

2018 ESC Guidelines for the diagnosis and management of syncope - Supplementary Data

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

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

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

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

Keywords

Guidelines • Syncope • Transient loss of consciousness • Vasovagal syncope • Reflex syncope • Orthostatic hypotension • Cardiac syncope • Sudden cardiac death • Electrophysiological study • Prolonged ECG monitoring • Tilt testing • Carotid sinus massage • Cardiac pacing • Implantable Cardioverter defibrillator • Syncope unit • Emergency department

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Supplementary Data Table I Frequency of the causes of syncope according to age

Age	Source	Reflex (%)	Orthostatic hypotension (%)	Cardiac (%)	Non-syncopal TLOC (%)	Unexplained (%)	Setting
<40 years	Olde Nordkamp ¹	51	2.5	1.1	18	27	ED and chest pain unit
40 – 60 years	Olde Nordkamp ¹	37	6	3	19	34	ED and chest pain unit
<65 years	Del Rosso ²	68.5	0.5	12	-	19	Cardiology department
>60/65 years	Del Rosso ²	52	3	34	-	11	Cardiology department
	Ungar ³	62	8	11	-	14	Geriatric department
	Olde Nordkamp ¹	25	8.5	13	12.5	41	ED and chest pain unit
>75 years	Ungar ³	36	30	16	-	9	Geriatric department. <i>Note. In a further 8% of patients, the diagnosis was multifactorial or drug-related</i>

ED = emergency department; TLOC = transient loss of consciousness.

Supplementary Data Table 2 Frequency of the causes of syncope in the general population, emergency departments, and specialized clinical settings

Setting	Source	Reflex (%)	Orthostatic hypotension (%)	Cardiac (%)	Non-syncopeal TLOC (%)	Unexplained (%)	Notes
General population	Framingham studies ⁴	21	9.4	9.5	9	37	Mean age at entry of 51 ± 14 years, adolescents excluded. Other causes of syncope (medication, etc.) were found in 14.3% of the population. Furthermore, 44% of population did not seek a medical visit
ED	Ammirati ⁵	35	6	21	20	17	
	Sarasin ⁶	38 ^a	24 ^a	11	8	19	
	Blanc ⁷	48	4	10	13	24	
	Disertori ⁸	45	6	11	17	19	
	Olde Nordkamp ¹	39	5	5	17	33	
	Range	35–48	4–24	5–21	8–20	17–33	
Syncope unit (dedicated facility)	Alboni ⁹	56	2	23	1	18	In the cardiology department
	Chen ¹⁰	56	6	37	3	20	In the cardiology department. Total percentage is greater than 100% because 18.4% of patients had multiple diagnoses
	Shen ¹¹	65	10	6	2	18	In the ED
	Brignole ¹²	65	10	13	6	5	Multicentre study of 19 syncope units with referral from ED and standardized diagnostic pathway (interactive decision-making software and central monitoring)
	Ammirati ¹³	73	1	6	2	18	Outpatient referral
	Range	56–73	1–10	6–37	1–6	5–20	

ED = emergency department; TLOC = transient loss of consciousness.

^aSome differences in diagnostic definitions.

Supplementary Data Table 3 Risk stratification at initial evaluation in prospective population studies

Study	Risk factors	Score	Endpoints	Results (validation cohort)
San Francisco ¹⁴	<ul style="list-style-type: none"> - Abnormal ECG - Congestive heart failure - Shortness of breath - Haematocrit <30% - Systolic blood pressure <90 mmHg 	No risk: 0 items Risk: ≥ 1 item	Serious events at 7 days	98% sensitive and 56% specific
Martin et al ¹⁵	<ul style="list-style-type: none"> - Abnormal ECG - History of ventricular arrhythmia - History of congestive heart failure - Age >45 years 	0 to 4 (1 point each item)	1-year severe arrhythmias or arrhythmic death	0% score 0 5% score 1 16% score 2 27% score 3 or 4
OESIL ¹⁶	<ul style="list-style-type: none"> - Abnormal ECG - History of cardiovascular diseases - Lack of prodromes - Age >65 years 	0 to 4 (1 point each item)	1-year total mortality	0% score 0 0.6% score 1 14% score 2 29% score 3 53% score 4
EGSYS ¹⁷	<ul style="list-style-type: none"> - Palpitations before syncope (+4) - Abnormal ECG and/or heart disease (+3) - Syncope during effort (+3) - Syncope while supine (+2) - Autonomic prodromes^a (-1) - Predisposing and/or precipitating factors^b (-1) 	Sum of + and - points	2-year total mortality <hr/> Cardiac syncope probability	2% score <3 21% score ≥ 3 <hr/> 2% score <3 13% score 3 33% score 4 77% score >4
ROSE ¹⁸	<ul style="list-style-type: none"> - BNP level ≥ 300 pg/mL - Bradycardia (HR ≤ 50 b.p.m.) - Faecal occult blood - Haemoglobin ≤ 90 g/L - Chest pain associated with syncope - ECG showing Q waves - Saturation $\leq 94\%$ on room air 	No risk: 0 items Risk: ≥ 1 item	1-month serious events or death (which occurred in 7.1%)	87% sensitivity and 65% specificity; 98% negative predictive value
Canadian ¹⁹	<ul style="list-style-type: none"> - Predisposition to vasovagal symptoms (-1) - History of heart disease (+1) - SBP <90 or >180 mmHg (+2) - Elevated troponin (+2) - QRS axis <-30° or >100° (+1) - QRS duration >130 ms (+1) - QTc interval >480 ms (+2) - Diagnosis of VVS in ED (-2) - Diagnosis of cardiac syncope in ED (+2) 	Sum of + and - points (from -3 to 11)	Serious events at 30 days	From 0.4% for a score of -3 to 84% for a score of 11

This table shows several different studies that have analysed the impact of different clinical data on the follow-up of patients presenting with syncope. Overall, an abnormal ECG, increased age, or data suggestive of heart disease, imply a worse prognosis at 1 - 2-year follow-up.

BNP = B-type natriuretic peptide; ECG = electrocardiogram; ED = emergency department; EGSYS = Evaluation of Guidelines in SYNcope Study; OESIL = Osservatorio Epidemiologico sulla Sincope nel Lazio; ROSE = Risk stratification Of Syncope in the Emergency department; QTc = corrected QT; SBP = systolic blood pressure; VVS = vasovagal syncope.

^aNausea/vomiting.

^bWarm, crowded place/prolonged orthostasis/fear, pain, or emotion.

Supplementary Data Table 4 Admission rate and composite estimate of short-term (7–30 day) outcomes of patients presenting to the emergency department with transient loss of consciousness

Author year, country	Patients with TLOC, n	Patients admitted, n (%)	7–30-day death, n (%)	7–30-day non-fatal severe outcome ^a , n (%)	7–30-day non-fatal severe outcome ^a identified in the ED, n (%)	7–30-day non-fatal severe outcome ^a identified after initial visit, n (%)
Brignole 2006, ²⁰ Italy	465	178 (38)	6 (1.3)	na	na	na
Costantino 2008, ²¹ Italy	676	218 (32)	5 (0.7)	36 (5.3)	na	na
Ungar 2016, ²² Italy	295	92 (31)	1 (0.3)	na	na	21 (7.1)
Reed 2010, ¹⁸ UK	1100	541 (49)	17 (1.5)	79 (7.2)	na	na
Quinn 2004, ²³ USA	684	376 (55)	5 (0.7)	79 (11.5)	na	na
Quinn 2006, ¹⁴ USA	760	448 (59)	3 (0.4)	108 (14.2)	54 (7.1)	54 (7.1)
Grossman 2007, ²⁴ USA	293	201 (69)	7 (2.4)	61 (21)	56 (19)	12 (4.1)
Birnbaum 2008, ²⁵ USA	713	613 (86)	4 (0.6)	57 (8.0)	32 (4.5)	25 (3.5)
Sun 2007, ²⁶ USA	477	277 (58)	na	56 (11.7)	40 (8.6)	16 (3.4)
Schladenhaufen 2008, ²⁷ USA	517	312 (60)	5 (1.0)	98 (19)	80 (15.5)	18 (3.4)
Daccarett 2011, ²⁸ USA	254	118 (46)	1 (0.4)	15 (5.9)	8 (3.1)	7 (2.8)
Thiruganasambanda-moorthy 2013, ²⁹ Canada	505	62 (12)	5 (1.0)	49 (9.7)	22 (4.4)	27 (5.3)
Thiruganasambanda-moorthy 2015, ³⁰ Canada	3662 ^b	474 (13)	31 (0.9)	345 (10.3)	225 (6.7)	120 (3.6)
Median (interquartile range), %		49 (32.59)	0.8 (0.6 1.1)	10.3 (7.6 13.0)	6.9 (4.5 10.3)	3.6 (3.4 5.3)

ED = emergency department; na = not available; TLOC = transient loss of consciousness.

^aNon-fatal severe outcomes were generally defined as a significant new diagnosis, a clinical deterioration, serious injury with recurrence, or a significant therapeutic intervention.

^bIn total, 3365 patients had 30-day follow-up.

Supplementary Data Table 5 Meta-analysis of randomized trials comparing diagnostic yields of an implantable loop recorder strategy versus a conventional strategy in patients with unexplained syncope

Study	ILR group, n/N (%)	Control group, n/N (%)	Relative probability	95% CI	P value
RAST 2001 ³¹	14/27 (52)	6/30 (20)	2.6	1.2–5.8	0.01
EaSyAS 2006 ³²	43/101 (43)	7/97 (7)	5.9	2.8–12	0.001
Da Costa 2013 ³³	15/41 (37)	4/37 (11)	3.4	1.2–9.3	0.01
FRESH 2014 ³⁴	18/39 (46)	2/39 (5)	9.0	2.2–36	0.001
EaSyAS II 2016 ³⁵	62/125 (50)	21/121 (17)	2.9	1.9–4.4	0.001
Total	152/333 (46)	40/324 (12)	3.6	2.45.3	0.001

Test for heterogeneity: $P = 0.26$.

CI = confidence interval; EaSyAS = Eastbourne Syncope Assessment Study; FRESH = French Study on implantable Holter recorders in syncope; ILR = implantable loop recorder; RAST = Randomized Assessment of Syncope Trial.

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Supplementary Data Table 6 ILR results in patients with unexplained syncope and bundle branch block

	Number of patients with ILR, n	ILR-documented attack, n	ILR- documented arrhythmias, n	ILR- documented AV block, n	No ILR documentation, n
Brignole 2001 ³⁶	52	24	22	12	28
Moya 2011 ³⁷	108	52	45	36	56
Da Costa 2013 ³³	41	15	15	11	26
Total	201	91 (45%)	82 (41%)	59 (29%)	110 (55%)

AV = atrioventricular; ILR = implantable loop recorder.

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Supplementary Data Table 7 ILR results in patients with suspected non-established epilepsy

	Patients with ILR, n	ILR-documented attack	ILR-documented arrhythmias	No ILR documentation
Simpson 2000 ³⁸	1	1 (100%)	0 (0%)	0 (0%)
Kanjwal 2009 ³⁹	3	3 (100%)	3 (100%)	0 (0%)
Zaidi 2000 ⁴⁰	10	2 (20%)	2 (20%)	9 (80%)
Ho 2006 ⁴¹	14	6 (43%)	0 (0%)	8 (57%)
Petkar 2012 ⁴²	103	69 (67%)	28 (27%)	34 (33%)
Maggi 2014 ⁴³	28	17 (61%)	8 (29%)	11 (39%)
Total	159	98 (62%)	41 (26%)	61 (38%)

ILR = implantable loop recorder; na = not available.

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Supplementary Data Table 8 ILR results in patients with unexplained falls

	Patients with ILR, n	ILR-documented attack, n (%)	ILR-documented diagnostic arrhythmias, n (%)	No ILR documentation, n (%)
Armstrong 2003 ⁴⁴	6	3 (50)	1 (15)	3 (50)
Ryan 2010 ⁴⁵	71	48 (68)	3 (4)	23 (32)
Maggi 2014 ⁴³	29	16 (55)	7 (24)	13 (45)
Bhangu 2016 ⁴⁶	70	56 (80)	14 (20)	14 (20)
Total	176	123 (70)	25 (14)	53 (36)

ILR = implantable loop recorder.

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Supplementary Data Table 9 Cardiac pacing for syncope: comparative results in different settings

Setting/condition	Diagnostic tool	Bradycardic mechanism of syncope	Recurrence of syncope with pacing	Reference(s)
Documented paroxysmal AVB	ECG (standard or prolonged monitoring)	Established	1% at 5 years 0% at 4 years ^a 0% at 3.5 years 7% at 5 years	Aste ⁴⁷ Brignole ⁴⁸ Sud ⁴⁹ Langenfeld ⁵⁰
Undocumented paroxysmal AVB in patients with BBB	Positive EPS	Likely	≈7% at 2 years	B4 ³⁷
	Clinical evaluation	Suspected	13.5% at 2 years 14% at 5 years	PRESS ⁵¹ Aste ⁴⁷
Sick sinus syndrome	Clinical evaluation	Suspected	15% at 5 years 22% at 5 years 28% at 5 years	Sgarbossa ⁵² DANPACE ⁵³ Langenfeld ⁵⁰
Asystolic pause, no structural heart disease, reflex syncope likely	ECG (standard or prolonged monitoring)	Established	12% at 2 years 24% at 3 years 25% at 2 years	ISSUE 2 ⁵⁴ SUP 2 ⁵⁵ ISSUE 3 ⁵⁶
Carotid sinus syndrome (cardioinhibitory form)	Carotid sinus massage	Likely	10% at 1 year 11% at 5 years 16% at 3 years 16% at 4 years 20% at 5 years	Claesson ⁵⁷ Lopes ⁵⁸ SUP 2 ⁵⁵ Brignole ⁵⁹ Gaggioli ⁶⁰
Tilt-induced syncope (asystolic form)	Tilt test	Likely	6% at 5 years 7% at 3 years 23% at 3 years 9% at 2 yrs	VASIS ⁶¹ SYDIT ⁶² SUP 2 ⁵⁵ SPAIN ⁷³
Tilt-induced syncope (non-asystolic form)	Tilt test	Possible	22% at 1 year 33% at 6 months 44% at 1 year	VPS I ⁶³ VPS II ⁶⁴ SYNPACE ⁶⁵
Unexplained syncope	ATP test	Suspected	23% at 3 years	ATP Study ⁶⁶

ATP = adenosine triphosphate; AVB = atrioventricular block; B4 = bradycardia detection in Bundle Branch Block; BBB = bundle branch block; DANPACE = Danish Multicenter Randomized Trial on single lead atrial pacing vs. dual-chamber pacing in sick sinus syndrome; ECG = electrocardiogram; EPS = electrophysiological study; ISSUE 2 = International Study on Syncope of Unknown Etiology; PRESS = Prevention of syncope through permanent cardiac pacing in patients with bifascicular block; SUP = Syncope Unit Project; SYDIT = Syncope Diagnosis and Treatment Study; SYNPACE = Vasovagal Syncope and Pacing Trial; VASIS = Vasovagal Syncope International Study; VPS = Vasovagal Pacemaker Study.

^aLow-adenosine idiopathic atrioventricular block.

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Supplementary Data Table 10 Recurrence of syncope in patients left untreated after diagnostic assessment (except for education and lifestyle modification)

Reference	Aetiology	Prevalence of syncopes per patient before diagnostic evaluation, median (IQR) or mean \pm SD	Patients with recurrence of syncope after diagnostic evaluation (%)	Additional comments
Sheldon et al ⁶⁷	VVS Tilt negative	Median 3 per year	41% at 2 years	No therapy
Sheldon et al ⁶⁷	VVS Tilt positive	Median 4 per year	37% at 2 years	No therapy
VPS I ⁶³	VVS Tilt positive	6 (3–40) during previous year	70% at 1 year	No therapy
PC-Trial ⁶⁸	VVS Tilt positive and negative	3 (2–5) during previous 2 years	51% at 14 months (-80% yearly burden)	Education, lifestyle modification
Aydin et al ⁶⁹	VVS Tilt positive and negative	4.2 \pm 0.4	27% at 2 years (-77% monthly burden)	Education, lifestyle modification
VASIS-Etilefrine ⁷⁰	VVS Tilt positive	4 (3–17) during previous 2 years	24% at 1 year	Placebo drug therapy
POST ⁷¹	VVS Tilt positive	3 (1–6) during previous year	35% at 1 year	Placebo drug therapy
Madrid et al ⁷²	VVS Tilt positive	Median 3 per year	46% at 1 year	Placebo drug therapy
VPS II ⁶⁴	VVS Tilt positive	4 (3–12) during previous year	40% at 6 months	Sham treatment (pacemaker off)
SYNPACE ⁶⁵	VVS Tilt positive	4 (3–6) during previous 6 months	44% at 1 year	Sham treatment (pacemaker off)
VASIS ⁶¹	Reflex – CI Tilt positive	3 (3–4.5) during previous 2 years	50% at 2 years	No therapy
SPAIN ⁷³	VVS – CI Tilt positive	>5 during life	46% at 2 years	Sham treatment (pacemaker off)
Solari et al ⁷⁴	Carotid sinus syndrome	0.5 (0–1) per year	0 (0–0) per year (-87% burden)	No therapy
SUP 2 ⁵⁵	Reflex	3 (2–4) during previous 2 years	33% at 2 years (-85% yearly burden)	ILR
ISSUE 2 ⁵⁴	Reflex	4 (3–5) during previous 2 years	49% at 2 years	ILR
ISSUE 3 ⁵⁶	Reflex	5 (3–6) during previous 2 years	57% at 2 years	Sham treatment (pacemaker off)
PICTURE ⁷⁵	Unexplained	Median 4 during previous 2 years	36% at 1 year	ILR
Donateo et al ⁷⁶	Unexplained ATP positive	3 (2–5) during previous year	50% at 18 months	ILR
ATP Study ⁶⁶	Unexplained ATP positive	na	69% at 2 years	Sham treatment (pacemaker off)

Continued

ISSUE ⁷⁷	Unexplained SHD	2 (1–4) during previous 2 years	19% at 15 months	ILR
ISSUE ³⁶	Cardiac – BBB	3 (2–4) during previous 2 years	48% at 15 months	ILR
B4 ³⁷	Cardiac – BBB	2 (1–3) during previous 6 months	33% at 19 months	ILR
PRESS ⁵¹	Cardiac – BBB	1 (1–2) during previous 6 months	14% at 2 years	Sham treatment (pacemaker off)
THEOPACE ⁷⁸	Sick sinus syndrome	3.2 ± 4.3	30% at 4 years	No therapy

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ATP = adenosine triphosphate; B4 = Bradycardia detection in Bundle Branch Block; BBB = bundle branch block; CI = cardioinhibitory; ILR = implantable loop recorder; IQR = interquartile range; ISSUE = International Study on Syncope of Unknown Etiology; na = not available; PC-Trial = Physical Counterpressure Manoeuvres Trial; PICTURE = Place of Reveal In the Care pathway and Treatment of patients with Unexplained Recurrent Syncope; POST = Prevention of Syncope Trial; PRESS = Prevention of syncope through permanent cardiac pacing in patients with bifascicular block; SD = standard deviation; SHD = structural heart disease; SUP = Syncope Unit Project; SYNPACE = Vasovagal Syncope and Pacing Trial; THEOPACE = the effects of oral theophylline and of a permanent pacemaker on the symptoms and complications of sick sinus syndrome; VASIS = Vasovagal Syncope International Study; VPS = Vasovagal Pacemaker Study; VVS = vasovagal syncope.

Comment on above table

It is a common finding that syncopal recurrences often decrease spontaneously after medical assessment, even in the absence of a specific therapy. In general, >50% of patients with recurrent syncopal episodes in the 1 or 2 years before evaluation do not have syncopal recurrences in the following 1 or 2 years and, in those with recurrences, the burden of syncope decreases by >70% compared with the period before. The decrease seems to be more evident when there is a lack of a clear anatomical substrate for syncope, such as in the case of reflex syncope and unexplained syncope. The reason for this decrease is not known. Several potential clinical, statistical, and psychological explanations have been suggested, and all probably play a role. The *education and reassurance effect* is probably the most likely reason for the decrease in syncope. As a consequence of the diagnostic evaluation, the patient understands the mechanism of syncope and is instructed on the recognition of the prodrome and triggers, thus learning how to prevent recurrences or to limit the consequences of loss of consciousness. Closely related to the education and reassurance effect is the *expectancy effect*.^{79–81} The *subject-expectancy effect* is a form of reactivity that occurs in medical treatments when a patient expects a given result, which unconsciously affects the outcome, or reports the expected result. In the *physician-expectancy effect*, the physician consciously or unconsciously influences patient behaviour. The expectancy effect can only be presumed in syncope. However, the expectancy effect of sham or placebo treatments seem modest, if any, as in controlled trials reported in *Supplementary Data Table 10* the recurrence rate with sham or placebo treatment was not different from that with no treatment.⁸² Finally, two pure statistical explanations have been advocated. One is the '*Regression-to-the-mean effect*'.⁸³ It is known that syncopal recurrence is not constant, but fluctuates over time, peaking at the time of evaluation (pre-test mean). If a variable is extreme on its first measurement, it will tend to be closer to the average on its second measurement (post-test mean). Thus, even in the absence of any therapy, the incidence of syncope in those under surveillance will regress towards the mean.^{84,85} The second is the '*Poisson distribution*'. In patients with frequently recurrent vasovagal syncope, the days were distributed

randomly in time with easily identifiable and idiosyncratic rate constants that tightly fit Poisson distributions.⁸⁶

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