS if attacks persist after explanation.	<b>Ilb</b>	<b>C</b>

1815 EEG = electroencephalogram; PPS = psychogenic pseudosyncope.

1816 <sup>a</sup> Class of recommendation.

1817 <sup>b</sup> 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,<sup>408,409</sup>  
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.<sup>9,50,410,411</sup>

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.<sup>412,413</sup> Bradycardia precedes asystole and AV block may occur,  
1836 resembling the ECG pattern of reflex syncope.<sup>412,414</sup> 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.<sup>415,416</sup> If asystole lasts  
1839 for more than about 8 seconds, syncope ensues.<sup>416</sup> 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.<sup>416,417</sup> Ictal bradycardia, asystole, and ictal AV block are likely self-terminating,<sup>412</sup> and are due to vagal  
1842 activation brought about by the seizure. Cessation of cortical activity due to syncopal cerebral hypoperfusion

1843 will end the seizure. Therapy requires antiepileptic drugs and possibly a pacemaker.<sup>418</sup> Ictal asystole is  
 1844 probably not involved in sudden death in epilepsy, as this typically occurs in patients after unwitnessed  
 1845 nocturnal generalized tonic-clonic seizures, i.e. another type of epilepsy.<sup>414,419</sup> Note that most cases of  
 1846 sudden cardiac arrest in patients with epilepsy are due to cardiovascular disease and not to ictal asystole.<sup>420</sup>  
 1847 The second form concerns a syncopal epileptic seizure. Hypoxia can trigger epileptic seizures.<sup>208,421</sup>  
 1848 Such syncopal epileptic seizures have been described in infants with reflex syncope or cyanotic breath-  
 1849 holding spells. A typical syncopal spell suddenly transforms into prolonged clonic movements that last for  
 1850 minutes; note that shorter epileptic seizures may remain unnoticed.

1851  
 1852 **Table 10 Differentiating syncope from epileptic seizures**<sup>9,50,410,411</sup>

Clinical feature	Syncope	Epileptic seizures
<b>Useful features</b>		
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"> <li>• &lt;10, irregular in amplitude, asynchronous, asymmetrical;</li> <li>• Starts after the onset of LOC</li> </ul>	<ul style="list-style-type: none"> <li>• 20–100, synchronous, symmetrical, hemilateral</li> <li>• the onset mostly coincides with LOC</li> <li>• Clear long-lasting automatisms as chewing or lip smacking at the mouth</li> </ul>
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
<b>Features of limited utility</b>		
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.		

1853

1854

### 8.1.3 Cerebrovascular disorders

1855

1856

1857

1858

1859

1860

1861

1862

1863

1864

1865

1866

1867

1868

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.<sup>422</sup> 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.<sup>423,424</sup>

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.<sup>425</sup>

1869

### 8.1.4 Migraine

1870

1871

1872

1873

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.<sup>426</sup> In migraineurs, syncope and migraine attacks rarely occur simultaneously.

1874

### 8.1.5 Cataplexy

1875

1876

1877

1878

1879

1880

1881

Cataplexy concerns paresis or paralysis triggered by emotions, usually laughter, but also by a range of other triggers.<sup>427</sup> 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.

1882

### 8.1.6 Drop attacks

1883

1884

1885

1886

1887

1888

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



1889 **Neurological evaluation**

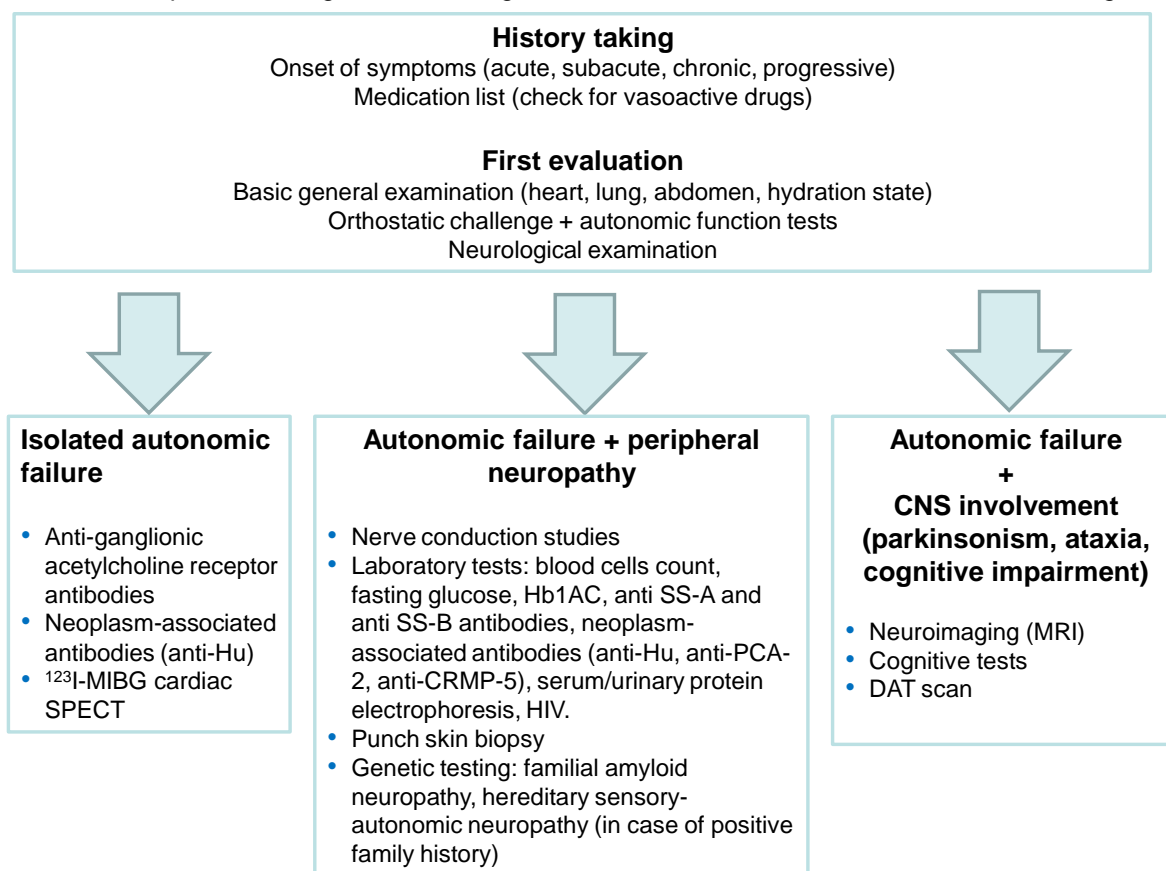
Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Neurological evaluation is indicated when syncope is due to autonomic failure to evaluate the underlying disease.	I	C
Neurological evaluation is indicated in patients in whom TLOC is suspected to be epilepsy.	I	C

TLOC = transient loss of consciousness.  
<sup>a</sup> Class of recommendation.  
<sup>b</sup> 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*<sup>429</sup>). <sup>123</sup>I-MIBG  
 1895 = <sup>123</sup>I-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.

1900  
1901  
1902  
1903  
1904  
1905  
1906  
1907  
1908  
1909  
1910  
1911  
1912  
1913  
1914  
1915  
1916  
1917  
1918  
1919  
1920  
1921  
1922  
1923  
1924  
1925

### 8.2.1 Electroencephalography

The results of interictal EEGs are normal in syncope.<sup>410,430</sup> 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.<sup>431</sup> Seropositivity for any of the above-mentioned antibodies may therefore prompt further investigation for occult malignancy (e.g. whole-body fluorodeoxyglucose-positron emission tomography).<sup>432</sup>

Seropositivity for antiganglionic acetylcholine receptors antibodies is the serological hallmark of autoimmune autonomic ganglionopathy.<sup>433,434</sup>

### Neurological tests

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

1926  
1927  
1928  
1929  
1930  
1931  
1932  
1933  
1934  
1935  
1936

## 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.<sup>63</sup> 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"><li>• The syncope unit should take the lead in service delivery for syncope, and in education and training of healthcare professionals who encounter syncope.</li></ul>
<ul style="list-style-type: none"><li>• 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.</li></ul>
<ul style="list-style-type: none"><li>• 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.</li></ul>
<ul style="list-style-type: none"><li>• 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.</li></ul>
<ul style="list-style-type: none"><li>• Syncope units should employ quality indicators, process indicators, and desirable outcome targets.</li></ul>

1937 ED = emergency department; OH = orthostatic hypotension; TLOC = transient loss of consciousness.

1938

#### 9.1.1 Definition of a syncope unit

1940 A syncope unit is a facility featuring a standardized approach to the diagnosis and management of TLOC  
1941 and related symptoms, with dedicated staff and access to appropriate diagnostics and therapies.

1942

#### 9.1.2 Definition of syncope specialist

1944 The syncope specialist is defined as one who has responsibility for the comprehensive management of the  
1945 patient from risk stratification to diagnosis, therapy, and follow-up, through a standardized protocol. A  
1946 syncope specialist is a physician who has sufficient knowledge of historical clues and physical findings to  
1947 recognize all major forms of TLOC, including mimics, as well as syndromes of orthostatic intolerance.

1948

#### 9.1.3 Goal of a syncope unit

1950 Although the benefit of a syncope unit or a syncope specialist in the different healthcare systems has not  
1951 been exposed to rigorous scientific or economic scrutiny, the consensus is that a dedicated service (a  
1952 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**

##### **Staffing of a syncope unit is composed of:**

1. One or more physicians of any specialty who are syncope specialists. Owing to the multidisciplinary nature of TLOC management, each syncope unit should identify specific specialists for the syncope unit and for consultancies.
2. A staff comprising professionals who will advance the care of patients with syncope. These may be physicians, specialized nurses, or others who bring multidisciplinary skills to the facility, coupled with administrative support. The roles played by members of the team may vary according to local circumstances and individual skill. Nurses may be expected to take very important roles including initial assessment, follow-up clinic evaluation, selection of investigations (including tilt testing), and implantation/insertion of ECG loop recorders according to predefined protocols and local regulations (see *Table 14*).
3. Given that the syncope unit is integrated within a hospital organization, syncope specialists and staff are not necessarily employed full-time, but frequently have other duties depending on the volume of activity in the unit.

##### **Facility, protocol, and equipment**

1. A syncope unit will deliver most of its care to outpatients in addition to ED and inpatients.
2. The syncope unit should follow an internal protocol, which applies to diagnosis and management and is agreed by stakeholders.
3. An equipped facility must be available.
4. Essential equipment/tests:
  - 12-lead ECG and 3-lead ECG monitoring
  - non-invasive beat-to-beat BP monitor with recording facilities for subsequent analysis
  - tilt-table
  - Holter monitors/external loop recorders
  - ILRs
  - follow-up of ILRs<sup>a</sup>
  - 24-hour BP monitoring
  - Basic autonomic function tests.
5. Established procedures for:
  - Echocardiography
  - EPS
  - Stress test

- Neuroimaging tests.

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

### Therapy

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

### Database management

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

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

<sup>a</sup> Implantation of loop recorders may be performed either by syncope unit physicians or by external cardiologists upon request of the syncope unit physicians.

1962  
1963  
1964  
1965

**Table 13 Test and assessments available in a syncope unit**

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

<sup>a</sup> Postural orthostatic tachycardia may require longer stands.

1966  
1967  
1968  
1969  
1970  
1971  
1972  
1973  
1974  
1975  
1976  
1977  
1978  
1979  
1980  
1981  
1982  
1983  
1984  
1985  
1986  
1987  
1988  
1989  
1990  
1991  
1992  
1993  
1994  
1995  
1996  
1997  
1998  
1999  
2000  
2001  
2002  
2003  
2004  
2005

### **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 Force<sup>63</sup> 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 ABPM<sup>63</sup> (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) <sup>a</sup>	x	
Basic autonomic function test		x	
ECG monitoring (Holter, external loop recorder): administration and interpretation	x	x	
ILR	x	(x) <sup>b</sup>	
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, <sup>c</sup> and instruction sheet on PCM	x	x	
Final report and clinic note	x		
Communication with patients, referring physicians, and stakeholders.	x	x	
Follow-up	x	x	

BP = blood pressure; CSM = carotid sinus massage; ECG = electrocardiogram; EEG = electroencephalogram; EPS = electrophysiological study; ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; PCM = physical counter-pressure manoeuvres.

<sup>a</sup> Physician need not be in the room, but a physician adequately trained in resuscitation needs to be in the vicinity of the test.

<sup>b</sup> Current practice limited to a few countries.

<sup>c</sup> 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.

2007

2008

2009

2010

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-ischæmia 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

2091 based on the best available scientific evidence, treatment should be tailored to an individual patient's  
2092 need.

2093  
2094

## 2095 **11. Gaps in evidence and areas for future research**

2096 Clinicians responsible for managing patients with TLOC must frequently make treatment decisions without  
2097 adequate evidence or a consensus of expert opinion. The following is a short list of selected, common issues  
2098 that deserve to be addressed in future clinical research.

2099

### 2100 **Diagnosis – gap between the best available scientific evidence and the need for** 2101 **dissemination of these concepts into clinical practice**

2102 There is wide variation in practice of syncope evaluation, and wide variation in adoption of recommendations  
2103 from published guidelines. The absence of a systematic approach to TLOC incurs higher health and social  
2104 care costs, unnecessary hospitalizations and diagnostic procedures, prolongation of hospital stays, lower  
2105 diagnostic rates, and higher rates of misdiagnoses and symptom recurrences.

2106 Therefore, there is a need for:

2107 1) *Large clinical studies that assess the diagnostic yield and compliance of a guideline-based*  
2108 *standardized systematic approach*

2109 Despite the recommendation from the ESC guidelines on syncope, syncope units are not widely established  
2110 in clinical practice. Barriers to establishing a syncope unit include lack of resources, lack of trained dedicated  
2111 staff, and complex presentations to multiple settings, necessitating involvement from multiple disciplines. The  
2112 evidence for usefulness of syncope units is controversial.

2113 Therefore, there is a need for:

2114 2) *Large clinical studies that test the superiority of management in a dedicated syncope facility versus*  
2115 *conventional management*

2116

### 2117 **Diagnosis – need for new diagnostic tests and devices**

2118 BP recording is crucial for the majority of clinical TLOC situations and will add important information for  
2119 treatment of syncope. Unfortunately, current long-term BP (or surrogate) recording systems are not optimal  
2120 for diagnostic use in the syncope evaluation setting.

2121 Therefore, there is a need for:

2122 3) *Development and validation of new diagnostic multiparametric devices that can record heart rhythm and*  
2123 *BP (and possibly other physiological parameters such as cerebral saturation or EEG) at the time of a*  
2124 *syncopal event.*

2125

### 2126 **Treatment – lack of evidence of efficacy of most available therapies**

2127 Only a few small randomized controlled trials have been done on treatment of syncope. In addition, syncopal  
2128 recurrences are unpredictable and often decrease spontaneously after medical assessment, even in the  
2129 absence of a specific therapy. The consequence of the spontaneous decrease is that any therapy for  
2130 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.*  
 2138

### 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
<b>Diagnostic criteria with initial evaluation</b>		
VVS is highly probable if syncope is precipitated by pain or fear or standing, and is associated with typical progressive prodrome (pallor, sweating, nausea). <sup>8,13-17</sup>	I	C
Situational reflex syncope is highly probable if syncope occurs during or immediately after specific triggers, listed in <i>Table 3</i> . <sup>8,13-17</sup>	I	C
Syncope due to OH is confirmed when syncope occurs while standing and there is concomitant OH. <sup>18-24</sup>	I	C
Arrhythmic syncope is highly probable when the ECG shows <sup>25-39</sup> : <ul style="list-style-type: none"> <li>• Persistent sinus bradycardia &lt;40 b.p.m. or sinus pauses &gt;3 seconds in the awake state and in the absence of physical training</li> <li>• Mobitz II second- and third-degree AV block</li> <li>• Alternating left and right BBB</li> <li>• VT or rapid paroxysmal SVT</li> <li>• Non-sustained episodes of polymorphic VT and long or short QT interval</li> <li>• Pacemaker or ICD malfunction with cardiac pauses.</li> </ul>	I	C

<b>Management of syncope in the ED</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. <sup>27,35,36,49-54,58,62,69</sup>	I	B
It is recommended that patients with high-risk features receive an early intensive prompt evaluation in a syncope unit or in <a href="#">an</a> ED observation unit (if available) or are hospitalized. <sup>26,27,35,36,44-46,50,55-57,59,60,70-76</sup>	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. <sup>40,63-65,77</sup>	I	B
<b>CSM</b>		
CSM is indicated in patients >40 years of age with syncope of unknown origin compatible with a reflex mechanism. <sup>92-94</sup>	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. <sup>89,90,92,93,98-102</sup>	I	B
<b>Active standing</b>		
Intermittent determination by sphygmomanometer of BP and HR while supine and during active standing for 3 minutes are indicated at initial syncope evaluation. <sup>20,103,104</sup>	I	C
Syncope due to OH is confirmed when there is a fall in systolic BP from baseline value $\geq 20$ mmHg or diastolic BP $\geq 10$ mmHg or a decrease in systolic BP to $< 90$ mmHg that reproduces spontaneous symptoms. <sup>6,20,103,104</sup>	I	C
<b>Electrocardiographic monitoring</b>		
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 <i>Table 6</i> ), and a high likelihood of recurrence within the battery life of the device. <sup>175,176,181-184,202 and Data Supplement Table 5</sup>	I	A
ILR is indicated in high-risk (criteria listed in <i>Table 6</i> ) 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. <sup>174,180,187,188,195 and Data Supplement Tables 5 and 6</sup>	I	A
Arrhythmic syncope is confirmed when a correlation between syncope and an arrhythmia (bradyarrhythmia or tachyarrhythmia) is detected. <sup>172,184-186,188,200</sup>	I	B
<b>EPS</b>		

In patients with syncope and previous myocardial infarction or other scar-related conditions, EPS is indicated when syncope remains unexplained after non-invasive evaluation. <sup>218</sup>	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 $\geq 70$ ms, or second- or third-degree His-Purkinje block during incremental atrial pacing, or with pharmacological challenge. <sup>188,214-217,221</sup>	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. <sup>46</sup>	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. <sup>46,222</sup>	I	C
<b>Echocardiography</b>		
Echocardiography is indicated for diagnosis and risk stratification in patients with suspected structural heart disease. <sup>235,236</sup>	I	B
<b>Exercise testing</b>		
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. <sup>253-257</sup>	I	C
Reflex syncope is confirmed when syncope is reproduced immediately after exercise in the presence of severe hypotension. <sup>250-252</sup>	I	C
<b>Treatment of reflex syncope</b>		
Explanation of the diagnosis, provision of reassurance, explanation of risk of recurrence, avoidance of triggers and situations are indicated in all patients. <sup>Web Data Supplement Table 10</sup>	I	B
Beta-adrenergic blocking drugs are not indicated. <sup>279,280</sup>	III	A
Cardiac pacing is not indicated in the absence of a documented cardioinhibitory reflex. <sup>299,300</sup>	III	B
<b>Treatment of OH</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. <sup>310,311</sup>	I	C
<b>Treatment of syncope due to cardiac arrhythmias</b>		
Cardiac pacing is indicated when there is an established relationship between syncope and	I	B

symptomatic bradycardia. <sup>200,210-212,255,334-338,341</sup>		
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. <sup>188,217</sup>	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 $\leq 35\%$ . <sup>46</sup>	I	A
An ICD is indicated in patients with syncope and previous myocardial infarction who have VT induced during EPS. <sup>218</sup>	I	C
<b>ICD indications in patients with unexplained syncope and left ventricular systolic dysfunction</b>		
ICD therapy is recommended to reduce SCD in patients with symptomatic heart failure (NYHA class II–III) and LVEF $\leq 35\%$ after $\geq 3$ months of optimal medical therapy who are expected to survive for at least 1 year with good functional status. <sup>46</sup>	I	A
<b>Syncope in patients with comorbidity and frailty</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. <sup>33,372-374,376-380</sup>	I	B
<b>Neurological evaluation</b>		
Neurological evaluation is indicated when syncope is suspected to be epilepsy or due to autonomic failure to evaluate the underlying disease.	I	C

2153 AF = atrial fibrillation; AV = atrioventricular; BP = blood pressure; b.p.m. = beats per minute; BBB = bundle  
2154 branch block; CSM = carotid sinus massage; CSS = carotid sinus syndrome; ECG = electrocardiogram; ED  
2155 = emergency department; EPS = electrophysiological study; ESC = European Society of Cardiology; HR =  
2156 heart rate; ICD = implantable cardioverter defibrillator; ILR = implantable loop recorder; LVEF = left  
2157 ventricular ejection fraction; NYHA = New York Heart Association; OH = orthostatic hypotension; SCD =  
2158 sudden cardiac death; SVT = supraventricular tachycardia; VA = ventricular arrhythmia; VT = ventricular  
2159 tachycardia; VVS = vasovagal syncope.

2160

### 2161 13. References

- 2162 1. Mosqueda-Garcia R, Furlan R, Tank J, Fernandez-Violante R. The elusive pathophysiology  
2163 of neurally mediated syncope. *Circulation* 2000;**102**:2898-2906.  
2164 2. Morillo CA, Eckberg DL, Ellenbogen KA, Beightol LA, Hoag JB, Tahvanainen KU, Kuusela  
2165 TA, Diedrich AM. Vagal and sympathetic mechanisms in patients with orthostatic vasovagal  
2166 syncope. *Circulation* 1997;**96**:2509-2513.  
2167 3. Alboni P, Alboni M. *Origin and evolution of the vasovagal reflex in Vasovagal Syncope*.  
2168 Heidelberg Springer; 2015. p. 3-17.

- 2169 4. Deharo JC, Guieu R, Mechulan A, Peyrouse E, Kipson N, Ruf J, Gerolami V, Devoto G,  
2170 Marre V, Brignole M. Syncope without prodromes in patients with normal heart and normal  
2171 electrocardiogram: a distinct entity. *J Am Coll Cardiol* 2013;**62**:1075-1080.
- 2172 5. Brignole M, Deharo JC, De Roy L, Menozzi C, Blommaert D, Dabiri L, Ruf J, Guieu R.  
2173 Syncope due to idiopathic paroxysmal atrioventricular block: long-term follow-up of a  
2174 distinct form of atrioventricular block. *J Am Coll Cardiol* 2011;**58**:167-173.
- 2175 6. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, Cheshire WP,  
2176 Chelimsky T, Cortelli P, Gibbons CH, Goldstein DS, Hainsworth R, Hilz MJ, Jacob G,  
2177 Kaufmann H, Jordan J, Lipsitz LA, Levine BD, Low PA, Mathias C, Raj SR, Robertson D,  
2178 Sandroni P, Schatz I, Schondorff R, Stewart JM, van Dijk JG. Consensus statement on the  
2179 definition of orthostatic hypotension, neurally mediated syncope and the postural  
2180 tachycardia syndrome. *Clin Auton Res* 2011;**21**:69-72.
- 2181 7. Fedorowski A, Melander O. Syndromes of orthostatic intolerance: a hidden danger. *J Intern  
2182 Med* 2013;**273**:322-335.
- 2183 8. Wieling W, Thijs RD, van Dijk N, Wilde AA, Benditt DG, van Dijk JG. Symptoms and signs  
2184 of syncope: a review of the link between physiology and clinical clues. *Brain*  
2185 2009;**132**:2630-2642.
- 2186 9. van Dijk JG, Thijs RD, van Zwet E, Tannemaat MR, van Niekerk J, Benditt DG, Wieling W.  
2187 The semiology of tilt-induced reflex syncope in relation to electroencephalographic  
2188 changes. *Brain* 2014;**137**:576-585.
- 2189 10. Breningstall GN. Breath-holding spells. *Pediatr Neurol* 1996;**14**:91-97.
- 2190 11. Stephenson JBP. *Fits and faints*: Mac Keith Press; 1991.
- 2191 12. van Dijk N, Boer KR, Colman N, Bakker A, Stam J, van Grieken JJ, Wilde AA, Linzer M,  
2192 Reitsma JB, Wieling W. High diagnostic yield and accuracy of history, physical  
2193 examination, and ECG in patients with transient loss of consciousness in FAST: the  
2194 Fainting Assessment study. *J Cardiovasc Electrophysiol* 2008;**19**:48-55.
- 2195 13. Stephenson J. *Fits and faints*. Oxford Blackwell Scientific Publications; 1990. p. 41-57.
- 2196 14. van Dijk JG, Sheldon R. Is there any point to vasovagal syncope? *Clin Auton Res*  
2197 2008;**18**:167-169.
- 2198 15. Alboni P, Alboni M, Bertorelle G. The origin of vasovagal syncope: to protect the heart or to  
2199 escape predation? *Clin Auton Res* 2008;**18**:170-178.
- 2200 16. Ganzeboom KS, Colman N, Reitsma JB, Shen WK, Wieling W. Prevalence and triggers of  
2201 syncope in medical students. *Am J Cardiol* 2003;**91**:1006-1008, A1008.
- 2202 17. Serletis A, Rose S, Sheldon AG, Sheldon RS. Vasovagal syncope in medical students and  
2203 their first-degree relatives. *Eur Heart J* 2006;**27**:1965-1970.
- 2204 18. Shibao C, Lipsitz LA, Biaggioni I. ASH position paper: evaluation and treatment of  
2205 orthostatic hypotension. *J Clin Hypertens (Greenwich)* 2013;**15**:147-153.
- 2206 19. Mathias CJ, Mallipeddi R, Bleasdale-Barr K. Symptoms associated with orthostatic  
2207 hypotension in pure autonomic failure and multiple system atrophy. *J Neurol* 1999;**246**:893-  
2208 898.
- 2209 20. Naschitz JE, Rosner I. Orthostatic hypotension: framework of the syndrome. *Postgrad Med  
2210 J* 2007;**83**:568-574.
- 2211 21. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure,  
2212 and multiple system atrophy. *J Neurol Sci* 1996;**144**:218-219.
- 2213 22. Wieling W, Krediet CT, van Dijk N, Linzer M, Tschakovsky ME. Initial orthostatic  
2214 hypotension: review of a forgotten condition. *Clin Sci (Lond)* 2007;**112**:157-165.
- 2215 23. Podoleanu C, Maggi R, Brignole M, Croci F, Incze A, Solano A, Puggioni E, Carasca E.  
2216 Lower limb and abdominal compression bandages prevent progressive orthostatic

- hypotension in elderly persons: a randomized single-blind controlled study. *J Am Coll Cardiol* 2006;**48**:1425-1432.
24. Gibbons CH, Freeman R. Delayed orthostatic hypotension: a frequent cause of orthostatic intolerance. *Neurology* 2006;**67**:28-32.
25. Sarasin FP, Hanusa BH, Perneger T, Louis-Simonet M, Rajeswaran A, Kapoor WN. A risk score to predict arrhythmias in patients with unexplained syncope. *Acad Emerg Med* 2003;**10**:1312-1317.
26. Quinn J, McDermott D, Stiell I, Kohn M, Wells G. Prospective validation of the San Francisco Syncope Rule to predict patients with serious outcomes. *Ann Emerg Med* 2006;**47**:448-454.
27. Middlekauff HR, Stevenson WG, Stevenson LW, Saxon LA. Syncope in advanced heart failure: high risk of sudden death regardless of origin of syncope. *J Am Coll Cardiol* 1993;**21**:110-116.
28. Brembilla-Perrot B, Suty-Selton C, Beurrier D, Houriez P, Nippert M, de la Chaise AT, Louis P, Claudon O, Andronache M, Abdelaal A, Sadoul N, Juilliere Y. Differences in mechanisms and outcomes of syncope in patients with coronary disease or idiopathic left ventricular dysfunction as assessed by electrophysiologic testing. *J Am Coll Cardiol* 2004;**44**:594-601.
29. Steinberg JS, Beckman K, Greene HL, Marinchak R, Klein RC, Greer SG, Ehler F, Foster P, Menchavez E, Raitt M, Wathen MS, Morris M, Hallstrom A. Follow-up of patients with unexplained syncope and inducible ventricular tachyarrhythmias: analysis of the AVID registry and an AVID substudy. *Antiarrhythmics Versus Implantable Defibrillators. J Cardiovasc Electrophysiol* 2001;**12**:996-1001.
30. Pezawas T, Stix G, Kastner J, Wolzt M, Mayer C, Moertl D, Schmidinger H. Unexplained syncope in patients with structural heart disease and no documented ventricular arrhythmias: value of electrophysiologically guided implantable cardioverter defibrillator therapy. *Europace* 2003;**5**:305-312.
31. Olshansky B, Poole JE, Johnson G, Anderson J, Hellkamp AS, Packer D, Mark DB, Lee KL, Bardy GH, SCD-HeFT Investigators. Syncope predicts the outcome of cardiomyopathy patients: analysis of the SCD-HeFT study. *J Am Coll Cardiol* 2008;**51**:1277-1282.
32. Goldberger JJ, Cain ME, Hohnloser SH, Kadish AH, Knight BP, Lauer MS, Maron BJ, Page RL, Passman RS, Siscovick D, Siscovick D, Stevenson WG, Zipes DP, American Heart Association, American College of Cardiology Foundation, Heart Rhythm Society. American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death: a scientific statement from the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention. *Circulation* 2008;**118**:1497-1518.
33. Del Rosso A, Alboni P, Brignole M, Menozzi C, Raviele A. Relation of clinical presentation of syncope to the age of patients. *Am J Cardiol* 2005;**96**:1431-1435.
34. Martin TP, Hanusa BH, Kapoor WN. Risk stratification of patients with syncope. *Ann Emerg Med* 1997;**29**:459-466.
35. Colivicchi F, Ammirati F, Melina D, Guido V, Imperoli G, Santini M, OESIL (Osservatorio Epidemiologico sulla Sincope nel Lazio) Study Investigators. Development and prospective validation of a risk stratification system for patients with syncope in the emergency department: the OESIL risk score. *Eur Heart J* 2003;**24**:811-819.
36. Del Rosso A, Ungar A, Maggi R, Giada F, Petix NR, De Santo T, Menozzi C, Brignole M. Clinical predictors of cardiac syncope at initial evaluation in patients referred urgently to a general hospital: the EGSYS score. *Heart* 2008;**94**:1620-1626.



- 2266 37. Mittal S, Hao SC, Iwai S, Stein KM, Markowitz SM, Slotwiner DJ, Lerman BB. Significance  
2267 of inducible ventricular fibrillation in patients with coronary artery disease and unexplained  
2268 syncope. *J Am Coll Cardiol* 2001;**38**:371-376.
- 2269 38. Alboni P, Brignole M, Menozzi C, Raviele A, Del Rosso A, Dinelli M, Solano A, Bottoni N.  
2270 Diagnostic value of history in patients with syncope with or without heart disease. *J Am Coll*  
2271 *Cardiol* 2001;**37**:1921-1928.
- 2272 39. Berecki-Gisolf J, Sheldon A, Wieling W, van Dijk N, Costantino G, Furlan R, Shen WK,  
2273 Sheldon R. Identifying cardiac syncope based on clinical history: a literature-based model  
2274 tested in four independent datasets. *PLoS One* 2013;**8**:e75255.
- 2275 40. Casagrande I, Brignole M, Cencetti S, Cervellin G, Costantino G, Furlan R, Mossini G,  
2276 Numeroso F, Pesenti Campagnoni M, Pinna Pargaglia P, Rafanelli M, Ungar A.  
2277 Management of transient loss of consciousness of suspected syncopal cause, after the  
2278 initial evaluation in the Emergency Department. *Emergency Care J* 2016;**12**:25-27.
- 2279 41. Crane SD. Risk stratification of patients with syncope in an accident and emergency  
2280 department. *Emerg Med J* 2002;**19**:23-27.
- 2281 42. Sheldon R, Rose S, Ritchie D, Connolly SJ, Koshman ML, Lee MA, Frenneaux M, Fisher  
2282 M, Murphy W. Historical criteria that distinguish syncope from seizures. *J Am Coll Cardiol*  
2283 2002;**40**:142-148.
- 2284 43. Numeroso F, Mossini G, Giovanelli M, Lippi G, Cervellin G. Short-term Prognosis and  
2285 Current Management of Syncopal Patients at Intermediate Risk: Results from the IRiS  
2286 (Intermediate-Risk Syncope) Study. *Acad Emerg Med* 2016;**23**:941-948.
- 2287 44. Reed MJ, Newby DE, Coull AJ, Prescott RJ, Jacques KG, Gray AJ. The ROSE (Risk  
2288 Stratification Of Syncope in the Emergency department) study. *J Am Coll Cardiol*  
2289 2010;**55**:713-721.
- 2290 45. Martin GJ, Adams SL, Martin HG, Mathews J, Zull D, Scanlon PJ. Prospective evaluation of  
2291 syncope. *Ann Emerg Med* 1984;**13**:499-504.
- 2292 46. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM,  
2293 Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid  
2294 A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ. 2015 ESC Guidelines for  
2295 the management of patients with ventricular arrhythmias and the prevention of sudden  
2296 cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias  
2297 and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC).  
2298 Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur*  
2299 *Heart J* 2015;**36**:2793-2867.
- 2300 47. Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ, Levy D. Incidence  
2301 and prognosis of syncope. *N Engl J Med* 2002;**347**:878-885.
- 2302 48. Ricci F, Fedorowski A, Radico F, Romanello M, Tatasciore A, Di Nicola M, Zimarino M, De  
2303 Caterina R. Cardiovascular morbidity and mortality related to orthostatic hypotension: a  
2304 meta-analysis of prospective observational studies. *Eur Heart J* 2015;**36**:1609-1617.
- 2305 49. Calkins H, Shyr Y, Frumin H, Schork A, Morady F. The value of the clinical history in the  
2306 differentiation of syncope due to ventricular tachycardia, atrioventricular block, and  
2307 neurocardiogenic syncope. *Am J Med* 1995;**98**:365-373.
- 2308 50. Sheldon R, Rose S, Connolly S, Ritchie D, Koshman ML, Frenneaux M. Diagnostic criteria  
2309 for vasovagal syncope based on a quantitative history. *Eur Heart J* 2006;**27**:344-350.
- 2310 51. Lipsitz LA. Syncope in the elderly patient. *Hosp Pract (Off Ed)* 1986;**21**:33-44.
- 2311 52. Dermksian G, Lamb LE. Syncope in a population of healthy young adults; incidence,  
2312 mechanisms, and significance. *J Am Med Assoc* 1958;**168**:1200-1207.
- 2313 53. Brignole M, Oddone D, Cogorno S, Menozzi C, Gianfranchi L, Bertulla A. Long-term  
2314 outcome in symptomatic carotid sinus hypersensitivity. *Am Heart J* 1992;**123**:687-692.

- 2315 54. Jamjoom AA, Nikkar-Esfahani A, Fitzgerald JE. Operating theatre related syncope in  
2316 medical students: a cross sectional study. *BMC Med Educ* 2009;**9**:14.
- 2317 55. Quinn JV, Stiell IG, McDermott DA, Sellers KL, Kohn MA, Wells GA. Derivation of the San  
2318 Francisco Syncope Rule to predict patients with short-term serious outcomes. *Ann Emerg*  
2319 *Med* 2004;**43**:224-232.
- 2320 56. Costantino G, Perego F, Dipaola F, Borella M, Galli A, Cantoni G, Dell'Orto S, Dassi S,  
2321 Filardo N, Duca PG, Montano N, Furlan R, STePS Investigators. Short- and long-term  
2322 prognosis of syncope, risk factors, and role of hospital admission: results from the STePS  
2323 (Short-Term Prognosis of Syncope) study. *J Am Coll Cardiol* 2008;**51**:276-283.
- 2324 57. Colman N, Bakker A, Linzer M, Reitsma JB, Wieling W, Wilde AA. Value of history-taking in  
2325 syncope patients: in whom to suspect long QT syndrome? *Europace* 2009;**11**:937-943.
- 2326 58. Kapoor WN, Peterson J, Wieand HS, Karpf M. Diagnostic and prognostic implications of  
2327 recurrences in patients with syncope. *Am J Med* 1987;**83**:700-708.
- 2328 59. Oh JH, Hanusa BH, Kapoor WN. Do symptoms predict cardiac arrhythmias and mortality in  
2329 patients with syncope? *Arch Intern Med* 1999;**159**:375-380.
- 2330 60. Grossman SA, Fischer C, Lipsitz LA, Mottley L, Sands K, Thompson S, Zimetbaum P,  
2331 Shapiro NI. Predicting adverse outcomes in syncope. *J Emerg Med* 2007;**33**:233-239.
- 2332 61. Surawicz B, Childers R, Deal BJ, Gettes LS, Bailey JJ, Gorgels A, Hancock EW,  
2333 Josephson M, Kligfield P, Kors JA, Macfarlane P, Mason JW, Mirvis DM, Okin P, Pahlm O,  
2334 Rautaharju PM, van Herpen G, Wagner GS, Wellens H, American Heart Association  
2335 Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology, American  
2336 College of Cardiology Foundation, Heart Rhythm Society. AHA/ACCF/HRS  
2337 recommendations for the standardization and interpretation of the electrocardiogram: part  
2338 III: intraventricular conduction disturbances: a scientific statement from the American Heart  
2339 Association Electrocardiography and Arrhythmias Committee, Council on Clinical  
2340 Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society.  
2341 Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll*  
2342 *Cardiol* 2009;**53**:976-981.
- 2343 62. Costantino G, Sun BC, Barbic F, Bossi I, Casazza G, Dipaola F, McDermott D, Quinn J,  
2344 Reed MJ, Sheldon RS, Solbiati M, Thiruganasambandamoorthy V, Beach D, Bodemer N,  
2345 Brignole M, Casagrande I, Del Rosso A, Duca P, Falavigna G, Grossman SA, Ippoliti R,  
2346 Krahn AD, Montano N, Morillo CA, Olshansky B, Raj SR, Ruwald MH, Sarasin FP, Shen  
2347 WK, Stiell I, Ungar A, Gert van Dijk J, van Dijk N, Wieling W, Furlan R. Syncope clinical  
2348 management in the emergency department: a consensus from the first international  
2349 workshop on syncope risk stratification in the emergency department. *Eur Heart J*  
2350 *2016*;**37**:1493-1498.
- 2351 63. Kenny RA, Brignole M, Dan GA, Deharo JC, van Dijk JG, Doherty C, Hamdan M, Moya A,  
2352 Parry SW, Sutton R, Ungar A, Wieling W. Syncope Unit: rationale and requirement--the  
2353 European Heart Rhythm Association position statement endorsed by the Heart Rhythm  
2354 Society. *Europace* 2015;**17**:1325-1340.
- 2355 64. Sun BC, McCreath H, Liang LJ, Bohan S, Baugh C, Ragsdale L, Henderson SO, Clark C,  
2356 Bastani A, Keeler E, An R, Mangione CM. Randomized clinical trial of an emergency  
2357 department observation syncope protocol versus routine inpatient admission. *Ann Emerg*  
2358 *Med* 2014;**64**:167-175.
- 2359 65. Shen WK, Decker WW, Smars PA, Goyal DG, Walker AE, Hodge DO, Trusty JM, Brekke  
2360 KM, Jahangir A, Brady PA, Munger TM, Gersh BJ, Hammill SC, Frye RL. Syncope  
2361 Evaluation in the Emergency Department Study (SEEDS): a multidisciplinary approach to  
2362 syncope management. *Circulation* 2004;**110**:3636-3645.

- 2363 66. Thiruganasambandamoorthy V, Stiell IG, Wells GA, Vaidyanathan A, Mukarram M, Taljaard  
2364 M. Outcomes in presyncope patients: a prospective cohort study. *Ann Emerg Med*  
2365 2015;**65**:268-276 e266.
- 2366 67. Greve Y, Geier F, Popp S, Bertsch T, Singler K, Meier F, Smolarsky A, Mang H, Muller C,  
2367 Christ M. The prevalence and prognostic significance of near syncope and syncope: a  
2368 prospective study of 395 cases in an emergency department (the SPEED study). *Dtsch*  
2369 *Arztebl Int* 2014;**111**:197-204.
- 2370 68. Krahn AD, Klein GJ, Yee R, Skanes AC, REVEAL Investigators. Predictive value of  
2371 presyncope in patients monitored for assessment of syncope. *Am Heart J* 2001;**141**:817-  
2372 821.
- 2373 69. Huff JS, Decker WW, Quinn JV, Perron AD, Napoli AM, Peeters S, Jagoda AS, American  
2374 College of Emergency Physicians. Clinical policy: critical issues in the evaluation and  
2375 management of adult patients presenting to the emergency department with syncope. *Ann*  
2376 *Emerg Med* 2007;**49**:431-444.
- 2377 70. Thiruganasambandamoorthy V, Hess EP, Alreesi A, Perry JJ, Wells GA, Stiell IG. External  
2378 validation of the San Francisco Syncope Rule in the Canadian setting. *Ann Emerg Med*  
2379 2010;**55**:464-472.
- 2380 71. Brignole M, Menozzi C, Bartoletti A, Giada F, Lagi A, Ungar A, Ponassi I, Mussi C, Maggi  
2381 R, Re G, Furlan R, Rovelli G, Ponzi P, Scivales A. A new management of syncope:  
2382 prospective systematic guideline-based evaluation of patients referred urgently to general  
2383 hospitals. *Eur Heart J* 2006;**27**:76-82.
- 2384 72. Del Greco M, Cozzio S, Scillieri M, Caprari F, Scivales A, Disertori M. Diagnostic pathway  
2385 of syncope and analysis of the impact of guidelines in a district general hospital. The ECSIT  
2386 study (epidemiology and costs of syncope in Trento). *Ital Heart J* 2003;**4**:99-106.
- 2387 73. McCarthy F, McMahon CG, Geary U, Plunkett PK, Kenny RA, Cunningham CJ, European  
2388 Society of Cardiology. Management of syncope in the Emergency Department: a single  
2389 hospital observational case series based on the application of European Society of  
2390 Cardiology Guidelines. *Europace* 2009;**11**:216-224.
- 2391 74. Numeroso F, Mossini G, Spaggiari E, Cervellin G. Syncope in the emergency department  
2392 of a large northern Italian hospital: incidence, efficacy of a short-stay observation ward and  
2393 validation of the OESIL risk score. *Emerg Med J* 2010;**27**:653-658.
- 2394 75. Lin M, Wolfe RE, Shapiro NI, Novack V, Lior Y, Grossman SA. Observation vs admission in  
2395 syncope: can we predict short length of stays? *Am J Emerg Med* 2015;**33**:1684-1686.
- 2396 76. Grossman AM, Volz KA, Shapiro NI, Salem R, Sanchez LD, Smulowitz P, Grossman SA.  
2397 Comparison of 1-Day Emergency Department Observation and Inpatient Ward for 1-Day  
2398 Admissions in Syncope Patients. *J Emerg Med* 2016;**50**:217-222.
- 2399 77. Ungar A, Tesi F, Chisciotti VM, Pepe G, Vanni S, Grifoni S, Balzi D, Rafanelli M,  
2400 Marchionni N, Brignole M. Assessment of a structured management pathway for patients  
2401 referred to the Emergency Department for syncope: results in a tertiary hospital. *Europace*  
2402 2016;**18**:457-462.
- 2403 78. Serrano LA, Hess EP, Bellolio MF, Murad MH, Montori VM, Erwin PJ, Decker WW.  
2404 Accuracy and quality of clinical decision rules for syncope in the emergency department: a  
2405 systematic review and meta-analysis. *Ann Emerg Med* 2010;**56**:362-373 e361.
- 2406 79. Dipaola F, Costantino G, Perego F, Borella M, Galli A, Cantoni G, Barbic F, Casella F,  
2407 Duca PG, Furlan R, STePS investigators. San Francisco Syncope Rule, Osservatorio  
2408 Epidemiologico sulla Sincope nel Lazio risk score, and clinical judgment in the assessment  
2409 of short-term outcome of syncope. *Am J Emerg Med* 2010;**28**:432-439.
- 2410 80. Sheldon RS, Morillo CA, Krahn AD, O'Neill B, Thiruganasambandamoorthy V, Parkash R,  
2411 Talajic M, Tu JV, Seifer C, Johnstone D, Leather R. Standardized approaches to the

- 2412 investigation of syncope: Canadian Cardiovascular Society position paper. *Can J Cardiol*  
 2413 2011;**27**:246-253.
- 2414 81. Perego F, Costantino G, Dipaola F, Scannella E, Borella M, Galli A, Barbic F, Casella F,  
 2415 Solbiati M, Angaroni L, Duca P, Furlan R. Predictors of hospital admission after syncope:  
 2416 relationships with clinical risk scores. *Int J Cardiol* 2012;**161**:182-183.
- 2417 82. Schladenhaufen R, Feilinger S, Pollack M, Benenson R, Kusmiesz AL. Application of San  
 2418 Francisco Syncope Rule in elderly ED patients. *Am J Emerg Med* 2008;**26**:773-778.
- 2419 83. Sun BC, Mangione CM, Merchant G, Weiss T, Shlamovitz GZ, Zargaraff G, Shiraga S,  
 2420 Hoffman JR, Mower WR. External validation of the San Francisco Syncope Rule. *Ann*  
 2421 *Emerg Med* 2007;**49**:420-427, 427 e421-424.
- 2422 84. Reed MJ, Henderson SS, Newby DE, Gray AJ. One-year prognosis after syncope and the  
 2423 failure of the ROSE decision instrument to predict one-year adverse events. *Ann Emerg*  
 2424 *Med* 2011;**58**:250-256.
- 2425 85. Birnbaum A, Esses D, Bijur P, Wollowitz A, Gallagher EJ. Failure to validate the San  
 2426 Francisco Syncope Rule in an independent emergency department population. *Ann Emerg*  
 2427 *Med* 2008;**52**:151-159.
- 2428 86. Costantino G, Casazza G, Reed M, Bossi I, Sun B, Del Rosso A, Ungar A, Grossman S,  
 2429 D'Ascenzo F, Quinn J, McDermott D, Sheldon R, Furlan R. Syncope risk stratification tools  
 2430 vs clinical judgment: an individual patient data meta-analysis. *Am J Med* 2014;**127**:1126  
 2431 e1113-1125.
- 2432 87. Canzoniero JV, Afshar E, Hedian H, Koch C, Morgan DJ. Unnecessary hospitalization and  
 2433 related harm for patients with low-risk syncope. *JAMA Intern Med* 2015;**175**:1065-1067.
- 2434 88. Thiruganasambandamoorthy V, Kwong K, Wells GA, Sivilotti ML, Mukarram M, Rowe BH,  
 2435 Lang E, Perry JJ, Sheldon R, Stiell IG, Taljaard M. Development of the Canadian Syncope  
 2436 Risk Score to predict serious adverse events after emergency department assessment of  
 2437 syncope. *CMAJ* 2016;**188**:E289-298.
- 2438 89. Kerr SR, Pearce MS, Brayne C, Davis RJ, Kenny RA. Carotid sinus hypersensitivity in  
 2439 asymptomatic older persons: implications for diagnosis of syncope and falls. *Arch Intern*  
 2440 *Med* 2006;**166**:515-520.
- 2441 90. Puggioni E, Guiducci V, Brignole M, Menozzi C, Oddone D, Donateo P, Croci F, Solano A,  
 2442 Lolli G, Tomasi C, Bottoni N. Results and complications of the carotid sinus massage  
 2443 performed according to the "method of symptoms". *Am J Cardiol* 2002;**89**:599-601.
- 2444 91. Wieling W, Krediet CT, Solari D, de Lange FJ, van Dijk N, Thijs RD, van Dijk JG, Brignole  
 2445 M, Jardine DL. At the heart of the arterial baroreflex: a physiological basis for a new  
 2446 classification of carotid sinus hypersensitivity. *J Intern Med* 2013;**273**:345-358.
- 2447 92. Solari D, Maggi R, Oddone D, Solano A, Croci F, Donateo P, Brignole M. Clinical context  
 2448 and outcome of carotid sinus syndrome diagnosed by means of the 'method of symptoms'.  
 2449 *Europace* 2014;**16**:928-934.
- 2450 93. Solari D, Maggi R, Oddone D, Solano A, Croci F, Donateo P, Wieling W, Brignole M.  
 2451 Assessment of the vasodepressor reflex in carotid sinus syndrome. *Circ Arrhythm*  
 2452 *Electrophysiol* 2014;**7**:505-510.
- 2453 94. Brignole M, Ungar A, Casagrande I, Gulizia M, Lunati M, Ammirati F, Del Rosso A, Sasdelli  
 2454 M, Santini M, Maggi R, Vitale E, Morrione A, Francese GM, Vecchi MR, Giada F, Syncope  
 2455 Unit Project (SUP) investigators. Prospective multicentre systematic guideline-based  
 2456 management of patients referred to the Syncope Units of general hospitals. *Europace*  
 2457 2010;**12**:109-118.
- 2458 95. Munro NC, McIntosh S, Lawson J, Morley CA, Sutton R, Kenny RA. Incidence of  
 2459 complications after carotid sinus massage in older patients with syncope. *J Am Geriatr Soc*  
 2460 1994;**42**:1248-1251.

- 2461 96. Ungar A, Rivasi G, Rafanelli M, Toffanello G, Mussi C, Ceccofiglio A, McDonagh R, Drumm  
2462 B, Marchionni N, Alboni P, Kenny RA. Safety and tolerability of Tilt Testing and Carotid  
2463 Sinus Massage in the octogenarians. *Age Ageing* 2016;**45**:242-248.
- 2464 97. Davies AJ, Kenny RA. Frequency of neurologic complications following carotid sinus  
2465 massage. *Am J Cardiol* 1998;**81**:1256-1257.
- 2466 98. Brignole M, Menozzi C, Lolli G, Bottoni N, Gaggioli G. Long-term outcome of paced and  
2467 nonpaced patients with severe carotid sinus syndrome. *Am J Cardiol* 1992;**69**:1039-1043.
- 2468 99. Claesson JE, Kristensson BE, Edvardsson N, Wahrborg P. Less syncope and milder  
2469 symptoms in patients treated with pacing for induced cardioinhibitory carotid sinus  
2470 syndrome: a randomized study. *Europace* 2007;**9**:932-936.
- 2471 100. Menozzi C, Brignole M, Lolli G, Bottoni N, Oddone D, Gianfranchi L, Gaggioli G. Follow-up  
2472 of asystolic episodes in patients with cardioinhibitory, neurally mediated syncope and VVI  
2473 pacemaker. *Am J Cardiol* 1993;**72**:1152-1155.
- 2474 101. Maggi R, Menozzi C, Brignole M, Podoleanu C, Iori M, Sutton R, Moya A, Giada F, Orazi S,  
2475 Grovale N. Cardioinhibitory carotid sinus hypersensitivity predicts an asystolic mechanism  
2476 of spontaneous neurally mediated syncope. *Europace* 2007;**9**:563-567.
- 2477 102. Thomas JE. Hyperactive carotid sinus reflex and carotid sinus syncope. *Mayo Clin Proc*  
2478 1969;**44**:127-139.
- 2479 103. Smit AA, Halliwill JR, Low PA, Wieling W. Pathophysiological basis of orthostatic  
2480 hypotension in autonomic failure. *J Physiol* 1999;**519 Pt 1**:1-10.
- 2481 104. Ricci F, De Caterina R, Fedorowski A. Orthostatic Hypotension: Epidemiology, Prognosis,  
2482 and Treatment. *J Am Coll Cardiol* 2015;**66**:848-860.
- 2483 105. Kenny RA, Ingram A, Bayliss J, Sutton R. Head-up tilt: a useful test for investigating  
2484 unexplained syncope. *Lancet* 1986;**1**:1352-1355.
- 2485 106. Bartoletti A, Alboni P, Ammirati F, Brignole M, Del Rosso A, Foglia Manzillo G, Menozzi C,  
2486 Raviele A, Sutton R. 'The Italian Protocol': a simplified head-up tilt testing potentiated with  
2487 oral nitroglycerin to assess patients with unexplained syncope. *Europace* 2000;**2**:339-342.
- 2488 107. Kenny RA, O'Shea D, Parry SW. The Newcastle protocols for head-up tilt table testing in  
2489 the diagnosis of vasovagal syncope, carotid sinus hypersensitivity, and related disorders.  
2490 *Heart* 2000;**83**:564-569.
- 2491 108. Benditt DG, Ferguson DW, Grubb BP, Kapoor WN, Kugler J, Lerman BB, Maloney JD,  
2492 Raviele A, Ross B, Sutton R, Wolk MJ, Wood DL. Tilt table testing for assessing syncope.  
2493 American College of Cardiology. *J Am Coll Cardiol* 1996;**28**:263-275.
- 2494 109. Morillo CA, Klein GJ, Zandri S, Yee R. Diagnostic accuracy of a low-dose isoproterenol  
2495 head-up tilt protocol. *Am Heart J* 1995;**129**:901-906.
- 2496 110. Forleo C, Guida P, Iacoviello M, Resta M, Monitillo F, Sorrentino S, Favale S. Head-up tilt  
2497 testing for diagnosing vasovagal syncope: a meta-analysis. *Int J Cardiol* 2013;**168**:27-35.
- 2498 111. Parry SW, Gray JC, Newton JL, Reeve P, O'Shea D, Kenny RA. 'Front-loaded' head-up tilt  
2499 table testing: validation of a rapid first line nitrate-provoked tilt protocol for the diagnosis of  
2500 vasovagal syncope. *Age Ageing* 2008;**37**:411-415.
- 2501 112. Verheyden B, Gisolf J, Beckers F, Karemaker JM, Wesseling KH, Aubert AE, Wieling W.  
2502 Impact of age on the vasovagal response provoked by sublingual nitroglycerine in routine  
2503 tilt testing. *Clin Sci (Lond)* 2007;**113**:329-337.
- 2504 113. Nilsson D, Sutton R, Tas W, Burri P, Melander O, Fedorowski A. Orthostatic Changes in  
2505 Hemodynamics and Cardiovascular Biomarkers in Dysautonomic Patients. *PLoS One*  
2506 2015;**10**:e0128962.
- 2507 114. Low PA, Sandroni P, Joyner M, Shen WK. Postural tachycardia syndrome (POTS). *J*  
2508 *Cardiovasc Electrophysiol* 2009;**20**:352-358.

- 2509 115. Petersen ME, Williams TR, Sutton R. Psychogenic syncope diagnosed by prolonged head-  
2510 up tilt testing. *QJM* 1995;**88**:209-213.
- 2511 116. Tannemaat MR, van Niekerk J, Reijntjes RH, Thijs RD, Sutton R, van Dijk JG. The  
2512 semiology of tilt-induced psychogenic pseudosyncope. *Neurology* 2013;**81**:752-758.
- 2513 117. Blad H, Lamberts RJ, van Dijk GJ, Thijs RD. Tilt-induced vasovagal syncope and  
2514 psychogenic pseudosyncope: Overlapping clinical entities. *Neurology* 2015;**85**:2006-2010.
- 2515 118. Moya A, Permanyer-Miralda G, Sagrista-Sauleda J, Carne X, Rius T, Mont L, Soler-Soler J.  
2516 Limitations of head-up tilt test for evaluating the efficacy of therapeutic interventions in  
2517 patients with vasovagal syncope: results of a controlled study of etilefrine versus placebo. *J*  
2518 *Am Coll Cardiol* 1995;**25**:65-69.
- 2519 119. Brignole M, Croci F, Menozzi C, Solano A, Donateo P, Oddone D, Puggioni E, Lolli G.  
2520 Isometric arm counter-pressure maneuvers to abort impending vasovagal syncope. *J Am*  
2521 *Coll Cardiol* 2002;**40**:2053-2059.
- 2522 120. Krediet CT, van Dijk N, Linzer M, van Lieshout JJ, Wieling W. Management of vasovagal  
2523 syncope: controlling or aborting faints by leg crossing and muscle tensing. *Circulation*  
2524 2002;**106**:1684-1689.
- 2525 121. van Dijk N, Quartieri F, Blanc JJ, Garcia-Civera R, Brignole M, Moya A, Wieling W, PCTrial  
2526 Investigators. Effectiveness of physical counterpressure maneuvers in preventing  
2527 vasovagal syncope: the Physical Counterpressure Manoeuvres Trial (PC-Trial). *J Am Coll*  
2528 *Cardiol* 2006;**48**:1652-1657.
- 2529 122. Deharo JC, Jego C, Lanteaume A, Djiane P. An implantable loop recorder study of highly  
2530 symptomatic vasovagal patients: the heart rhythm observed during a spontaneous syncope  
2531 is identical to the recurrent syncope but not correlated with the head-up tilt test or  
2532 adenosine triphosphate test. *J Am Coll Cardiol* 2006;**47**:587-593.
- 2533 123. Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Moya A, Wieling W, Andresen D,  
2534 Benditt DG, Grovale N, De Santo T, Vardas P, International Study on Syncope of Uncertain  
2535 Etiology 2 (ISSUE 2) Group. Lack of correlation between the responses to tilt testing and  
2536 adenosine triphosphate test and the mechanism of spontaneous neurally mediated  
2537 syncope. *Eur Heart J* 2006;**27**:2232-2239.
- 2538 124. Flevari P, Leftheriotis D, Komborozos C, Fountoulaki K, Dages N, Theodorakis G,  
2539 Kremastinos D. Recurrent vasovagal syncope: comparison between clomipramine and  
2540 nitroglycerin as drug challenges during head-up tilt testing. *Eur Heart J* 2009;**30**:2249-2253.
- 2541 125. Petersen ME, Williams TR, Gordon C, Chamberlain-Webber R, Sutton R. The normal  
2542 response to prolonged passive head up tilt testing. *Heart* 2000;**84**:509-514.
- 2543 126. Furukawa T, Maggi R, Solano A, Croci F, Brignole M. Effect of clinical triggers on positive  
2544 responses to tilt-table testing potentiated with nitroglycerin or clomipramine. *Am J Cardiol*  
2545 2011;**107**:1693-1697.
- 2546 127. Petix NR, Del Rosso A, Furlan R, Guarnaccia V, Zipoli A. Nitrate-potentiated head-up tilt  
2547 testing (HUT) has a low diagnostic yield in patients with likely vasovagal syncope. *Pacing*  
2548 *Clin Electrophysiol* 2014;**37**:164-172.
- 2549 128. Raviele A, Menozzi C, Brignole M, Gasparini G, Alboni P, Musso G, Lolli G, Oddone D,  
2550 Dinelli M, Mureddu R. Value of head-up tilt testing potentiated with sublingual nitroglycerin  
2551 to assess the origin of unexplained syncope. *Am J Cardiol* 1995;**76**:267-272.
- 2552 129. Ungar A, Sgobino P, Russo V, Vitale E, Sutton R, Melissano D, Beiras X, Bottoni N, Ebert  
2553 HH, Gulizia M, Jorfida M, Moya A, Andresen D, Grovale N, Brignole M, International Study  
2554 on Syncope of Uncertain Etiology 3 (ISSUE-3) Investigators. Diagnosis of neurally  
2555 mediated syncope at initial evaluation and with tilt table testing compared with that revealed  
2556 by prolonged ECG monitoring. An analysis from the Third International Study on Syncope  
2557 of Uncertain Etiology (ISSUE-3). *Heart* 2013;**99**:1825-1831.

- 2558 130. Brignole M, Gianfranchi L, Menozzi C, Raviele A, Oddone D, Lolli G, Bottoni N. Role of  
2559 autonomic reflexes in syncope associated with paroxysmal atrial fibrillation. *J Am Coll*  
2560 *Cardiol* 1993;**22**:1123-1129.
- 2561 131. Leitch JW, Klein GJ, Yee R, Leather RA, Kim YH. Syncope associated with  
2562 supraventricular tachycardia. An expression of tachycardia rate or vasomotor response?  
2563 *Circulation* 1992;**85**:1064-1071.
- 2564 132. Sutton R, Brignole M. Twenty-eight years of research permit reinterpretation of tilt-testing:  
2565 hypotensive susceptibility rather than diagnosis. *Eur Heart J* 2014;**35**:2211-2212.
- 2566 133. Taneja I, Marney A, Robertson D. Aortic stenosis and autonomic dysfunction: co-  
2567 conspirators in syncope. *Am J Med Sci* 2004;**327**:281-283.
- 2568 134. Thomson HL, Morris-Thurgood J, Atherton J, Frenneaux M. Reduced cardiopulmonary  
2569 baroreflex sensitivity in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*  
2570 1998;**31**:1377-1382.
- 2571 135. Brignole M, Menozzi C, Gianfranchi L, Oddone D, Lolli G, Bertulla A. Neurally mediated  
2572 syncope detected by carotid sinus massage and head-up tilt test in sick sinus syndrome.  
2573 *Am J Cardiol* 1991;**68**:1032-1036.
- 2574 136. Alboni P, Menozzi C, Brignole M, Paparella N, Lolli G, Oddone D, Dinelli M. An abnormal  
2575 neural reflex plays a role in causing syncope in sinus bradycardia. *J Am Coll Cardiol*  
2576 1993;**22**:1130-1134.
- 2577 137. Zaidi A, Clough P, Cooper P, Scheepers B, Fitzpatrick AP. Misdiagnosis of epilepsy: many  
2578 seizure-like attacks have a cardiovascular cause. *J Am Coll Cardiol* 2000;**36**:181-184.
- 2579 138. Goldstein DS, Pechnik S, Holmes C, Eldadah B, Sharabi Y. Association between supine  
2580 hypertension and orthostatic hypotension in autonomic failure. *Hypertension* 2003;**42**:136-  
2581 142.
- 2582 139. Novak P. Assessment of sympathetic index from the Valsalva maneuver. *Neurology*  
2583 2011;**76**:2010-2016.
- 2584 140. Fanciulli A, Strano S, Ndayisaba JP, Goebel G, Gioffre L, Rizzo M, Colosimo C,  
2585 Caltagirone C, Poewe W, Wenning GK, Pontieri FE. Detecting nocturnal hypertension in  
2586 Parkinson's disease and multiple system atrophy: proposal of a decision-support algorithm.  
2587 *J Neurol* 2014;**261**:1291-1299.
- 2588 141. Jones PK, Gibbons CH. The role of autonomic testing in syncope. *Auton Neurosci*  
2589 2014;**184**:40-45.
- 2590 142. Baschieri F, Calandra-Buonaura G, Doria A, Mastrolilli F, Palareti A, Barletta G, Solieri L,  
2591 Guaraldi P, Martinelli P, Cortelli P. Cardiovascular autonomic testing performed with a new  
2592 integrated instrumental approach is useful in differentiating MSA-P from PD at an early  
2593 stage. *Parkinsonism Relat Disord* 2015;**21**:477-482.
- 2594 143. Rocchi C, Pierantozzi M, Galati S, Chiaravallotti A, Pisani V, Prosperetti C, Lauretti B,  
2595 Stampanoni Bassi M, Olivola E, Schillaci O, Stefani A. Autonomic Function Tests and MIBG  
2596 in Parkinson's Disease: Correlation to Disease Duration and Motor Symptoms. *CNS*  
2597 *Neurosci Ther* 2015;**21**:727-732.
- 2598 144. Kim AJ, Frishman WH. Laughter-induced syncope. *Cardiol Rev* 2012;**20**:194-196.
- 2599 145. Ndayisaba JP, Fanciulli A, Granata R, Duerr S, Hintringer F, Goebel G, Krismer F, Wenning  
2600 GK. Sex and age effects on cardiovascular autonomic function in healthy adults. *Clin Auton*  
2601 *Res* 2015;**25**:317-326.
- 2602 146. Bonuccelli U, Lucetti C, Del Dotto P, Ceravolo R, Gambaccini G, Bernardini S, Rossi G,  
2603 Piaggese A. Orthostatic hypotension in de novo Parkinson disease. *Arch Neurol*  
2604 2003;**60**:1400-1404.

- 2605 147. Struhal W, Javor A, Brunner C, Benesch T, Schmidt V, Vosko MR, Ransmayr G. The  
2606 phoenix from the ashes: cardiovascular autonomic dysfunction in behavioral variant of  
2607 frontotemporal dementia. *J Alzheimers Dis* 2014;**42**:1041-1046.
- 2608 148. Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, Clement D, de la Sierra A, de  
2609 Leeuw P, Dolan E, Fagard R, Graves J, Head GA, Imai Y, Kario K, Lurbe E, Mallion JM,  
2610 Mancia G, Mengden T, Myers M, Ogedegbe G, Ohkubo T, Omboni S, Palatini P, Redon J,  
2611 Ruilope LM, Shennan A, Staessen JA, vanMontfrans G, Verdecchia P, Waeber B, Wang J,  
2612 Zanchetti A, Zhang Y, European Society of Hypertension Working Group on Blood  
2613 Pressure Monitoring and Cardiovascular Variability. European Society of Hypertension  
2614 practice guidelines for ambulatory blood pressure monitoring. *J Hypertens* 2014;**32**:1359-  
2615 1366.
- 2616 149. Schmidt C, Berg D, Herting, Prieur S, Junghanns S, Schweitzer K, Globas C, Schols L,  
2617 Reichmann H, Ziemssen T. Loss of nocturnal blood pressure fall in various extrapyramidal  
2618 syndromes. *Mov Disord* 2009;**24**:2136-2142.
- 2619 150. Voichanski S, Grossman C, Leibowitz A, Peleg E, Koren-Morag N, Sharabi Y, Shamiss A,  
2620 Grossman E. Orthostatic hypotension is associated with nocturnal change in systolic blood  
2621 pressure. *Am J Hypertens* 2012;**25**:159-164.
- 2622 151. Fanciulli A, Strano S, Colosimo C, Caltagirone C, Spalletta G, Pontieri FE. The potential  
2623 prognostic role of cardiovascular autonomic failure in alpha-synucleinopathies. *Eur J Neurol*  
2624 2013;**20**:231-235.
- 2625 152. Stuebner E, Vichayanrat E, Low DA, Mathias CJ, Isenmann S, Haensch CA. Twenty-four  
2626 hour non-invasive ambulatory blood pressure and heart rate monitoring in Parkinson's  
2627 disease. *Front Neurol* 2013;**4**:49.
- 2628 153. Norcliffe-Kaufmann L, Kaufmann H. Is ambulatory blood pressure monitoring useful in  
2629 patients with chronic autonomic failure? *Clin Auton Res* 2014;**24**:189-192.
- 2630 154. Tannemaat MR, Thijs RD, van Dijk JG. Managing psychogenic pseudosyncope: Facts and  
2631 experiences. *Cardiol J* 2014;**21**:658-664.
- 2632 155. Braune S, Auer A, Schulte-Monting J, Schwerbrock S, Lucking CH. Cardiovascular  
2633 parameters: sensitivity to detect autonomic dysfunction and influence of age and sex in  
2634 normal subjects. *Clin Auton Res* 1996;**6**:3-15.
- 2635 156. Low PA, Denq JC, Opfer-Gehrking TL, Dyck PJ, O'Brien PC, Slezak JM. Effect of age and  
2636 gender on sudomotor and cardiovascular function and blood pressure response to tilt in  
2637 normal subjects. *Muscle Nerve* 1997;**20**:1561-1568.
- 2638 157. Barnett SR, Morin RJ, Kiely DK, Gagnon M, Azhar G, Knight EL, Nelson JC, Lipsitz LA.  
2639 Effects of age and gender on autonomic control of blood pressure dynamics. *Hypertension*  
2640 1999;**33**:1195-1200.
- 2641 158. Chiu DT, Shapiro NI, Sun BC, Mottley JL, Grossman SA. Are echocardiography, telemetry,  
2642 ambulatory electrocardiography monitoring, and cardiac enzymes in emergency  
2643 department patients presenting with syncope useful tests? A preliminary investigation. *J*  
2644 *Emerg Med* 2014;**47**:113-118.
- 2645 159. Benezet-Mazuecos J, Ibanez B, Rubio JM, Navarro F, Martin E, Romero J, Farre J. Utility  
2646 of in-hospital cardiac remote telemetry in patients with unexplained syncope. *Europace*  
2647 2007;**9**:1196-1201.
- 2648 160. Croci F, Brignole M, Alboni P, Menozzi C, Raviele A, Del Rosso A, Dinelli M, Solano A,  
2649 Bottoni N, Donato P. The application of a standardized strategy of evaluation in patients  
2650 with syncope referred to three syncope units. *Europace* 2002;**4**:351-355.
- 2651 161. Bass EB, Curtiss EI, Arena VC, Hanusa BH, Cecchetti A, Karpf M, Kapoor WN. The  
2652 duration of Holter monitoring in patients with syncope. Is 24 hours enough? *Arch Intern*  
2653 *Med* 1990;**150**:1073-1078.



- 2654 162. Rockx MA, Hoch JS, Klein GJ, Yee R, Skanes AC, Gula LJ, Krahn AD. Is ambulatory  
2655 monitoring for "community-acquired" syncope economically attractive? A cost-effectiveness  
2656 analysis of a randomized trial of external loop recorders versus Holter monitoring. *Am Heart*  
2657 *J* 2005;**150**:1065.
- 2658 163. Kinlay S, Leitch JW, Neil A, Chapman BL, Hardy DB, Fletcher PJ. Cardiac event recorders  
2659 yield more diagnoses and are more cost-effective than 48-hour Holter monitoring in patients  
2660 with palpitations. A controlled clinical trial. *Ann Intern Med* 1996;**124**:16-20.
- 2661 164. Bruining N, Caiani E, Chronaki C, Guzik P, van der Velde E, Task Force of the e-  
2662 Cardiology Working. Acquisition and analysis of cardiovascular signals on smartphones:  
2663 potential, pitfalls and perspectives: by the Task Force of the e-Cardiology Working Group of  
2664 European Society of Cardiology. *Eur J Prev Cardiol* 2014;**21**:4-13.
- 2665 165. Waks JW, Fein AS, Das S. Wide complex tachycardia recorded with a smartphone cardiac  
2666 rhythm monitor. *JAMA Intern Med* 2015;**175**:437-439.
- 2667 166. Locati ET, Moya A, Oliveira M, Tanner H, Willems R, Lunati M, Brignole M. External  
2668 prolonged electrocardiogram monitoring in unexplained syncope and palpitations: results of  
2669 the SYNARR-Flash study. *Europace* 2016;**18**:1265-1272.
- 2670 167. Linzer M, Pritchett EL, Pontinen M, McCarthy E, Divine GW. Incremental diagnostic yield of  
2671 loop electrocardiographic recorders in unexplained syncope. *Am J Cardiol* 1990;**66**:214-  
2672 219.
- 2673 168. Schuchert A, Maas R, Kretzschmar C, Behrens G, Kratzmann I, Meinertz T. Diagnostic  
2674 yield of external electrocardiographic loop recorders in patients with recurrent syncope and  
2675 negative tilt table test. *Pacing Clin Electrophysiol* 2003;**26**:1837-1840.
- 2676 169. Drak-Hernandez Y, Toquero-Ramos J, Fernandez JM, Perez-Pereira E, Castro-Urda V,  
2677 Fernandez-Lozano I. Effectiveness and safety of remote monitoring of patients with an  
2678 implantable loop recorder. *Rev Esp Cardiol (Engl Ed)* 2013;**66**:943-948.
- 2679 170. Furukawa T, Maggi R, Bertolone C, Ammirati F, Santini M, Ricci R, Giada F, Brignole M.  
2680 Effectiveness of remote monitoring in the management of syncope and palpitations.  
2681 *Europace* 2011;**13**:431-437.
- 2682 171. Rothman SA, Laughlin JC, Seltzer J, Walia JS, Baman RI, Siouffi SY, Sangrigoli RM,  
2683 Kowey PR. The diagnosis of cardiac arrhythmias: a prospective multi-center randomized  
2684 study comparing mobile cardiac outpatient telemetry versus standard loop event  
2685 monitoring. *J Cardiovasc Electrophysiol* 2007;**18**:241-247.
- 2686 172. Farwell DJ, Freemantle N, Sulke N. The clinical impact of implantable loop recorders in  
2687 patients with syncope. *Eur Heart J* 2006;**27**:351-356.
- 2688 173. Krahn AD, Klein GJ, Yee R, Skanes AC. Randomized assessment of syncope trial:  
2689 conventional diagnostic testing versus a prolonged monitoring strategy. *Circulation*  
2690 2001;**104**:46-51.
- 2691 174. Da Costa A, Defaye P, Romeyer-Bouchard C, Roche F, Dauphinot V, Deharo JC, Jacon P,  
2692 Lamaison D, Bathelemy JC, Isaaz K, Laurent G. Clinical impact of the implantable loop  
2693 recorder in patients with isolated syncope, bundle branch block and negative workup: a  
2694 randomized multicentre prospective study. *Arch Cardiovasc Dis* 2013;**106**:146-154.
- 2695 175. Podoleanu C, DaCosta A, Defaye P, Taieb J, Galley D, Bru P, Maury P, Mabo P, Boveda  
2696 S, Cellarier G, Anselme F, Kouakam C, Delarche N, Deharo JC, FRESH investigators.  
2697 Early use of an implantable loop recorder in syncope evaluation: a randomized study in the  
2698 context of the French healthcare system (FRESH study). *Arch Cardiovasc Dis*  
2699 2014;**107**:546-552.
- 2700 176. Sulke N, Sugihara C, Hong P, Patel N, Freemantle N. The benefit of a remotely monitored  
2701 implantable loop recorder as a first line investigation in unexplained syncope: the EaSyAS II  
2702 trial. *Europace* 2016;**18**:912-918.

- 2703 177. Edvardsson N, Garutti C, Rieger G, Linker NJ, PICTURE Study Investigators. Unexplained  
2704 syncope: implications of age and gender on patient characteristics and evaluation, the  
2705 diagnostic yield of an implantable loop recorder, and the subsequent treatment. *Clin Cardiol*  
2706 2014;**37**:618-625.
- 2707 178. Edvardsson N, Wolff C, Tsintzos S, Rieger G, Linker NJ. Costs of unstructured  
2708 investigation of unexplained syncope: insights from a micro-costing analysis of the  
2709 observational PICTURE registry. *Europace* 2015;**17**:1141-1148.
- 2710 179. Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, Ricci R, Sulke N, Wieling W,  
2711 Auricchio A, Lip GY, Almendral J, Kirchhof P, Aliot E, Gasparini M, Braunschweig F, Lip  
2712 GY, Almendral J, Kirchhof P, Botto GL, EHRA Scientific Documents Committee. Indications  
2713 for the use of diagnostic implantable and external ECG loop recorders. *Europace*  
2714 2009;**11**:671-687.
- 2715 180. Menozzi C, Brignole M, Garcia-Civera R, Moya A, Botto G, Tercedor L, Migliorini R,  
2716 Navarro X, International Study on Syncope of Uncertain Etiology (ISSUE) Investigators.  
2717 Mechanism of syncope in patients with heart disease and negative electrophysiologic test.  
2718 *Circulation* 2002;**105**:2741-2745.
- 2719 181. Linker NJ, Voulgaraki D, Garutti C, Rieger G, Edvardsson N, PICTURE Study Investigators.  
2720 Early versus delayed implantation of a loop recorder in patients with unexplained syncope--  
2721 effects on care pathway and diagnostic yield. *Int J Cardiol* 2013;**170**:146-151.
- 2722 182. Edvardsson N, Frykman V, van Mechelen R, Mitro P, Mohii-Oskarsson A, Pasquie JL,  
2723 Ramanna H, Schwertfeger F, Ventura R, Voulgaraki D, Garutti C, Stolt P, Linker NJ,  
2724 PICTURE Study Investigators. Use of an implantable loop recorder to increase the  
2725 diagnostic yield in unexplained syncope: results from the PICTURE registry. *Europace*  
2726 2011;**13**:262-269.
- 2727 183. Lacunza-Ruiz FJ, Moya-Mitjans A, Martinez-Alday J, Baron-Esquivias G, Ruiz-Granell R,  
2728 Rivas-Gandara N, Gonzalez-Enriquez S, Leal-del-Ojo J, Arcocha-Torres MF, Perez-  
2729 Villacastin J, Garcia-Heil N, Garcia-Alberola A. Implantable loop recorder allows an  
2730 etiologic diagnosis in one-third of patients. Results of the Spanish reveal registry. *Circ J*  
2731 2013;**77**:2535-2541.
- 2732 184. Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Moya A, Wieling W, Andresen D,  
2733 Benditt DG, Vardas P, International Study on Syncope of Uncertain Etiology 2 (ISSUE 2)  
2734 Group. Early application of an implantable loop recorder allows effective specific therapy in  
2735 patients with recurrent suspected neurally mediated syncope. *Eur Heart J* 2006;**27**:1085-  
2736 1092.
- 2737 185. Brignole M, Menozzi C, Moya A, Andresen D, Blanc JJ, Krahn AD, Wieling W, Beiras X,  
2738 Deharo JC, Russo V, Tomaino M, Sutton R, International Study on Syncope of Uncertain  
2739 Etiology 3 (ISSUE-3) Investigators. Pacemaker therapy in patients with neurally mediated  
2740 syncope and documented asystole: Third International Study on Syncope of Uncertain  
2741 Etiology (ISSUE-3): a randomized trial. *Circulation* 2012;**125**:2566-2571.
- 2742 186. Brignole M, Ammirati F, Arabia F, Quartieri F, Tomaino M, Ungar A, Lunati M, Russo V, Del  
2743 Rosso A, Gaggioli G, Syncope Unit Project (SUP) Two Investigators. Assessment of a  
2744 standardized algorithm for cardiac pacing in older patients affected by severe unpredictable  
2745 reflex syncopes. *Eur Heart J* 2015;**36**:1529-1535.
- 2746 187. Brignole M, Menozzi C, Moya A, Garcia-Civera R, Mont L, Alvarez M, Errazquin F, Beiras J,  
2747 Bottoni N, Donateo P, International Study on Syncope of Uncertain Etiology (ISSUE)  
2748 Investigators. Mechanism of syncope in patients with bundle branch block and negative  
2749 electrophysiological test. *Circulation* 2001;**104**:2045-2050.
- 2750 188. Moya A, Garcia-Civera R, Croci F, Menozzi C, Brugada J, Ammirati F, Del Rosso A,  
2751 Bellver-Navarro A, Garcia-Sacristan J, Bortnik M, Mont L, Ruiz-Granell R, Navarro X,

- 2752 Bradycardia detection in Bundle Branch Block (B4) study. Diagnosis, management, and  
2753 outcomes of patients with syncope and bundle branch block. *Eur Heart J* 2011;**32**:1535-  
2754 1541.
- 2755 189. Ho RT, Wicks T, Wyeth D, Nei M. Generalized tonic-clonic seizures detected by  
2756 implantable loop recorder devices: diagnosing more than cardiac arrhythmias. *Heart*  
2757 *Rhythm* 2006;**3**:857-861.
- 2758 190. Petkar S, Hamid T, Iddon P, Clifford A, Rice N, Claire R, McKee D, Curtis N, Cooper PN,  
2759 Fitzpatrick AP. Prolonged implantable electrocardiographic monitoring indicates a high rate  
2760 of misdiagnosis of epilepsy--REVISE study. *Europace* 2012;**14**:1653-1660.
- 2761 191. Maggi R, Rafanelli M, Ceccofiglio A, Solari D, Brignole M, Ungar A. Additional diagnostic  
2762 value of implantable loop recorder in patients with initial diagnosis of real or apparent  
2763 transient loss of consciousness of uncertain origin. *Europace* 2014;**16**:1226-1230.
- 2764 192. Armstrong VL, Lawson J, Kamper AM, Newton J, Kenny RA. The use of an implantable  
2765 loop recorder in the investigation of unexplained syncope in older people. *Age Ageing*  
2766 2003;**32**:185-188.
- 2767 193. Ryan DJ, Nick S, Colette SM, Roseanne K. Carotid sinus syndrome, should we pace? A  
2768 multicentre, randomised control trial (Safespace 2). *Heart* 2010;**96**:347-351.
- 2769 194. Bhangu J, McMahan CG, Hall P, Bennett K, Rice C, Crean P, Sutton R, Kenny RA. Long-  
2770 term cardiac monitoring in older adults with unexplained falls and syncope. *Heart*  
2771 2016;**102**:681-686.
- 2772 195. Krahn AD, Klein GJ, Norris C, Yee R. The etiology of syncope in patients with negative tilt  
2773 table and electrophysiological testing. *Circulation* 1995;**92**:1819-1824.
- 2774 196. Krahn AD, Klein GJ, Yee R, Takle-Newhouse T, Norris C. Use of an extended monitoring  
2775 strategy in patients with problematic syncope. Reveal Investigators. *Circulation*  
2776 1999;**99**:406-410.
- 2777 197. Krahn AD, Klein GJ, Yee R, Skanes AC. Detection of asymptomatic arrhythmias in  
2778 unexplained syncope. *Am Heart J* 2004;**148**:326-332.
- 2779 198. Ermis C, Zhu AX, Pham S, Li JM, Guerrero M, Vrudney A, Hiltner L, Lu F, Sakaguchi S,  
2780 Lurie KG, Benditt DG. Comparison of automatic and patient-activated arrhythmia  
2781 recordings by implantable loop recorders in the evaluation of syncope. *Am J Cardiol*  
2782 2003;**92**:815-819.
- 2783 199. Moya A, Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Wieling W, Andresen D,  
2784 Benditt DG, Garcia-Sacristan JF, Beiras X, Grovale N, Vardas P, International Study on  
2785 Syncope of Uncertain Etiology 2 (ISSUE 2) Group. Reproducibility of electrocardiographic  
2786 findings in patients with suspected reflex neurally-mediated syncope. *Am J Cardiol*  
2787 2008;**102**:1518-1523.
- 2788 200. Sud S, Klein GJ, Skanes AC, Gula LJ, Yee R, Krahn AD. Implications of mechanism of  
2789 bradycardia on response to pacing in patients with unexplained syncope. *Europace*  
2790 2007;**9**:312-318.
- 2791 201. Olmos C, Franco E, Suarez-Barrientos A, Fortuny E, Martin-Garcia A, Viliani D, Macaya C,  
2792 Perez de Isla L. Wearable wireless remote monitoring system: an alternative for prolonged  
2793 electrocardiographic monitoring. *Int J Cardiol* 2014;**172**:e43-44.
- 2794 202. Moya A, Brignole M, Menozzi C, Garcia-Civera R, Tognarini S, Mont L, Botto G, Giada F,  
2795 Cornacchia D, International Study on Syncope of Uncertain Etiology (ISSUE) Investigators.  
2796 Mechanism of syncope in patients with isolated syncope and in patients with tilt-positive  
2797 syncope. *Circulation* 2001;**104**:1261-1267.
- 2798 203. Furukawa T, Maggi R, Bertolone C, Fontana D, Brignole M. Additional diagnostic value of  
2799 very prolonged observation by implantable loop recorder in patients with unexplained  
2800 syncope. *J Cardiovasc Electrophysiol* 2012;**23**:67-71.

- 2801 204. LaFrance WC, Jr., Baker GA, Duncan R, Goldstein LH, Reuber M. Minimum requirements  
 2802 for the diagnosis of psychogenic nonepileptic seizures: a staged approach: a report from  
 2803 the International League Against Epilepsy Nonepileptic Seizures Task Force. *Epilepsia*  
 2804 2013;**54**:2005-2018.
- 2805 205. Saal DP, Thijs RD, Bootsma M, Brignole M, Benditt DG, van Dijk JG. Temporal relationship  
 2806 of asystole to onset of transient loss of consciousness in tilt-induced reflex syncope. *JACC*  
 2807 *Clinical Electrophysiol (in press)* 2017.
- 2808 206. Whittaker RG. Video telemetry: current concepts and recent advances. *Pract Neurol*  
 2809 2015;**15**:445-450.
- 2810 207. Goodwin E, Kandler RH, Alix JJ. The value of home video with ambulatory EEG: a  
 2811 prospective service review. *Seizure* 2014;**23**:480-482.
- 2812 208. Stephenson J, Breningstall G, Steer C, Kirkpatrick M, Horrocks I, Nechay A, Zuberi S.  
 2813 Anoxic-epileptic seizures: home video recordings of epileptic seizures induced by  
 2814 syncopes. *Epileptic Disord* 2004;**6**:15-19.
- 2815 209. Linzer M, Yang EH, Estes NA, 3rd, Wang P, Vorperian VR, Kapoor WN. Diagnosing  
 2816 syncope. Part 2: Unexplained syncope. Clinical Efficacy Assessment Project of the  
 2817 American College of Physicians. *Ann Intern Med* 1997;**127**:76-86.
- 2818 210. Dhingra RC. Sinus node dysfunction. *Pacing Clin Electrophysiol* 1983;**6**:1062-1069.
- 2819 211. Gann D, Tolentino A, Samet P. Electrophysiologic evaluation of elderly patients with sinus  
 2820 bradycardia: a long-term follow-up study. *Ann Intern Med* 1979;**90**:24-29.
- 2821 212. Menozzi C, Brignole M, Alboni P, Boni L, Paparella N, Gaggioli G, Lolli G. The natural  
 2822 course of untreated sick sinus syndrome and identification of the variables predictive of  
 2823 unfavorable outcome. *Am J Cardiol* 1998;**82**:1205-1209.
- 2824 213. McAnulty JH, Rahimtoola SH, Murphy E, DeMots H, Ritzmann L, Kanarek PE, Kauffman S.  
 2825 Natural history of "high-risk" bundle-branch block: final report of a prospective study. *N Engl*  
 2826 *J Med* 1982;**307**:137-143.
- 2827 214. Gronda M, Magnani A, Occhetta E, Sauro G, D'Aulerio M, Carfora A, Rossi P.  
 2828 Electrophysiological study of atrio-ventricular block and ventricular conduction defects.  
 2829 Prognostic and therapeutical implications. *G Ital Cardiol* 1984;**14**:768-773.
- 2830 215. Bergfeldt L, Edvardsson N, Rosenqvist M, Vallin H, Edhag O. Atrioventricular block  
 2831 progression in patients with bifascicular block assessed by repeated electrocardiography  
 2832 and a bradycardia-detecting pacemaker. *Am J Cardiol* 1994;**74**:1129-1132.
- 2833 216. Kaul U, Dev V, Narula J, Malhotra AK, Talwar KK, Bhatia ML. Evaluation of patients with  
 2834 bundle branch block and "unexplained" syncope: a study based on comprehensive  
 2835 electrophysiologic testing and ajmaline stress. *Pacing Clin Electrophysiol* 1988;**11**:289-297.
- 2836 217. Kalscheur MM, Donato P, Wenzke KE, Aste M, Oddone D, Solano A, Maggi R, Croci F,  
 2837 Page RL, Brignole M, Hamdan MH. Long-Term Outcome of Patients with Bifascicular Block  
 2838 and Unexplained Syncope Following Cardiac Pacing. *Pacing Clin Electrophysiol*  
 2839 2016;**39**:1126-1131.
- 2840 218. Olshansky B, Hahn EA, Hartz VL, Prater SP, Mason JW. Clinical significance of syncope in  
 2841 the electrophysiologic study versus electrocardiographic monitoring (ESVEM) trial. The  
 2842 ESVEM Investigators. *Am Heart J* 1999;**137**:878-886.
- 2843 219. Link MS, Kim KM, Homoud MK, Estes NA, 3rd, Wang PJ. Long-term outcome of patients  
 2844 with syncope associated with coronary artery disease and a nondiagnostic  
 2845 electrophysiologic evaluation. *Am J Cardiol* 1999;**83**:1334-1337.
- 2846 220. Sroubek J, Probst V, Mazzanti A, Delise P, Hevia JC, Ohkubo K, Zorzi A, Champagne J,  
 2847 Kostopoulou A, Yin X, Napolitano C, Milan DJ, Wilde A, Sacher F, Borggrefe M, Ellinor PT,  
 2848 Theodorakis G, Nault I, Corrado D, Watanabe I, Antzelevitch C, Allocca G, Priori SG, Lubitz

- 2849 SA. Programmed Ventricular Stimulation for Risk Stratification in the Brugada Syndrome: A  
 2850 Pooled Analysis. *Circulation* 2016;**133**:622-630.
- 2851 221. Scheinman MM, Peters RW, Suave MJ, Desai J, Abbott JA, Cogan J, Wohl B, Williams K.  
 2852 Value of the H-Q interval in patients with bundle branch block and the role of prophylactic  
 2853 permanent pacing. *Am J Cardiol* 1982;**50**:1316-1322.
- 2854 222. Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ,  
 2855 Campbell WB, Haines DE, Kuck KH, Lerman BB, Miller DD, Shaeffer CW, Jr., Stevenson  
 2856 WG, Tomaselli GF, Antman EM, Smith SC, Jr., Alpert JS, Faxon DP, Fuster V, Gibbons RJ,  
 2857 Gregoratos G, Hiratzka LF, Hunt SA, Jacobs AK, Russell RO, Jr., Priori SG, Blanc JJ,  
 2858 Budaj A, Burgos EF, Cowie M, Deckers JW, Garcia MA, Klein WW, Lekakis J, Lindahl B,  
 2859 Mazzotta G, Morais JC, Oto A, Smiseth O, Trappe HJ, American College of Cardiology,  
 2860 American Heart Association Task Force on Practice Guidelines, European Society of  
 2861 Cardiology Committee for Practice Guidelines, Writing Committee to Develop Guidelines for  
 2862 the Management of Patients With Supraventricular Arrhythmias. ACC/AHA/ESC guidelines  
 2863 for the management of patients with supraventricular arrhythmias--executive summary: a  
 2864 report of the American College of Cardiology/American Heart Association Task Force on  
 2865 Practice Guidelines and the European Society of Cardiology Committee for Practice  
 2866 Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With  
 2867 Supraventricular Arrhythmias). *Circulation* 2003;**108**:1871-1909.
- 2868 223. Pfister R, Hagemester J, Esser S, Hellmich M, Erdmann E, Schneider CA. NT-pro-BNP for  
 2869 diagnostic and prognostic evaluation in patients hospitalized for syncope. *Int J Cardiol*  
 2870 2012;**155**:268-272.
- 2871 224. Costantino G, Solbiati M, Casazza G, Bonzi M, Vago T, Montano N, McDermott D, Quinn J,  
 2872 Furlan R. Usefulness of N-terminal pro-B-type natriuretic Peptide increase as a marker for  
 2873 cardiac arrhythmia in patients with syncope. *Am J Cardiol* 2014;**113**:98-102.
- 2874 225. Thiruganasambandamoorthy V, Ramaekers R, Rahman MO, Stiell IG, Sikora L, Kelly SL,  
 2875 Christ M, Claret PG, Reed MJ. Prognostic value of cardiac biomarkers in the risk  
 2876 stratification of syncope: a systematic review. *Intern Emerg Med* 2015;**10**:1003-1014.
- 2877 226. Guieu R, Deharo JC, Ruf J, Mottola G, Kipson N, Bruzzese L, Gerolami V, Franceschi F,  
 2878 Ungar A, Tomaino M, Iori M, Brignole M. Adenosine and Clinical Forms of Neurally-  
 2879 Mediated Syncope. *J Am Coll Cardiol* 2015;**66**:204-205.
- 2880 227. Flammang D, Church TR, De Roy L, Blanc JJ, Leroy J, Mairesse GH, Otmani A, Graux PJ,  
 2881 Frank R, Purnode P, ATP Multicenter Study. Treatment of unexplained syncope: a  
 2882 multicenter, randomized trial of cardiac pacing guided by adenosine 5'-triphosphate testing.  
 2883 *Circulation* 2012;**125**:31-36.
- 2884 228. Brignole M, Gaggioli G, Menozzi C, Gianfranchi L, Bartoletti A, Bottoni N, Lolli G, Oddone  
 2885 D, Del Rosso A, Pellinghelli G. Adenosine-induced atrioventricular block in patients with  
 2886 unexplained syncope: the diagnostic value of ATP testing. *Circulation* 1997;**96**:3921-3927.
- 2887 229. Donato P, Brignole M, Menozzi C, Bottoni N, Alboni P, Dinelli M, Del Rosso A, Croci F,  
 2888 Oddone D, Solano A, Puggioni E. Mechanism of syncope in patients with positive  
 2889 adenosine triphosphate tests. *J Am Coll Cardiol* 2003;**41**:93-98.
- 2890 230. Krishnan B, Patarroyo-Aponte M, Duprez D, Pritzker M, Missov E, Benditt DG. Orthostatic  
 2891 hypotension of unknown cause: Unanticipated association with elevated circulating N-  
 2892 terminal brain natriuretic peptide (NT-proBNP). *Heart Rhythm* 2015;**12**:1287-1294.
- 2893 231. Fedorowski A, Burri P, Struck J, Juul-Moller S, Melander O. Novel cardiovascular  
 2894 biomarkers in unexplained syncopal attacks: the SYSTEMA cohort. *J Intern Med*  
 2895 2013;**273**:359-367.

- 2896 232. Li H, Kem DC, Reim S, Khan M, Vanderlinde-Wood M, Zillner C, Collier D, Liles C, Hill MA,  
2897 Cunningham MW, Aston CE, Yu X. Agonistic autoantibodies as vasodilators in orthostatic  
2898 hypotension: a new mechanism. *Hypertension* 2012;**59**:402-408.
- 2899 233. Li H, Yu X, Liles C, Khan M, Vanderlinde-Wood M, Galloway A, Zillner C, Benbrook A,  
2900 Reim S, Collier D, Hill MA, Raj SR, Okamoto LE, Cunningham MW, Aston CE, Kem DC.  
2901 Autoimmune basis for postural tachycardia syndrome. *J Am Heart Assoc* 2014;**3**:e000755.
- 2902 234. Fedorowski A, Li H, Yu X, Koelsch KA, Harris VM, Liles C, Murphy TA, Quadri SMS,  
2903 Scofield RH, Sutton R, Melander O, Kem DC. Antiadrenergic autoimmunity in postural  
2904 tachycardia syndrome. *Europace* 2017;**19**:1211-1219.
- 2905 235. Recchia D, Barzilai B. Echocardiography in the evaluation of patients with syncope. *J Gen  
2906 Intern Med* 1995;**10**:649-655.
- 2907 236. Sarasin FP, Junod AF, Carballo D, Slama S, Unger PF, Louis-Simonet M. Role of  
2908 echocardiography in the evaluation of syncope: a prospective study. *Heart* 2002;**88**:363-  
2909 367.
- 2910 237. Hoegholm A, Clementsen P, Mortensen SA. Syncope due to right atrial thromboembolism:  
2911 diagnostic importance of two-dimensional echocardiography. *Acta Cardiol* 1987;**42**:469-  
2912 473.
- 2913 238. Omran H, Fehske W, Rabahieh R, Hagendorff A, Pizzulli L, Zirbes M, Luderitz B. Valvular  
2914 aortic stenosis: risk of syncope. *J Heart Valve Dis* 1996;**5**:31-34.
- 2915 239. Bogaert AM, De Scheerder I, Colardyn F. Successful treatment of aortic rupture presenting  
2916 as a syncope: the role of echocardiography in diagnosis. *Int J Cardiol* 1987;**16**:212-214.
- 2917 240. Acikel M, Yekeler I, Ates A, Erkut B. A giant left atrial myxoma: an unusual cause of  
2918 syncope and cerebral emboli. *Int J Cardiol* 2004;**94**:325-326.
- 2919 241. Nogueira DC, Bontempo D, Menardi AC, Vicente WV, Ribeiro PJ, Evora PR. Left atrial  
2920 myxoma as the cause of syncope in an adolescent. *Arq Bras Cardiol* 2003;**81**:206-209,  
2921 202-205.
- 2922 242. Sinha AK, Singh BP. LA myxoma presenting as recurrent syncope. *Indian Heart J*  
2923 2013;**65**:643.
- 2924 243. Rahman MS, Michael H. A rare presentation of chest pain and syncope: massive right atrial  
2925 myxoma. *Postgrad Med J* 2012;**88**:671-672.
- 2926 244. Han H, Li Y, Guo S, Yu X. Right atrial myxoma-induced syncope. *Postgrad Med J*  
2927 2011;**87**:438-439.
- 2928 245. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA,  
2929 Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri  
2930 S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC  
2931 Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force  
2932 for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European  
2933 Society of Cardiology (ESC). *Eur Heart J* 2014;**35**:2733-2779.
- 2934 246. Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, Kuvin JT, Nistri S, Cecchi F,  
2935 Udelson JE, Maron BJ. Hypertrophic cardiomyopathy is predominantly a disease of left  
2936 ventricular outflow tract obstruction. *Circulation* 2006;**114**:2232-2239.
- 2937 247. Shah JS, Esteban MT, Thaman R, Sharma R, Mist B, Pantazis A, Ward D, Kohli SK, Page  
2938 SP, Demetrescu C, Sevdalis E, Keren A, Pellerin D, McKenna WJ, Elliott PM. Prevalence  
2939 of exercise-induced left ventricular outflow tract obstruction in symptomatic patients with  
2940 non-obstructive hypertrophic cardiomyopathy. *Heart* 2008;**94**:1288-1294.
- 2941 248. Dimitrow PP, Bober M, Michalowska J, Sorysz D. Left ventricular outflow tract gradient  
2942 provoked by upright position or exercise in treated patients with hypertrophic  
2943 cardiomyopathy without obstruction at rest. *Echocardiography* 2009;**26**:513-520.

- 2944 249. Marwick TH, Nakatani S, Haluska B, Thomas JD, Lever HM. Provocation of latent left  
2945 ventricular outflow tract gradients with amyl nitrite and exercise in hypertrophic  
2946 cardiomyopathy. *Am J Cardiol* 1995;**75**:805-809.
- 2947 250. Sneddon JF, Scalia G, Ward DE, McKenna WJ, Camm AJ, Frenneaux MP. Exercise  
2948 induced vasodepressor syncope. *Br Heart J* 1994;**71**:554-557.
- 2949 251. Sakaguchi S, Shultz JJ, Remole SC, Adler SW, Lurie KG, Benditt DG. Syncope associated  
2950 with exercise, a manifestation of neurally mediated syncope. *Am J Cardiol* 1995;**75**:476-  
2951 481.
- 2952 252. Colivicchi F, Ammirati F, Biffi A, Verdile L, Pelliccia A, Santini M. Exercise-related syncope  
2953 in young competitive athletes without evidence of structural heart disease. Clinical  
2954 presentation and long-term outcome. *Eur Heart J* 2002;**23**:1125-1130.
- 2955 253. Woelfel AK, Simpson RJ, Jr., Gettes LS, Foster JR. Exercise-induced distal atrioventricular  
2956 block. *J Am Coll Cardiol* 1983;**2**:578-581.
- 2957 254. Byrne JM, Marais HJ, Cheek GA. Exercise-induced complete heart block in a patient with  
2958 chronic bifascicular block. *J Electrocardiol* 1994;**27**:339-342.
- 2959 255. Aste M, Oddone D, Donateo P, Solano A, Maggi R, Croci F, Solari D, Brignole M. Syncope  
2960 in patients paced for atrioventricular block. *Europace* 2016;**18**:1735-1739.
- 2961 256. Sumiyoshi M, Nakata Y, Yasuda M, Tokano T, Ogura S, Nakazato Y, Yamaguchi H.  
2962 Clinical and electrophysiologic features of exercise-induced atrioventricular block. *Am Heart*  
2963 *J* 1996;**132**:1277-1281.
- 2964 257. Wissocq L, Ennezat PV, Mouquet F. Exercise-induced high-degree atrioventricular block.  
2965 *Arch Cardiovasc Dis* 2009;**102**:733-735.
- 2966 258. Anderson LL, Dai D, Miller AL, Roe MT, Messenger JC, Wang TY. Percutaneous coronary  
2967 intervention for older adults who present with syncope and coronary artery disease?  
2968 Insights from the National Cardiovascular Data Registry. *Am Heart J* 2016;**176**:1-9.
- 2969 259. El-Sayed H, Hainsworth R. Salt supplement increases plasma volume and orthostatic  
2970 tolerance in patients with unexplained syncope. *Heart* 1996;**75**:134-140.
- 2971 260. Solari D, Tesi F, Unterhuber M, Gaggioli G, Ungar A, Tomaino M, Brignole M. Stop  
2972 vasodepressor drugs in reflex syncope: a randomised controlled trial. *Heart* 2017;**103**:449-  
2973 455.
- 2974 261. SPRINT Research Group, Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM,  
2975 Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff  
2976 DC, Jr., Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT. A Randomized Trial  
2977 of Intensive versus Standard Blood-Pressure Control. *N Engl J Med* 2015;**373**:2103-2116.
- 2978 262. Brignole M, Menozzi C, Gaggioli G, Musso G, Foglia-Manzillo G, Mascioli G, Fradella G,  
2979 Bottoni N, Mureddu R. Effects of long-term vasodilator therapy in patients with carotid sinus  
2980 hypersensitivity. *Am Heart J* 1998;**136**:264-268.
- 2981 263. Kim KH, Cho JG, Lee KO, Seo TJ, Shon CY, Lim SY, Yun KH, Sohn IS, Hong YJ, Park  
2982 HW, Kim JH, Kim W, Ahn YK, Jeong MH, Park JC, Kang JC. Usefulness of physical  
2983 maneuvers for prevention of vasovagal syncope. *Circ J* 2005;**69**:1084-1088.
- 2984 264. Tomaino M, Romeo C, Vitale E, Kus T, Moya A, van Dijk N, Giuli S, D'Ippolito G, Gentili A,  
2985 Sutton R, International Study on Syncope of Uncertain Etiology 3 (ISSUE 3) Investigators.  
2986 Physical counter-pressure manoeuvres in preventing syncopal recurrence in patients older  
2987 than 40 years with recurrent neurally mediated syncope: a controlled study from the Third  
2988 International Study on Syncope of Uncertain Etiology (ISSUE-3)dagger. *Europace*  
2989 2014;**16**:1515-1520.
- 2990 265. Reybrouck T, Heidbuchel H, Van De Werf F, Ector H. Long-term follow-up results of tilt  
2991 training therapy in patients with recurrent neurocardiogenic syncope. *Pacing Clin*  
2992 *Electrophysiol* 2002;**25**:1441-1446.

- 2993 266. Zeng H, Ge K, Zhang W, Wang G, Guo L. The effect of orthostatic training in the prevention  
2994 of vasovagal syncope and its influencing factors. *Int Heart J* 2008;**49**:707-712.
- 2995 267. Jang WJ, Yim HR, Lee SH, Park SJ, Kim JS, On YK. Prognosis after tilt training in patients  
2996 with recurrent vasovagal syncope. *Int J Cardiol* 2013;**168**:4264-4265.
- 2997 268. Foglia-Manzillo G, Giada F, Gaggioli G, Bartoletti A, Lolli G, Dinelli M, Del Rosso A,  
2998 Santarone M, Raviele A, Brignole M. Efficacy of tilt training in the treatment of neurally  
2999 mediated syncope. A randomized study. *Europace* 2004;**6**:199-204.
- 3000 269. Kinay O, Yazici M, Nazli C, Acar G, Gedikli O, Altinbas A, Kahraman H, Dogan A, Ozaydin  
3001 M, Tuzun N, Ergene O. Tilt training for recurrent neurocardiogenic syncope: effectiveness,  
3002 patient compliance, and scheduling the frequency of training sessions. *Jpn Heart J*  
3003 2004;**45**:833-843.
- 3004 270. On YK, Park J, Huh J, Kim JS. Is home orthostatic self-training effective in preventing  
3005 neurally mediated syncope? *Pacing Clin Electrophysiol* 2007;**30**:638-643.
- 3006 271. Duygu H, Zoghi M, Turk U, Akyuz S, Ozerkan F, Akilli A, Erturk U, Onder R, Akin M. The  
3007 role of tilt training in preventing recurrent syncope in patients with vasovagal syncope: a  
3008 prospective and randomized study. *Pacing Clin Electrophysiol* 2008;**31**:592-596.
- 3009 272. Tan MP, Newton JL, Chadwick TJ, Gray JC, Nath S, Parry SW. Home orthostatic training in  
3010 vasovagal syncope modifies autonomic tone: results of a randomized, placebo-controlled  
3011 pilot study. *Europace* 2010;**12**:240-246.
- 3012 273. Verheyden B, Liu J, van Dijk N, Westerhof BE, Reybrouck T, Aubert AE, Wieling W. Steep  
3013 fall in cardiac output is main determinant of hypotension during drug-free and  
3014 nitroglycerine-induced orthostatic vasovagal syncope. *Heart Rhythm* 2008;**5**:1695-1701.
- 3015 274. Burklow TR, Moak JP, Bailey JJ, Makhlof FT. Neurally mediated cardiac syncope:  
3016 autonomic modulation after normal saline infusion. *J Am Coll Cardiol* 1999;**33**:2059-2066.
- 3017 275. Sheldon R, Raj SR, Rose MS, Morillo CA, Krahn AD, Medina E, Talajic M, Kus T, Seifer  
3018 CM, Lelonek M, Klingenheben T, Parkash R, Ritchie D, McRae M, POST 2 Investigators.  
3019 Fludrocortisone for the Prevention of Vasovagal Syncope: A Randomized, Placebo-  
3020 Controlled Trial. *J Am Coll Cardiol* 2016;**68**:1-9.
- 3021 276. Salim MA, Di Sessa TG. Effectiveness of fludrocortisone and salt in preventing syncope  
3022 recurrence in children: a double-blind, placebo-controlled, randomized trial. *J Am Coll*  
3023 *Cardiol* 2005;**45**:484-488.
- 3024 277. Raviele A, Brignole M, Sutton R, Alboni P, Giani P, Menozzi C, Moya A. Effect of etilefrine  
3025 in preventing syncopal recurrence in patients with vasovagal syncope: a double-blind,  
3026 randomized, placebo-controlled trial. The Vasovagal Syncope International Study.  
3027 *Circulation* 1999;**99**:1452-1457.
- 3028 278. Izcovich A, Gonzalez Malla C, Manzotti M, Catalano HN, Guyatt G. Midodrine for  
3029 orthostatic hypotension and recurrent reflex syncope: A systematic review. *Neurology*  
3030 2014;**83**:1170-1177.
- 3031 279. Madrid AH, Ortega J, Rebollo JG, Manzano JG, Segovia JG, Sanchez A, Pena G, Moro C.  
3032 Lack of efficacy of atenolol for the prevention of neurally mediated syncope in a highly  
3033 symptomatic population: a prospective, double-blind, randomized and placebo-controlled  
3034 study. *J Am Coll Cardiol* 2001;**37**:554-559.
- 3035 280. Sheldon R, Connolly S, Rose S, Klingenheben T, Krahn A, Morillo C, Talajic M, Ku T,  
3036 Fouad-Tarazi F, Ritchie D, Koshman ML, POST Investigators. Prevention of Syncope Trial  
3037 (POST): a randomized, placebo-controlled study of metoprolol in the prevention of  
3038 vasovagal syncope. *Circulation* 2006;**113**:1164-1170.
- 3039 281. Di Girolamo E, Di Iorio C, Sabatini P, Leonzio L, Barbone C, Barsotti A. Effects of  
3040 paroxetine hydrochloride, a selective serotonin reuptake inhibitor, on refractory vasovagal



- 3041 syncope: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol*  
 3042 1999;**33**:1227-1230.
- 3043 282. Theodorakis GN, Markianos M, Zarvalis E, Livanis EG, Flevari P, Kremastinos DT.  
 3044 Provocation of neurocardiogenic syncope by clomipramine administration during the head-  
 3045 up tilt test in vasovagal syndrome. *J Am Coll Cardiol* 2000;**36**:174-178.
- 3046 283. Marquez MF, Urias-Medina K, Gomez-Flores J, Sobrino A, Sotomayor-Gonzalez A,  
 3047 Gonzalez-Hermosillo A, Cardenas M. [Comparison of metoprolol vs clonazepam as a first  
 3048 treatment choice among patients with neurocardiogenic syncope]. *Gac Med Mex*  
 3049 2008;**144**:503-507.
- 3050 284. Kanjwal K, Saeed B, Karabin B, Kanjwal Y, Grubb BP. Use of octreotide in the treatment of  
 3051 refractory orthostatic intolerance. *Am J Ther* 2012;**19**:7-10.
- 3052 285. Brignole M, Solari D, Iori M, Bottoni N, Guieu R, Deharo JC. Efficacy of theophylline in  
 3053 patients affected by low adenosine syncope. *Heart Rhythm* 2016;**13**:1151-1154.
- 3054 286. Brignole M, Guieu R, Tomaino M, Iori M, Ungar A, Bertolone C, Unterhuber M, Bottoni N,  
 3055 Tesi F, Claude Deharo J. Mechanism of syncope without prodromes with normal heart and  
 3056 normal electrocardiogram. *Heart Rhythm* 2017;**14**:234-239.
- 3057 287. Vaddadi G, Guo L, Esler M, Socratous F, Schlaich M, Chopra R, Eikelis N, Lambert G,  
 3058 Trauer T, Lambert E. Recurrent postural vasovagal syncope: sympathetic nervous system  
 3059 phenotypes. *Circ Arrhythm Electrophysiol* 2011;**4**:711-718.
- 3060 288. Schroeder C, Birkenfeld AL, Mayer AF, Tank J, Diedrich A, Luft FC, Jordan J.  
 3061 Norepinephrine transporter inhibition prevents tilt-induced pre-syncope. *J Am Coll Cardiol*  
 3062 2006;**48**:516-522.
- 3063 289. Sheldon RS, Ritchie D, McRae M, Raj S. Norepinephrine transport inhibition for treatment  
 3064 of vasovagal syncope. *J Cardiovasc Electrophysiol* 2013;**24**:799-803.
- 3065 290. Pachon JC, Pachon EI, Cunha Pachon MZ, Lobo TJ, Pachon JC, Santillana TG. Catheter  
 3066 ablation of severe neurally mediated reflex (neurocardiogenic or vasovagal) syncope:  
 3067 cardioneuroablation long-term results. *Europace* 2011;**13**:1231-1242.
- 3068 291. Aksu T, Guler TE, Bozyel S, Ozcan KS, Yalin K, Mutluer FO. Cardioneuroablation in the  
 3069 treatment of neurally mediated reflex syncope: a review of the current literature. *Turk*  
 3070 *Kardiyol Dern Ars* 2017;**45**:33-41.
- 3071 292. Brignole M, Arabia F, Ammirati F, Tomaino M, Quartieri F, Rafanelli M, Del Rosso A, Rita  
 3072 Vecchi M, Russo V, Gaggioli G, Syncope Unit Project 2 (SUP 2) investigators.  
 3073 Standardized algorithm for cardiac pacing in older patients affected by severe unpredictable  
 3074 reflex syncope: 3-year insights from the Syncope Unit Project 2 (SUP 2) study. *Europace*  
 3075 2016;**18**:1427-1433.
- 3076 293. Brignole M, Menozzi C. The natural history of carotid sinus syncope and the effect of  
 3077 cardiac pacing. *Europace* 2011;**13**:462-464.
- 3078 294. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA,  
 3079 Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C,  
 3080 Mont L, Padeletti L, Sutton R, Vardas PE. 2013 ESC Guidelines on cardiac pacing and  
 3081 cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization  
 3082 therapy of the European Society of Cardiology (ESC). Developed in collaboration with the  
 3083 European Heart Rhythm Association (EHRA). *Eur Heart J* 2013;**34**:2281-2329.
- 3084 295. Gaggioli G, Brignole M, Menozzi C, Devoto G, Oddone D, Gianfranchi L, Gostoli E, Bottoni  
 3085 N, Lolli G. A positive response to head-up tilt testing predicts syncopal recurrence in carotid  
 3086 sinus syndrome patients with permanent pacemakers. *Am J Cardiol* 1995;**76**:720-722.
- 3087 296. Connolly SJ, Sheldon R, Roberts RS, Gent M. The North American Vasovagal Pacemaker  
 3088 Study (VPS). A randomized trial of permanent cardiac pacing for the prevention of  
 3089 vasovagal syncope. *J Am Coll Cardiol* 1999;**33**:16-20.

- 3090 297. Sutton R, Brignole M, Menozzi C, Raviele A, Alboni P, Giani P, Moya A. Dual-chamber  
3091 pacing in the treatment of neurally mediated tilt-positive cardioinhibitory syncope :  
3092 pacemaker versus no therapy: a multicenter randomized study. The Vasovagal Syncope  
3093 International Study (VASIS) Investigators. *Circulation* 2000;**102**:294-299.
- 3094 298. Ammirati F, Colivicchi F, Santini M, Syncope Diagnosis and Treatment Study Investigators.  
3095 Permanent cardiac pacing versus medical treatment for the prevention of recurrent  
3096 vasovagal syncope: a multicenter, randomized, controlled trial. *Circulation* 2001;**104**:52-57.
- 3097 299. Connolly SJ, Sheldon R, Thorpe KE, Roberts RS, Ellenbogen KA, Wilkoff BL, Morillo C,  
3098 Gent M, VPS II Investigators. Pacemaker therapy for prevention of syncope in patients with  
3099 recurrent severe vasovagal syncope: Second Vasovagal Pacemaker Study (VPS II): a  
3100 randomized trial. *JAMA* 2003;**289**:2224-2229.
- 3101 300. Raviele A, Giada F, Menozzi C, Speca G, Orazi S, Gasparini G, Sutton R, Brignole M,  
3102 Vasovagal Syncope and Pacing Trial Investigators. A randomized, double-blind, placebo-  
3103 controlled study of permanent cardiac pacing for the treatment of recurrent tilt-induced  
3104 vasovagal syncope. The Vasovagal Syncope and Pacing Trial (SYNPACE). *Eur Heart J*  
3105 2004;**25**:1741-1748.
- 3106 301. Sud S, Massel D, Klein GJ, Leong-Sit P, Yee R, Skanes AC, Gula LJ, Krahn AD. The  
3107 expectation effect and cardiac pacing for refractory vasovagal syncope. *Am J Med*  
3108 2007;**120**:54-62.
- 3109 302. Brignole M, Donateo P, Tomaino M, Massa R, Iori M, Beiras X, Moya A, Kus T, Deharo JC,  
3110 Giuli S, Gentili A, Sutton R, International Study on Syncope of Uncertain Etiology 3 (ISSUE-  
3111 3) Investigators. Benefit of pacemaker therapy in patients with presumed neurally mediated  
3112 syncope and documented asystole is greater when tilt test is negative: an analysis from the  
3113 third International Study on Syncope of Uncertain Etiology (ISSUE-3). *Circ Arrhythm*  
3114 *Electrophysiol* 2014;**7**:10-16.
- 3115 303. Baron-Esquivias G, Morillo CA, Moya-Mitjans A, Martinez-Alday J, Ruiz-Granell R,  
3116 Lacunza-Ruiz J, Garcia-Civera R, Gutierrez-Carretero E, Romero-Garrido R. Dual-  
3117 Chamber Pacing With Closed Loop Stimulation in Recurrent Reflex Vasovagal Syncope:  
3118 The SPAIN Study. *J Am Coll Cardiol* 2017;**70**:1720-1728.
- 3119 304. Madigan NP, Flaker GC, Curtis JJ, Reid J, Mueller KJ, Murphy TJ. Carotid sinus  
3120 hypersensitivity: beneficial effects of dual-chamber pacing. *Am J Cardiol* 1984;**53**:1034-  
3121 1040.
- 3122 305. Brignole M, Sartore B, Barra M, Menozzi C, Lolli G. Is DDD superior to VVI pacing in mixed  
3123 carotid sinus syndrome? An acute and medium-term study. *Pacing Clin Electrophysiol*  
3124 1988;**11**:1902-1910.
- 3125 306. Sutton R. Pacing in patients with carotid sinus and vasovagal syndromes. *Pacing Clin*  
3126 *Electrophysiol* 1989;**12**:1260-1263.
- 3127 307. Palmisano P, Dell'Era G, Russo V, Zaccaria M, Mangia R, Bortnik M, De Vecchi F,  
3128 Giubertoni A, Patti F, Magnani A, Nigro G, Rago A, Occhetta E, Accogli M. Effects of  
3129 closed-loop stimulation vs. DDD pacing on haemodynamic variations and occurrence of  
3130 syncope induced by head-up tilt test in older patients with refractory cardioinhibitory  
3131 vasovagal syncope: the Tilt test-Induced REsponse in Closed-loop Stimulation multicentre,  
3132 prospective, single blind, randomized study. *Europace* 2017.
- 3133 308. Russo V, Rago A, Papa AA, Golino P, Calabro R, Russo MG, Nigro G. The effect of dual-  
3134 chamber closed-loop stimulation on syncope recurrence in healthy patients with tilt-induced  
3135 vasovagal cardioinhibitory syncope: a prospective, randomised, single-blind, crossover  
3136 study. *Heart* 2013;**99**:1609-1613.

- 3137 309. Brignole M, Deharo JC, Menozzi C, Moya A, Sutton R, Tomaino M, Ungar A. The benefit of  
3138 pacemaker therapy in patients with neurally-mediated syncope and documented asystole: a  
3139 meta-analysis of implantable loop recorder studies. *Europace* 2017;In press.
- 3140 310. Claydon VE, Hainsworth R. Salt supplementation improves orthostatic cerebral and  
3141 peripheral vascular control in patients with syncope. *Hypertension* 2004;**43**:809-813.
- 3142 311. Schroeder C, Bush VE, Norcliffe LJ, Luft FC, Tank J, Jordan J, Hainsworth R. Water  
3143 drinking acutely improves orthostatic tolerance in healthy subjects. *Circulation*  
3144 2002;**106**:2806-2811.
- 3145 312. Zia A, Kamaruzzaman SB, Tan MP. Blood pressure lowering therapy in older people: Does  
3146 it really cause postural hypotension or falls? *Postgrad Med* 2015;**127**:186-193.
- 3147 313. Verwoert GC, Mattace-Raso FU, Hofman A, Heeringa J, Stricker BH, Breteler MM,  
3148 Witteman JC. Orthostatic hypotension and risk of cardiovascular disease in elderly people:  
3149 the Rotterdam study. *J Am Geriatr Soc* 2008;**56**:1816-1820.
- 3150 314. Kamaruzzaman S, Watt H, Carson C, Ebrahim S. The association between orthostatic  
3151 hypotension and medication use in the British Women's Heart and Health Study. *Age*  
3152 *Ageing* 2010;**39**:51-56.
- 3153 315. Valbusa F, Labat C, Salvi P, Vivian ME, Hanon O, Benetos A, PARTAGE investigators.  
3154 Orthostatic hypotension in very old individuals living in nursing homes: the PARTAGE  
3155 study. *J Hypertens* 2012;**30**:53-60.
- 3156 316. Romero-Ortuno R, O'Connell MD, Finucane C, Soraghan C, Fan CW, Kenny RA. Insights  
3157 into the clinical management of the syndrome of supine hypertension--orthostatic  
3158 hypotension (SH-OH): the Irish Longitudinal Study on Ageing (TILDA). *BMC Geriatr*  
3159 2013;**13**:73.
- 3160 317. Canney M, O'Connell MD, Murphy CM, O'Leary N, Little MA, O'Seaghdha CM, Kenny RA.  
3161 Single Agent Antihypertensive Therapy and Orthostatic Blood Pressure Behaviour in Older  
3162 Adults Using Beat-to-Beat Measurements: The Irish Longitudinal Study on Ageing. *PLoS*  
3163 *One* 2016;**11**:e0146156.
- 3164 318. Fogari R, Zoppi A, Mugellini A, Corradi L, Lazzari P, Preti P, Derosa G. Efficacy and safety  
3165 of two treatment combinations of hypertension in very elderly patients. *Arch Gerontol*  
3166 *Geriatr* 2009;**48**:401-405.
- 3167 319. van Lieshout JJ, ten Harkel AD, Wieling W. Physical manoeuvres for combating orthostatic  
3168 dizziness in autonomic failure. *Lancet* 1992;**339**:897-898.
- 3169 320. Smit AA, Wieling W, Fujimura J, Denq JC, Opfer-Gehrking TL, Akarriou M, Karemaker JM,  
3170 Low PA. Use of lower abdominal compression to combat orthostatic hypotension in patients  
3171 with autonomic dysfunction. *Clin Auton Res* 2004;**14**:167-175.
- 3172 321. Fanciulli A, Goebel G, Metzler B, Sprenger F, Poewe W, Wenning GK, Seppi K. Elastic  
3173 Abdominal Binders Attenuate Orthostatic Hypotension in Parkinson's Disease. *Mov Dis Clin*  
3174 *Practice* 2015;**3**:156-160.
- 3175 322. Ten Harkel AD, Van Lieshout JJ, Wieling W. Treatment of orthostatic hypotension with  
3176 sleeping in the head-up tilt position, alone and in combination with fludrocortisone. *J Intern*  
3177 *Med* 1992;**232**:139-145.
- 3178 323. Omboni S, Smit AA, van Lieshout JJ, Settels JJ, Langewouters GJ, Wieling W.  
3179 Mechanisms underlying the impairment in orthostatic tolerance after nocturnal recumbency  
3180 in patients with autonomic failure. *Clin Sci (Lond)* 2001;**101**:609-618.
- 3181 324. Jankovic J, Gilden JL, Hiner BC, Kaufmann H, Brown DC, Coghlan CH, Rubin M, Fouad-  
3182 Tarazi FM. Neurogenic orthostatic hypotension: a double-blind, placebo-controlled study  
3183 with midodrine. *Am J Med* 1993;**95**:38-48.

- 3184 325. Low PA, Gilden JL, Freeman R, Sheng KN, McElligott MA. Efficacy of midodrine vs placebo  
3185 in neurogenic orthostatic hypotension. A randomized, double-blind multicenter study.  
3186 Midodrine Study Group. *JAMA* 1997;**277**:1046-1051.
- 3187 326. Wright RA, Kaufmann HC, Perera R, Opfer-Gehrking TL, McElligott MA, Sheng KN, Low  
3188 PA. A double-blind, dose-response study of midodrine in neurogenic orthostatic  
3189 hypotension. *Neurology* 1998;**51**:120-124.
- 3190 327. van Lieshout JJ, ten Harkel AD, Wieling W. Fludrocortisone and sleeping in the head-up  
3191 position limit the postural decrease in cardiac output in autonomic failure. *Clin Auton Res*  
3192 2000;**10**:35-42.
- 3193 328. Finke J, Sagemuller I. [Fludrocortisone in the treatment of orthostatic hypotension:  
3194 ophthalmodynamography during standing(author's transl)]. *Dtsch Med Wochenschr*  
3195 1975;**100**:1790-1792.
- 3196 329. Kaufmann H, Freeman R, Biaggioni I, Low P, Pedder S, Hewitt LA, Mauney J, Feirtag M,  
3197 Mathias CJ, NOH301 Investigators. Droxidopa for neurogenic orthostatic hypotension: a  
3198 randomized, placebo-controlled, phase 3 trial. *Neurology* 2014;**83**:328-335.
- 3199 330. Hauser RA, Isaacson S, Lisk JP, Hewitt LA, Rowse G. Droxidopa for the short-term  
3200 treatment of symptomatic neurogenic orthostatic hypotension in Parkinson's disease  
3201 (nOH306B). *Mov Disord* 2015;**30**:646-654.
- 3202 331. Biaggioni I, Freeman R, Mathias CJ, Low P, Hewitt LA, Kaufmann H, Droxidopa 302  
3203 Investigators. Randomized withdrawal study of patients with symptomatic neurogenic  
3204 orthostatic hypotension responsive to droxidopa. *Hypertension* 2015;**65**:101-107.
- 3205 332. Hauser RA, Hewitt LA, Isaacson S. Droxidopa in patients with neurogenic orthostatic  
3206 hypotension associated with Parkinson's disease (NOH306A). *J Parkinsons Dis* 2014;**4**:57-  
3207 65.
- 3208 333. Elgebaly A, Abdelazeim B, Mattar O, Gadelkarim M, Salah R, Negida A. Meta-analysis of  
3209 the safety and efficacy of droxidopa for neurogenic orthostatic hypotension. *Clin Auton Res*  
3210 2016;**26**:171-180.
- 3211 334. Alboni P, Menozzi C, Brignole M, Paparella N, Gaggioli G, Lolli G, Cappato R. Effects of  
3212 permanent pacemaker and oral theophylline in sick sinus syndrome the THEOPACE study:  
3213 a randomized controlled trial. *Circulation* 1997;**96**:260-266.
- 3214 335. Breivik K, Ohm OJ, Segadal L. Sick sinus syndrome treated with permanent pacemaker in  
3215 109 patients. A follow-up study. *Acta Med Scand* 1979;**206**:153-159.
- 3216 336. Hartel G, Talvensaari T. Treatment of sinoatrial syndrome with permanent cardiac pacing in  
3217 90 patients. *Acta Med Scand* 1975;**198**:341-347.
- 3218 337. Rasmussen K. Chronic sinus node disease: natural course and indications for pacing. *Eur*  
3219 *Heart J* 1981;**2**:455-459.
- 3220 338. Sasaki Y, Shimotori M, Akahane K, Yonekura H, Hirano K, Endoh R, Koike S, Kawa S,  
3221 Furuta S, Homma T. Long-term follow-up of patients with sick sinus syndrome: a  
3222 comparison of clinical aspects among unpaced, ventricular inhibited paced, and  
3223 physiologically paced groups. *Pacing Clin Electrophysiol* 1988;**11**:1575-1583.
- 3224 339. Sgarbossa EB, Pinski SL, Jaeger FJ, Trohman RG, Maloney JD. Incidence and predictors  
3225 of syncope in paced patients with sick sinus syndrome. *Pacing Clin Electrophysiol*  
3226 1992;**15**:2055-2060.
- 3227 340. Ng Kam Chuen MJ, Kirkfeldt RE, Andersen HR, Nielsen JC. Syncope in paced patients  
3228 with sick sinus syndrome from the DANPACE trial: incidence, predictors and prognostic  
3229 implication. *Heart* 2014;**100**:842-847.
- 3230 341. Langenfeld H, Grimm W, Maisch B, Kochsiek K. Course of symptoms and spontaneous  
3231 ECG in pacemaker patients: a 5-year follow-up study. *Pacing Clin Electrophysiol*  
3232 1988;**11**:2198-2206.

- 3233 342. Donateo P, Brignole M, Alboni P, Menozzi C, Raviele A, Del Rosso A, Dinelli M, Solano A,  
3234 Bottoni N, Croci F. A standardized conventional evaluation of the mechanism of syncope in  
3235 patients with bundle branch block. *Europace* 2002;**4**:357-360.
- 3236 343. Azocar D, Ruiz-Granell R, Ferrero A, Martinez-Brotons A, Izquierdo M, Dominguez E,  
3237 Palau P, Morell S, Garcia-Civera R. Syncope and bundle branch block. Diagnostic yield of  
3238 a stepped use of electrophysiology study and implantable loop recorders. *Rev Esp Cardiol*  
3239 2011;**64**:213-219.
- 3240 344. Santini M, Castro A, Giada F, Ricci R, Inama G, Gaggioli G, Calo L, Orazi S, Viscusi M,  
3241 Chiodi L, Bartoletti A, Foglia-Manzillo G, Ammirati F, Loricchio ML, Pedrinazzi C, Turreni F,  
3242 Gasparini G, Accardi F, Raciti G, Raviele A. Prevention of syncope through permanent  
3243 cardiac pacing in patients with bifascicular block and syncope of unexplained origin: the  
3244 PRESS study. *Circ Arrhythm Electrophysiol* 2013;**6**:101-107.
- 3245 345. Englund A, Bergfeldt L, Rehnqvist N, Astrom H, Rosenqvist M. Diagnostic value of  
3246 programmed ventricular stimulation in patients with bifascicular block: a prospective study  
3247 of patients with and without syncope. *J Am Coll Cardiol* 1995;**26**:1508-1515.
- 3248 346. Morady F, Higgins J, Peters RW, Schwartz AB, Shen EN, Bhandari A, Scheinman MM,  
3249 Sauve MJ. Electrophysiologic testing in bundle branch block and unexplained syncope. *Am*  
3250 *J Cardiol* 1984;**54**:587-591.
- 3251 347. Tabrizi F, Rosenqvist M, Bergfeldt L, Englund A. Long-term prognosis in patients with  
3252 bifascicular block--the predictive value of noninvasive and invasive assessment. *J Intern*  
3253 *Med* 2006;**260**:31-38.
- 3254 348. Ruwald MH, Okumura K, Kimura T, Aonuma K, Shoda M, Kutuyifa V, Ruwald AC, McNitt S,  
3255 Zareba W, Moss AJ. Syncope in high-risk cardiomyopathy patients with implantable  
3256 defibrillators: frequency, risk factors, mechanisms, and association with mortality: results  
3257 from the multicenter automatic defibrillator implantation trial-reduce inappropriate therapy  
3258 (MADIT-RIT) study. *Circulation* 2014;**129**:545-552.
- 3259 349. Sacher F, Probst V, Maury P, Babuty D, Mansourati J, Komatsu Y, Marquie C, Rosa A,  
3260 Diallo A, Cassagneau R, Loizeau C, Martins R, Field ME, Derval N, Miyazaki S, Denis A,  
3261 Nogami A, Ritter P, Gourraud JB, Ploux S, Rollin A, Zemmoura A, Lamaison D, Bordachar  
3262 P, Pierre B, Jais P, Pasquie JL, Hocini M, Legal F, Defaye P, Boveda S, Iesaka Y, Mabo P,  
3263 Haissaguerre M. Outcome after implantation of a cardioverter-defibrillator in patients with  
3264 Brugada syndrome: a multicenter study-part 2. *Circulation* 2013;**128**:1739-1747.
- 3265 350. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno  
3266 JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM, Hypertrophic Cardiomyopathy  
3267 Outcomes Investigators. A novel clinical risk prediction model for sudden cardiac death in  
3268 hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J* 2014;**35**:2010-2020.
- 3269 351. Corrado D, Calkins H, Link MS, Leoni L, Favale S, Bevilacqua M, Basso C, Ward D, Boriani  
3270 G, Ricci R, Piccini JP, Dalal D, Santini M, Buja G, Iliceto S, Estes NA, 3rd, Wichter T,  
3271 McKenna WJ, Thiene G, Marcus FI. Prophylactic implantable defibrillator in patients with  
3272 arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior ventricular  
3273 fibrillation or sustained ventricular tachycardia. *Circulation* 2010;**122**:1144-1152.
- 3274 352. Liu JF, Jons C, Moss AJ, McNitt S, Peterson DR, Qi M, Zareba W, Robinson JL,  
3275 Barsheshet A, Ackerman MJ, Benhorin J, Kaufman ES, Locati EH, Napolitano C, Priori SG,  
3276 Schwartz PJ, Towbin J, Vincent M, Zhang L, Goldenberg I, International Long QT  
3277 Syndrome Registry. Risk factors for recurrent syncope and subsequent fatal or near-fatal  
3278 events in children and adolescents with long QT syndrome. *J Am Coll Cardiol* 2011;**57**:941-  
3279 950.
- 3280 353. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, Babuty D, Sacher F,  
3281 Giustetto C, Schulze-Bahr E, Borggrefe M, Haissaguerre M, Mabo P, Le Marec H, Wolpert

- 3282 C, Wilde AA. Long-term prognosis of patients diagnosed with Brugada syndrome: Results  
3283 from the FINGER Brugada Syndrome Registry. *Circulation* 2010;**121**:635-643.
- 3284 354. Spirito P, Autore C, Rapezzi C, Bernabo P, Badagliacca R, Maron MS, Bongioanni S,  
3285 Coccolo F, Estes NA, Barilla CS, Biagini E, Quarta G, Conte MR, Bruzzi P, Maron BJ.  
3286 Syncope and risk of sudden death in hypertrophic cardiomyopathy. *Circulation*  
3287 2009;**119**:1703-1710.
- 3288 355. Conte G, Sieira J, Ciconte G, de Asmundis C, Chierchia GB, Baltogiannis G, Di Giovanni  
3289 G, La Meir M, Wellens F, Czaplá J, Wauters K, Levinstein M, Saitoh Y, Irfan G, Julia J,  
3290 Pappaert G, Brugada P. Implantable cardioverter-defibrillator therapy in Brugada  
3291 syndrome: a 20-year single-center experience. *J Am Coll Cardiol* 2015;**65**:879-888.
- 3292 356. Olde Nordkamp LR, Vink AS, Wilde AA, de Lange FJ, de Jong JS, Wieling W, van Dijk N,  
3293 Tan HL. Syncope in Brugada syndrome: prevalence, clinical significance, and clues from  
3294 history taking to distinguish arrhythmic from nonarrhythmic causes. *Heart Rhythm*  
3295 2015;**12**:367-375.
- 3296 357. Olde Nordkamp LR, Wilde AA, Tijssen JG, Knops RE, van Dessel PF, de Groot JR. The  
3297 ICD for primary prevention in patients with inherited cardiac diseases: indications, use, and  
3298 outcome: a comparison with secondary prevention. *Circ Arrhythm Electrophysiol* 2013;**6**:91-  
3299 100.
- 3300 358. Spezzacatene A, Sinagra G, Merlo M, Barbati G, Graw SL, Brun F, Slavov D, Di Lenarda A,  
3301 Salcedo EE, Towbin JA, Saffitz JE, Marcus FI, Zareba W, Taylor MR, Mestroni L, Familial  
3302 Cardiomyopathy Registry. Arrhythmogenic Phenotype in Dilated Cardiomyopathy: Natural  
3303 History and Predictors of Life-Threatening Arrhythmias. *J Am Heart Assoc* 2015;**4**:e002149.
- 3304 359. Russo AM, Verdino R, Schorr C, Nicholas M, Dias D, Hsia H, Callans D, Marchlinski FE.  
3305 Occurrence of implantable defibrillator events in patients with syncope and nonischemic  
3306 dilated cardiomyopathy. *Am J Cardiol* 2001;**88**:1444-1446, A1449.
- 3307 360. Phang RS, Kang D, Tighiouart H, Estes NA, 3rd, Link MS. High risk of ventricular  
3308 arrhythmias in patients with nonischemic dilated cardiomyopathy presenting with syncope.  
3309 *Am J Cardiol* 2006;**97**:416-420.
- 3310 361. Christiaans I, van Engelen K, van Langen IM, Birnie E, Bonse GJ, Elliott PM, Wilde AA.  
3311 Risk stratification for sudden cardiac death in hypertrophic cardiomyopathy: systematic  
3312 review of clinical risk markers. *Europace* 2010;**12**:313-321.
- 3313 362. Corrado D, Wichter T, Link MS, Hauer R, Marchlinski F, Anastasakis A, Baucé B, Basso C,  
3314 Brunckhorst C, Tsatsopoulou A, Tandri H, Paul M, Schmied C, Pelliccia A, Duru F,  
3315 Protonotarios N, Estes NA, 3rd, McKenna WJ, Thiene G, Marcus FI, Calkins H. Treatment  
3316 of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force  
3317 consensus statement. *Eur Heart J* 2015;**36**:3227-3237.
- 3318 363. Bhonsale A, James CA, Tichnell C, Murray B, Gagarin D, Philips B, Dalal D, Tedford R,  
3319 Russell SD, Abraham T, Tandri H, Judge DP, Calkins H. Incidence and predictors of  
3320 implantable cardioverter-defibrillator therapy in patients with arrhythmogenic right  
3321 ventricular dysplasia/cardiomyopathy undergoing implantable cardioverter-defibrillator  
3322 implantation for primary prevention. *J Am Coll Cardiol* 2011;**58**:1485-1496.
- 3323 364. Jons C, Moss AJ, Goldenberg I, Liu J, McNitt S, Zareba W, Qi M, Robinson JL. Risk of fatal  
3324 arrhythmic events in long QT syndrome patients after syncope. *J Am Coll Cardiol*  
3325 2010;**55**:783-788.
- 3326 365. Giustetto C, Cerrato N, Ruffino E, Gribaudo E, Scrocco C, Barbonaglia L, Bianchi F, Bortnik  
3327 M, Rossetti G, Carvalho P, Riccardi R, Castagno D, Anselmino M, Bergamasco L, Gaita F.  
3328 Etiological diagnosis, prognostic significance and role of electrophysiological study in  
3329 patients with Brugada ECG and syncope. *Int J Cardiol* 2017;**241**:188-193.

- 3330 366. Kubala M, Aissou L, Traulle S, Gugenheim AL, Hermida JS. Use of implantable loop  
3331 recorders in patients with Brugada syndrome and suspected risk of ventricular arrhythmia.  
3332 *Europace* 2012;**14**:898-902.
- 3333 367. Delise P, Allocca G, Marras E, Giustetto C, Gaita F, Sciarra L, Calo L, Proclemer A,  
3334 Marziali M, Rebellato L, Berton G, Coro L, Sitta N. Risk stratification in individuals with the  
3335 Brugada type 1 ECG pattern without previous cardiac arrest: usefulness of a combined  
3336 clinical and electrophysiologic approach. *Eur Heart J* 2011;**32**:169-176.
- 3337 368. Maury P, Rollin A, Sacher F, Gourraud JB, Raczka F, Pasquie JL, Duparc A, Mondoly P,  
3338 Cardin C, Delay M, Derval N, Chatel S, Bongard V, Sadron M, Denis A, Davy JM, Hocini M,  
3339 Jais P, Jesel L, Haissaguerre M, Probst V. Prevalence and prognostic role of various  
3340 conduction disturbances in patients with the Brugada syndrome. *Am J Cardiol*  
3341 2013;**112**:1384-1389.
- 3342 369. Maury P, Sacher F, Gourraud JB, Pasquie JL, Raczka F, Bongard V, Duparc A, Mondoly P,  
3343 Sadron M, Chatel S, Derval N, Denis A, Cardin C, Davy JM, Hocini M, Jais P, Jesel L,  
3344 Carrie D, Galinier M, Haissaguerre M, Probst V, Rollin A. Increased Tpeak-Tend interval is  
3345 highly and independently related to arrhythmic events in Brugada syndrome. *Heart Rhythm*  
3346 2015;**12**:2469-2476.
- 3347 370. Morita H, Kusano KF, Miura D, Nagase S, Nakamura K, Morita ST, Ohe T, Zipes DP, Wu J.  
3348 Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of  
3349 Brugada syndrome. *Circulation* 2008;**118**:1697-1704.
- 3350 371. Priori SG, Gasparini M, Napolitano C, Della Bella P, Ottonelli AG, Sassone B, Giordano U,  
3351 Pappone C, Mascioli G, Rossetti G, De Nardis R, Colombo M. Risk stratification in Brugada  
3352 syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDICTive valuE)  
3353 registry. *J Am Coll Cardiol* 2012;**59**:37-45.
- 3354 372. McIntosh SJ, Lawson J, Kenny RA. Clinical characteristics of vasodepressor,  
3355 cardioinhibitory, and mixed carotid sinus syndrome in the elderly. *Am J Med* 1993;**95**:203-  
3356 208.
- 3357 373. Ungar A, Mussi C, Del Rosso A, Noro G, Abete P, Ghirelli L, Cellai T, Landi A, Salvioli G,  
3358 Rengo F, Marchionni N, Masotti G, Italian Group for the Study of Syncope in the Elderly.  
3359 Diagnosis and characteristics of syncope in older patients referred to geriatric departments.  
3360 *J Am Geriatr Soc* 2006;**54**:1531-1536.
- 3361 374. Galizia G, Abete P, Mussi C, Noro G, Morrione A, Langellotto A, Landi A, Cacciatore F,  
3362 Masotti G, Rengo F, Marchionni N, Ungar A. Role of early symptoms in assessment of  
3363 syncope in elderly people: results from the Italian group for the study of syncope in the  
3364 elderly. *J Am Geriatr Soc* 2009;**57**:18-23.
- 3365 375. Romme JJ, van Dijk N, Boer KR, Dekker LR, Stam J, Reitsma JB, Wieling W. Influence of  
3366 age and gender on the occurrence and presentation of reflex syncope. *Clin Auton Res*  
3367 2008;**18**:127-133.
- 3368 376. Bhangu JS, King-Kallimanis B, Cunningham C, Kenny RA. The relationship between  
3369 syncope, depression and anti-depressant use in older adults. *Age Ageing* 2014;**43**:502-509.
- 3370 377. Jansen S, Frewen J, Finucane C, de Rooij SE, van der Velde N, Kenny RA. AF is  
3371 associated with self-reported syncope and falls in a general population cohort. *Age Ageing*  
3372 2015;**44**:598-603.
- 3373 378. Jansen S, Kenny RA, de Rooij SE, van der Velde N. Self-reported cardiovascular  
3374 conditions are associated with falls and syncope in community-dwelling older adults. *Age*  
3375 *Ageing* 2015;**44**:525-529.
- 3376 379. Aronow WS. Heart disease and aging. *Med Clin North Am* 2006;**90**:849-862.

- 3377 380. Jansen S, Bhangu J, de Rooij S, Daams J, Kenny RA, van der Velde N. The Association of  
3378 Cardiovascular Disorders and Falls: A Systematic Review. *J Am Med Dir Assoc*  
3379 2016;**17**:193-199.
- 3380 381. van der Velde N, van den Meiracker AH, Pols HA, Stricker BH, van der Cammen TJ.  
3381 Withdrawal of fall-risk-increasing drugs in older persons: effect on tilt-table test outcomes. *J*  
3382 *Am Geriatr Soc* 2007;**55**:734-739.
- 3383 382. Ruwald MH, Hansen ML, Lamberts M, Hansen CM, Nume AK, Vinther M, Kober L, Torp-  
3384 Pedersen C, Hansen J, Gislason GH. Comparison of incidence, predictors, and the impact  
3385 of co-morbidity and polypharmacy on the risk of recurrent syncope in patients <85 versus  
3386 >=85 years of age. *Am J Cardiol* 2013;**112**:1610-1615.
- 3387 383. Mossello E, Pieraccioli M, Nesti N, Bulgaresi M, Lorenzi C, Caleri V, Tonon E, Cavallini MC,  
3388 Baroncini C, Di Bari M, Baldasseroni S, Cantini C, Biagini CA, Marchionni N, Ungar A.  
3389 Effects of low blood pressure in cognitively impaired elderly patients treated with  
3390 antihypertensive drugs. *JAMA Intern Med* 2015;**175**:578-585.
- 3391 384. McLachlan CY, Yi M, Ling A, Jardine DL. Adverse drug events are a major cause of acute  
3392 medical admission. *Intern Med J* 2014;**44**:633-638.
- 3393 385. Ungar A, Mussi C, Ceccofiglio A, Bellelli G, Nicosia F, Bo M, Riccio D, Martone AM,  
3394 Guadagno L, Noro G, Ghidoni G, Rafanelli M, Marchionni N, Abete P. Etiology of Syncope  
3395 and Unexplained Falls in Elderly Adults with Dementia: Syncope and Dementia (SYD)  
3396 Study. *J Am Geriatr Soc* 2016;**64**:1567-1573.
- 3397 386. Ryan DJ, Harbison JA, Meaney JF, Rice CP, King-Kallimanis B, Kenny RA. Syncope  
3398 causes transient focal neurological symptoms. *QJM* 2015;**108**:711-718.
- 3399 387. Parry SW, Kenny RA. Drop attacks in older adults: systematic assessment has a high  
3400 diagnostic yield. *J Am Geriatr Soc* 2005;**53**:74-78.
- 3401 388. Parry SW, Steen IN, Baptist M, Kenny RA. Amnesia for loss of consciousness in carotid  
3402 sinus syndrome: implications for presentation with falls. *J Am Coll Cardiol* 2005;**45**:1840-  
3403 1843.
- 3404 389. O'Dwyer C, Bennett K, Langan Y, Fan CW, Kenny RA. Amnesia for loss of consciousness  
3405 is common in vasovagal syncope. *Europace* 2011;**13**:1040-1045.
- 3406 390. Rafanelli M, Ruffolo E, Chisciotti VM, Brunetti MA, Ceccofiglio A, Tesi F, Morrione A,  
3407 Marchionni N, Ungar A. Clinical aspects and diagnostic relevance of neuroautonomic  
3408 evaluation in patients with unexplained falls. *Ageing Clin Exp Res* 2014;**26**:33-37.
- 3409 391. Shaw FE, Bond J, Richardson DA, Dawson P, Steen IN, McKeith IG, Kenny RA.  
3410 Multifactorial intervention after a fall in older people with cognitive impairment and dementia  
3411 presenting to the accident and emergency department: randomised controlled trial. *BMJ*  
3412 2003;**326**:73.
- 3413 392. Frewen J, Finucane C, Savva GM, Boyle G, Kenny RA. Orthostatic hypotension is  
3414 associated with lower cognitive performance in adults aged 50 plus with supine  
3415 hypertension. *J Gerontol A Biol Sci Med Sci* 2014;**69**:878-885.
- 3416 393. Robertson DA, Savva GM, Coen RF, Kenny RA. Cognitive function in the prefrailty and  
3417 frailty syndrome. *J Am Geriatr Soc* 2014;**62**:2118-2124.
- 3418 394. Frewen J, King-Kallimanis B, Boyle G, Kenny RA. Recent syncope and unexplained falls  
3419 are associated with poor cognitive performance. *Age Ageing* 2015;**44**:282-286.
- 3420 395. Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment--a review of the  
3421 evidence and causal mechanisms. *Ageing Res Rev* 2013;**12**:840-851.
- 3422 396. Kenny RA, Richardson DA, Steen N, Bexton RS, Shaw FE, Bond J. Carotid sinus  
3423 syndrome: a modifiable risk factor for nonaccidental falls in older adults (SAFE PACE). *J*  
3424 *Am Coll Cardiol* 2001;**38**:1491-1496.



- 3425 397. Ungar A, Galizia G, Morrione A, Mussi C, Noro G, Ghirelli L, Masotti G, Rengo F,  
3426 Marchionni N, Abete P. Two-year morbidity and mortality in elderly patients with syncope.  
3427 *Age Ageing* 2011;**40**:696-702.
- 3428 398. Finucane C, O'Connell MD, Fan CW, Savva GM, Soraghan CJ, Nolan H, Cronin H, Kenny  
3429 RA. Age-related normative changes in phasic orthostatic blood pressure in a large  
3430 population study: findings from The Irish Longitudinal Study on Ageing (TILDA). *Circulation*  
3431 2014;**130**:1780-1789.
- 3432 399. DiMario FJ, Jr. Prospective study of children with cyanotic and pallid breath-holding spells.  
3433 *Pediatrics* 2001;**107**:265-269.
- 3434 400. Vlahos AP, Kolettis TM. Family history of children and adolescents with neurocardiogenic  
3435 syncope. *Pediatr Cardiol* 2008;**29**:227.
- 3436 401. Vlahos AP, Tzoufi M, Katsouras CS, Barka T, Sionti I, Michalis LK, Siamopoulou A, Kolettis  
3437 TM. Provocation of neurocardiogenic syncope during head-up tilt testing in children:  
3438 comparison between isoproterenol and nitroglycerin. *Pediatrics* 2007;**119**:e419-425.
- 3439 402. McLeod KA, Wilson N, Hewitt J, Norrie J, Stephenson JB. Cardiac pacing for severe  
3440 childhood neurally mediated syncope with reflex anoxic seizures. *Heart* 1999;**82**:721-725.
- 3441 403. Raj V, Rowe AA, Fleisch SB, Paranjape SY, Arain AM, Nicolson SE. Psychogenic  
3442 pseudosyncope: diagnosis and management. *Auton Neurosci* 2014;**184**:66-72.
- 3443 404. LaFrance WC, Jr., Reuber M, Goldstein LH. Management of psychogenic nonepileptic  
3444 seizures. *Epilepsia* 2013;**54 Suppl 1**:53-67.
- 3445 405. Saal DP, Overdijk MJ, Thijs RD, van Vliet IM, van Dijk JG. Long-term follow-up of  
3446 psychogenic pseudosyncope. *Neurology* 2016;**87**:2214-2219.
- 3447 406. LaFrance WC, Jr., Baird GL, Barry JJ, Blum AS, Frank Webb A, Keitner GI, Machan JT,  
3448 Miller I, Szaflarski JP, NES Treatment Trial (NEST-T) Consortium. Multicenter pilot  
3449 treatment trial for psychogenic nonepileptic seizures: a randomized clinical trial. *JAMA*  
3450 *Psychiatry* 2014;**71**:997-1005.
- 3451 407. Benbadis SR, Chichkova R. Psychogenic pseudosyncope: an underestimated and provable  
3452 diagnosis. *Epilepsy Behav* 2006;**9**:106-110.
- 3453 408. Jecmenica-Lukic M, Poewe W, Tolosa E, Wenning GK. Premotor signs and symptoms of  
3454 multiple system atrophy. *Lancet Neurol* 2012;**11**:361-368.
- 3455 409. Siderowf A, Lang AE. Premotor Parkinson's disease: concepts and definitions. *Mov Disord*  
3456 2012;**27**:608-616.
- 3457 410. Hoefnagels WA, Padberg GW, Overweg J, van der Velde EA, Roos RA. Transient loss of  
3458 consciousness: the value of the history for distinguishing seizure from syncope. *J Neurol*  
3459 1991;**238**:39-43.
- 3460 411. Benbadis SR, Wolgamuth BR, Goren H, Brener S, Fouad-Tarazi F. Value of tongue biting  
3461 in the diagnosis of seizures. *Arch Intern Med* 1995;**155**:2346-2349.
- 3462 412. van der Lende M, Surges R, Sander JW, Thijs RD. Cardiac arrhythmias during or after  
3463 epileptic seizures. *J Neurol Neurosurg Psychiatry* 2016;**87**:69-74.
- 3464 413. Rugg-Gunn FJ, Simister RJ, Squirrell M, Holdright DR, Duncan JS. Cardiac arrhythmias in  
3465 focal epilepsy: a prospective long-term study. *Lancet* 2004;**364**:2212-2219.
- 3466 414. Benditt DG, van Dijk G, Thijs RD. Ictal asystole: life-threatening vagal storm or a benign  
3467 seizure self-termination mechanism? *Circ Arrhythm Electrophysiol* 2015;**8**:11-14.
- 3468 415. Rocamora R, Kurthen M, Lickfett L, Von Oertzen J, Elger CE. Cardiac asystole in epilepsy:  
3469 clinical and neurophysiologic features. *Epilepsia* 2003;**44**:179-185.
- 3470 416. Schuele SU, Bermeo AC, Alexopoulos AV, Locatelli ER, Burgess RC, Dinner DS, Foldvary-  
3471 Schaefer N. Video-electrographic and clinical features in patients with ictal asystole.  
3472 *Neurology* 2007;**69**:434-441.

- 3473 417. Ghearing GR, Munger TM, Jaffe AS, Benarroch EE, Britton JW. Clinical cues for detecting  
3474 ictal asystole. *Clin Auton Res* 2007;**17**:221-226.
- 3475 418. Bestawros M, Darbar D, Arain A, Abou-Khalil B, Plummer D, Dupont WD, Raj SR. Ictal  
3476 asystole and ictal syncope: insights into clinical management. *Circ Arrhythm Electrophysiol*  
3477 2015;**8**:159-164.
- 3478 419. Lamberts RJ, Thijs RD, Laffan A, Langan Y, Sander JW. Sudden unexpected death in  
3479 epilepsy: people with nocturnal seizures may be at highest risk. *Epilepsia* 2012;**53**:253-257.
- 3480 420. Lamberts RJ, Blom MT, Wassenaar M, Bardai A, Leijten FS, de Haan GJ, Sander JW, Thijs  
3481 RD, Tan HL. Sudden cardiac arrest in people with epilepsy in the community:  
3482 Circumstances and risk factors. *Neurology* 2015;**85**:212-218.
- 3483 421. Horrocks IA, Nechay A, Stephenson JB, Zuberi SM. Anoxic-epileptic seizures:  
3484 observational study of epileptic seizures induced by syncopes. *Arch Dis Child*  
3485 2005;**90**:1283-1287.
- 3486 422. Hennerici M, Klemm C, Rautenberg W. The subclavian steal phenomenon: a common  
3487 vascular disorder with rare neurologic deficits. *Neurology* 1988;**38**:669-673.
- 3488 423. Melgar MA, Weinand ME. Thyrocervical trunk-external carotid artery bypass for positional  
3489 cerebral ischemia due to common carotid artery occlusion. Report of three cases.  
3490 *Neurosurg Focus* 2003;**14**:e7.
- 3491 424. Dobkin BH. Orthostatic hypotension as a risk factor for symptomatic occlusive  
3492 cerebrovascular disease. *Neurology* 1989;**39**:30-34.
- 3493 425. Savitz SI, Caplan LR. Vertebrobasilar disease. *N Engl J Med* 2005;**352**:2618-2626.
- 3494 426. Thijs RD, Kruit MC, van Buchem MA, Ferrari MD, Launer LJ, van Dijk JG. Syncope in  
3495 migraine: the population-based CAMERA study. *Neurology* 2006;**66**:1034-1037.
- 3496 427. Overeem S, van Nues SJ, van der Zande WL, Donjacour CE, van Mierlo P, Lammers GJ.  
3497 The clinical features of cataplexy: a questionnaire study in narcolepsy patients with and  
3498 without hypocretin-1 deficiency. *Sleep Med* 2011;**12**:12-18.
- 3499 428. Stevens DL, Matthews WB. Cryptogenic drop attacks: an affliction of women. *Br Med J*  
3500 1973;**1**:439-442.
- 3501 429. Fanciulli A, Indelicato E, Wenning GK. Autonomic History Taking and Key Symptoms:  
3502 Where Is the Autonomic Disease? In: Struhal W, Lahrmann H, Fanciulli A, Wenning GK,  
3503 (eds). *Bedside Approach to Autonomic Disorders A Clinical Tutor*. Springer Verlag; 2017.
- 3504 430. Abubakr A, Wambacq I. The diagnostic value of EEGs in patients with syncope. *Epilepsy*  
3505 *Behav* 2005;**6**:433-434.
- 3506 431. Freeman R. Clinical practice. Neurogenic orthostatic hypotension. *N Engl J Med*  
3507 2008;**358**:615-624.
- 3508 432. Lucchinetti CF, Kimmel DW, Lennon VA. Paraneoplastic and oncologic profiles of patients  
3509 seropositive for type 1 antineuronal nuclear autoantibodies. *Neurology* 1998;**50**:652-657.
- 3510 433. Vernino S, Low PA, Fealey RD, Stewart JD, Farrugia G, Lennon VA. Autoantibodies to  
3511 ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. *N Engl J Med*  
3512 2000;**343**:847-855.
- 3513 434. McKeon A, Lennon VA, Lachance DH, Fealey RD, Pittock SJ. Ganglionic acetylcholine  
3514 receptor autoantibody: oncological, neurological, and serological accompaniments. *Arch*  
3515 *Neurol* 2009;**66**:735-741.
- 3516 435. Dantas FG, Cavalcanti AP, Rodrigues Maciel BD, Ribeiro CD, Napy Charara GC, Lopes  
3517 JM, Martins Filho PF, Junior LA. The role of EEG in patients with syncope. *J Clin*  
3518 *Neurophysiol* 2012;**29**:55-57.
- 3519 436. Kapoor WN, Karpf M, Maher Y, Miller RA, Levey GS. Syncope of unknown origin. The need  
3520 for a more cost-effective approach to its diagnosis evaluation. *JAMA* 1982;**247**:2687-2691.

- 3521 437. Farwell DJ, Sulke AN. Does the use of a syncope diagnostic protocol improve the  
3522 investigation and management of syncope? *Heart* 2004;**90**:52-58.
- 3523 438. Mendu ML, McAvay G, Lampert R, Stoehr J, Tinetti ME. Yield of diagnostic tests in  
3524 evaluating syncopal episodes in older patients. *Arch Intern Med* 2009;**169**:1299-1305.
- 3525 439. Schnipper JL, Ackerman RH, Krier JB, Honour M. Diagnostic yield and utility of  
3526 neurovascular ultrasonography in the evaluation of patients with syncope. *Mayo Clin Proc*  
3527 2005;**80**:480-488.
- 3528 440. Kadian-Dodov D, Papolos A, Olin JW. Diagnostic utility of carotid artery duplex  
3529 ultrasonography in the evaluation of syncope: a good test ordered for the wrong reason.  
3530 *Eur Heart J Cardiovasc Imaging* 2015;**16**:621-625.  
3531