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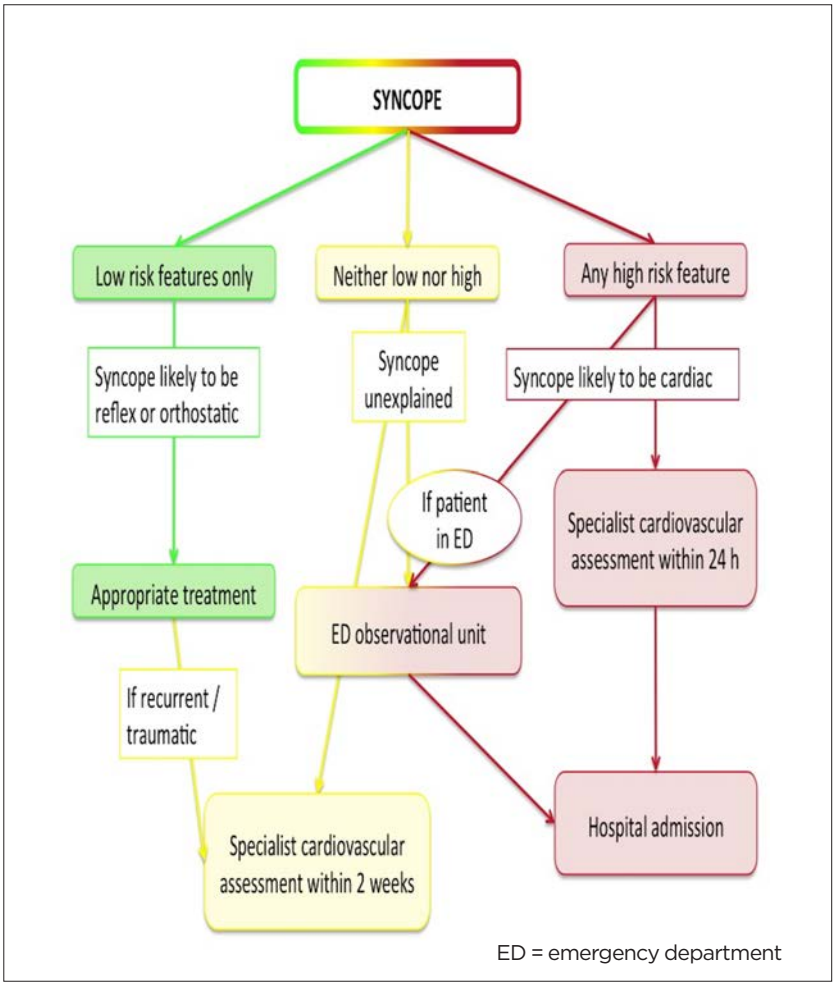


FIGURE 1
Risk stratification flow chart for management of patients with syncope after initial evaluation (modified from the 2018 ESC guidelines on syncope[2])

What are the mechanisms involved?

How should risk stratification be carried out?

What are the management strategies?

EVENTS OF A SUSPECTED SYNCOPAL NATURE ARE EXTREMELY FREQUENT IN THE GENERAL POPULATION, with 50% of people having at least one episode in their lifetime. The incidence is similar in men and women and increases with age, with two peaks of prevalence at 10-30 years and > 65 years.[1]

Syncope is a transient loss of consciousness (T-LOC) caused by cerebral hypoperfusion, characterised by a rapid onset, short duration and spontaneous complete recovery. It needs to be differentiated from other conditions that can cause T-LOC such as seizures, hypoglycaemia, trauma and psychogenic causes.[2,3]

From a pathophysiological viewpoint, three principal types of syncope can be identified: reflex or neurally mediated, orthostatic hypotensive and cardiac.[2,3] The common denominator of all these conditions is low systemic blood pressure (BP) causing global cerebral hypoperfusion and hence syncope.

Reflex syncopal episodes are caused by inappropriate functioning of normal cardiovascular reflexes in response to specific triggers, resulting in vasodilatation (vasopressor response), bradycardia (cardioinhibitory response) or a combination of both (mixed response). According to the trigger, reflex syncope can be classified as vasovagal (orthostatic or emotional), situational (triggered by micturition, gastrointestinal stimulation, coughing, sneezing, exercise, etc), carotid sinus syncope (caused by carotid sinus hypersensitivity), or atypical forms (without prodromes and/or without apparent triggers and/or atypical presentation).

Orthostatic hypotensive syncopal episodes are caused by hypotension in the setting of postural changes, i.e. going from a lying or sitting position to standing. They can be drug-induced (e.g. by vasodilators, diuretics, phenothiazines, antidepressants), result from volume depletion (haemorrhage, diarrhoea, vomiting) or caused by chronic impairment of the sympathetic tone resulting in insufficient peripheral vasoconstriction in response to orthostatic stress (Parkinson's disease, dementia, diabetes, kidney failure etc). Of note, a possible causal effect of orthostatic hypotension in dementia has also been recently suggested.[4]

Cardiac forms of syncope result from reduced cardiac output caused by »

cardiac arrhythmias (bradyarrhythmias or tachyarrhythmias) or structural cardiovascular conditions (aortic stenosis, acute myocardial infarction/ischaemia, hypertrophic cardiomyopathy, cardiac masses, pericardial disease/tamponade, congenital anomalies of coronary arteries, prosthetic valve dysfunction, pulmonary embolism, acute aortic dissection, pulmonary hypertension).

Reflex syncope is the most frequent cause of syncope in any setting and at all ages, followed by cardiac syncope and orthostatic hypotension. In individuals under 40 years of age, orthostatic hypotensive syncopal episodes are extremely rare.[5-7] The prognosis of syncope is dependent on the cause and the presence of underlying disease.

Table 1

Clinical history in a patient with suspected syncope

Patient's posture immediately before the event
- Upright
- Supine
- Seated

Precipitating factors
- Fatigue, sleep, food deprivation
- Ambient temperature
- Alcohol consumption
- Pain, strong emotions such as fear or apprehension
- Physical exercise

Prodromal symptoms
- Dizziness, lightheadedness
- Vertigo, sweating, epigastric discomfort, nausea, blurred vision, paraesthesia, chest pain, palpitations, headache, focal neurological deficits, déjà vu, confusion

Appearance during event
- Pallor, tongue biting, any body movements

Recovery
- Rapid
- Persisting somnolence, fatigue for minutes/hours
- Headache, neurological deficits
- Chest pain, palpitations

Medications
- Cardiac and antihypertensive medications, Parkinson's drug therapy, alpha-blockers for prostatism

Personal history
- Cardiac disease
- Parkinson's disease, dementia, diabetes

Family history
- Sudden cardiac death in young relatives
- Syncope, arrhythmias, cardiomyopathy, inherited cardiac conditions and channelopathies

There is also the consequential risk of syncope i.e. the impact that the syncope has on a patient's life through physical trauma and frequency of episodes. Cardiac syncope is often associated with high morbidity and considerable mortality, while reflex syncope has a more favourable, benign prognosis.

EXAMINATION

The initial assessment of patients with suspected syncope should aim to:
- Determine if the T-LOC event was due to syncope or to non-syncopal causes
- Identify the underlying cause of syncope
- Stratify the patient's risk of a serious outcome, and determine the urgency of any additional investigations and/or treatment required and the need for hospital admission (see figure 1, p11).[2,3]

It should include taking a clinical history, physical examination and a 12-lead ECG. The clinical history should be focused on: a detailed recollection of the T-LOC event (by the patient and any witnesses), the patient's medical history and drug history, and any family history of cardiac disease, see table 1, left.

The physical examination should include general inspection, cardiovascular examination with repeated systemic BP measurements, basic neurological examinations, see table 2, below.

A stepwise approach should be applied to the analysis of the ECG to identify abnormalities suggestive of cardiac syncope, see figure 2, opposite.

Table 2

Physical examination in a patient with suspected syncope

General inspection
- Head injury, lacerations, extremity fractures or other signs of trauma
- Tongue biting

Cardiopulmonary examination
- Heart rhythm abnormalities
- Heart murmurs
- Carotid bruits
- Peripheral oedema, raised jugular venous pressure, bilateral crackles or other signs of heart failure
- Peripheral SaO_2

Repeated blood pressure measurements
- While lying
- During active standing (after 3 min)

Neurological examination
- Focal neurological deficits

The initial assessment should also be used to stratify the patient's risk of serious cardiovascular events or sudden arrhythmic death through the identification of low- and high-risk features, see figure 3, opposite.[1]

Recent data show that approximately 50% of patients who present to emergency departments with syncope are currently admitted. Of these, 0.8% will die in the next 7-30 days, 6.9% will have a non-fatal severe outcome in the emergency department, and 3.6% will have a non-fatal severe outcome after discharge. Almost 90% will not come to serious harm and with hindsight did not require urgent admission and could have been managed with outpatient investigations.[2]

The 2014 NICE guideline on loss of consciousness and the 2018 ESC guidelines on syncope both stress that an accurate risk stratification of patients with syncope could potentially avoid unnecessary admissions of low-risk patients while ensuring early and comprehensive investigation and treatment in high-risk patients.[2,3]

CONFIRMING DIAGNOSIS

In approximately 60% of cases the clinical history alone is sufficient to differentiate syncope from other causes of T-LOC.[8] The combination of clinical history, physical examination and 12-lead ECG can provide a certain or suspected aetiology of syncope in up to 50% of cases.[9]

The 2018 ESC guidelines suggest diagnostic criteria for nearly certain or highly probable aetiological diagnosis after first evaluation.[2]
- Vasovagal syncope can be considered highly probable if syncope is precipitated by pain, fear or standing and is associated with a typical progressive prodrome (pallor, sweating and/or nausea).
- Situational syncope can be considered highly probable or confirmed if syncope occurs during or immediately after specific triggers.
- Syncope due to classical orthostatic hypotension can be considered confirmed if spontaneous symptoms are reproduced by a fall in systolic BP of at least 20 mmHg, a fall in diastolic BP of at least 10 mmHg or a decrease in systolic BP to < 90 mmHg within three minutes of standing.
- Cardiac syncope should be suspected in the presence of concomitant sustained cardiac arrhythmias, myocardial infarction, pulmonary embolism or aortic dissection; it can be

considered highly probable in the presence of known structural or electrical cardiac diseases (severe aortic stenosis, hypertrophic cardiomyopathy, Long QT syndrome, Brugada syndrome, etc) or in the presence of abnormal ECG findings, as indicated in figure 2, right.

The 2018 ESC guidelines on syncope continue to favour tilt testing in patients with suspected reflex or orthostatic syncope,[2] although the strength of recommendation has changed from I in the 2009 guidelines to IIa in the most recent version. Because of its low specificity, the test is not suggested in cases of unexplained syncope. False positives occur in up to 47% of patients with cardiac syncope.[10] The new concept of hypotensive susceptibility, i.e. susceptibility to orthostatic stress, has been introduced in the 2018 ESC guidelines to explain the positivity of tilt testing in most patients with unexplained syncope regardless of the cause.[2]

Of note, the 2014 NICE guideline[3] suggests no additional investigations in uncomplicated cases of vasovagal, situational or orthostatic hypotensive syncope with no high-risk features. In particular, tilt testing is only suggested in patients with recurrent severe episodes of reflex syncope to assess if the syncope is accompanied by a severe cardioinhibitory response which may then influence subsequent treatment.

As stated in both guidelines,[2,3] carotid sinus massage should be performed to reproduce symptoms in cases of suspected carotid sinus syncope. This test can be performed in the primary care setting if ECG monitoring and BP recording is available. With the patient lying supine, after checking there are no carotid bruits, the right carotid pulse is firmly massaged for 3-5 seconds while recording BP and a rhythm strip on the ECG. A ventricular pause lasting >3 seconds and/or a fall in systolic BP of > 50 mmHg is known as carotid sinus hypersensitivity.

However, carotid sinus syncope can only be confirmed in the case of symptoms during carotid sinus massage, usually occurring in the presence of ventricular pauses > 6 seconds, and clinical features of reflex syncope. Carotid sinus hypersensitivity is a common incidental finding in older men without syncope.[10] A potential complication of carotid sinus massage is TIA/stroke in 0.24% of cases.[2] Therefore, it should be undertaken with caution in patients with previous TIA, stroke, or known carotid stenosis >70%. The carotids should be ausculated for bruits before performing massage. »

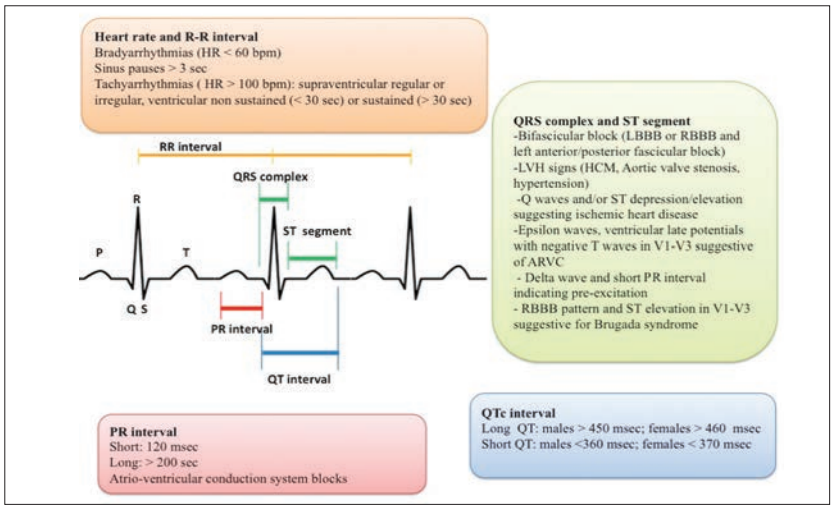


FIGURE 2
ECG features suggesting cardiac syncope

FIGURE 3
Low- and high-risk features at initial evaluation in patients with syncope[2]

	LOW-RISK FEATURES	HIGH-RISK FEATURES
CLINICAL HISTORY	- Prodrome and precipitating factors typical of reflex syncope - Long history of recurrent syncopal episodes with same characteristics - No history of previous cardiac disease	- New chest discomfort, breathlessness, abdominal pain, headache - Palpitations preceding syncope - History of severe structural or coronary artery disease - No warning or short prodrome * - Syncope while sitting * - Family history of SCD at young age *
PHYSICAL EXAMINATION	Normal physical examination	- Persistent bradycardia < 40 bpm - Heart murmur - Unexplained systolic BP< 90 mmHg - Serious injury
ECG	Normal ECG	- ST Elevation Myocardial Infarction - Brugada/ARVC pattern - Persistent sinus bradycardia or AF < 40 bpm or sinus pauses > 3 sec in awake state - Mobitz II type second degree AV block - Third degree AV block - BBB, ventricular hypertrophy, Q waves - Sustained/non sustained VT - PPM/ICD dysfunction - Short/Long QT interval - Paroxysmal AF/SVT ** - Mobitz I second degree AV block ** - First degree AV block with marked prolongation of PR interval ** - Asymptomatic inappropriate mild sinus bradycardia or AF (40-50 bpm) **

Key: AF = atrial fibrillation; ARVC = arrhythmogenic right ventricular cardiomyopathy; AV = atrioventricular; BBB = bundle branch block; PPM = permanent pacemaker; ICD = implantable cardioverter defibrillator; SCD = sudden cardiac death; SVT= supraventricular tachycardia; VT = ventricular tachycardia.
* High-risk feature only in association with abnormal ECG or structural heart disease
** High-risk feature only if history consistent with arrhythmic syncope

key points

SELECTED BY

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Events of a suspected syncopal nature are extremely frequent in the general population, with 50% of people having at least one episode in their lifetime. Syncope is a transient loss of consciousness (T-LOC) caused by cerebral hypoperfusion, characterised by a rapid onset, short duration and spontaneous complete recovery. It needs to be differentiated from other conditions that can cause T-LOC such as seizures, hypoglycaemia, trauma and psychogenic causes.

Three principal types of syncope can be identified: reflex or neurally mediated, orthostatic hypotensive and cardiac. The common denominator of all these conditions is low systemic BP causing global cerebral hypoperfusion. Reflex syncope is the most frequent cause of syncope in any setting and at all ages, followed by cardiac syncope and orthostatic hypotension. In individuals under 40 years of age, orthostatic hypotensive syncopal episodes are extremely rare. Cardiac syncope is often associated with high morbidity and considerable mortality, while reflex syncope has a more favourable, benign prognosis.

Recent data show that around 50% of patients who present to emergency departments with syncope are admitted. Of these, 0.8% will die in the next 7-30 days, 6.9% will have a non-fatal severe outcome in the emergency department, and 3.6% will have a non-fatal severe outcome after discharge. Almost 90% will not come to serious harm and with hindsight did not require urgent admission and could have been managed with outpatient investigations.

In around 60% of cases the clinical history alone is sufficient to differentiate syncope from other causes of T-LOC. The combination of clinical history, physical examination and 12-lead ECG can provide a certain or suspected aetiology of syncope in up to 50% of cases. NICE guidance suggests no additional investigations in uncomplicated cases of vasovagal, situational or orthostatic hypotensive syncope with no high-risk features. In particular, tilt testing is only suggested in patients with recurrent severe episodes of reflex syncope. Additional investigations are usually required in cases of suspected cardiac syncope to confirm the diagnosis and/or stratify the patient's risk of serious outcomes.

In patients with reflex syncope and with orthostatic hypotension lifestyle modifications are recommended as first-line therapy. The treatment of cardiac syncope is mainly directed at the underlying cardiac disease. Patients with infrequent episodes and low-risk features (and who are likely to have reflex, situational or orthostatic syncope), should be reassured about the benign nature of the event and treated appropriately. All other patients need an expert syncope review within two weeks and can be safely managed in an outpatient setting.

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Additional investigations are usually required in cases of suspected cardiac syncope to confirm the diagnosis and/or stratify the risk of serious outcomes.[2,3]

- Echocardiography is indicated in the case of suspected structural heart disease.
- Exercise testing should be performed in patients who experience syncope during or shortly after exertion.
- Prolonged ECG monitoring is indicated in the case of suspected arrhythmic syncope. Different ECG monitoring systems with different duration and features are currently available. The choice should be based on frequency of symptoms and on the ability of the patient or the bystander to activate a recorder before or during a syncopal episode.

Continuous ECG monitors can record the ECG continuously for up to 14 days. The 24-48 hr ECG Holter monitoring has a very low diagnostic yield (1.8-4% in patients with syncope);[12,13] it should be used only in patients with daily episodes. Apart from the traditional ECG Holter devices that use leads, leadless devices consisting of single-use patch electrodes, are currently available (ZIO,[14] Carnation) and they can record continuously for up to 7 or 14 days.

Event monitors make patient-activated recordings when the patient either places the device against their chest or presses their thumbs on two electrodes. They can record symptoms during prodromes or associated palpitations, but the device will not be activated when the patient is unconscious.

External loop recorders are event monitors with a loop memory. The ECG is continuously recorded and deleted, unless activated by the patient. Devices will also make automated recordings if the heart rate drops below or exceeds predefined rates. They are useful when symptoms occur every few weeks.

Implantable loop recorders (ILRs) are small devices that are inserted subcutaneously under local anaesthesia. They have a battery life of up to five years and a loop memory that stores retrospective ECG recordings automatically in the case of predefined arrhythmia recurring or if activated by the patient. The recordings can be downloaded wirelessly for analysis.[15] ILRs are ideally suited to individuals with very infrequent, potentially high-risk syncope.

- An electrophysiological study is suggested in selected cases of unexplained syncope despite non-invasive evaluation in patients with previous myocardial infarction (to identify patients who could benefit from an ICD), in patients with bifascicular block (to diagnose high degree AV block requiring permanent pacing) and in patients with palpitations during syncope (to diagnose a treatable cause such as supraventricular tachycardia).

In cases of unexplained T-LOC events or recurrent syncopal episodes of unknown cause, patients and their relatives should be encouraged to record videos during the event.

MANAGEMENT

In patients with reflex syncope and with orthostatic hypotension lifestyle modifications are recommended as first-line therapy. Lifestyle changes such as increasing dietary salt and water intake, avoiding triggers and hot crowded environments, reducing alcohol consumption, plus moderate exercise training can have a huge impact in reducing the frequency of syncopal episodes. Any hypotensive and psychotropic drugs should be reduced or discontinued, if possible.[16] Compression stockings should be considered to reduce the venous pooling in patients with orthostatic hypotension. In the case of prodromal symptoms, physical counterpressure manoeuvres (sitting or lying down in order to avoid injury, leg crossing, squatting), should be performed at the onset of symptoms to increase BP in the hope of averting syncope.

Tilt training, consisting of progressively longer periods of prescribed upright posture, seems to have only little efficacy in reducing syncope by increasing the peripheral vascular compliance to orthostatic stress.

Midodrine, an alpha-agonist, and fludrocortisone[17] have shown contrasting results in reducing syncopal recurrences in patients with vasovagal syncope and therefore they are not currently recommended other than in cases of severe recurrent forms of reflex or orthostatic syncope not responsive to lifestyle measures. They seem to be most beneficial as adjunctive therapy in patients with orthostatic hypotension.

A pacemaker is only rarely indicated in reflex syncope. It could be considered in order to reduce the recurrence of syncope in patients older than 40 years with recurrent, severe and unpredictable episodes that have a predominant cardioinhibitory component, i.e. pauses of > 10 seconds. Of note, recent data show a high spontaneous remission rate in patients with frequent vasovagal syncope. It might be worth following the

patient up for a brief period before starting a specific therapy.[18]

The treatment of cardiac syncope is mainly directed at the underlying cardiac disease. Potential reversible causes of arrhythmias (drugs, electrolyte imbalances) should be investigated in the first instance and treated if present. Critical obstruction such as severe aortic stenosis or hypertrophic cardiomyopathy may be amenable to surgical intervention. Cardiac pacing is recommended for treatment of bradycardia-induced syncope resulting from significant conduction disease. Catheter ablation and drugs are potential treatment options for tachycardia-induced syncope.

ICD therapy might be indicated in the case of ventricular tachycardia with structural or electrical heart disease and in the case of unexplained syncope (suspected as arrhythmic) in patients with high-risk conditions including severely depressed left ventricular systolic function (LVEF < 35%), hypertrophic cardiomyopathy, Brugada syndrome and long QT syndrome.

The goal of treatment of syncope secondary to structural heart disease is treatment of the underlying disease with reduction of the associated risk of death.

Patients with syncope may be subject to driving restrictions, see DVLA guidance for medical professionals, Useful information box, below right.

REFERRAL

Patients with infrequent episodes and low-risk features (and who are likely to have reflex, situational or orthostatic syncope), should be reassured about the benign nature of the event and treated appropriately. Specialist cardiovascular assessment is not required.

Patients with any high-risk features and thus likely to have cardiac syncope, or those with recurrent traumatic syncopal episodes should be admitted to hospital (or to an emergency department observational unit) and/or referred for urgent specialist cardiovascular assessment within 24 hours.

All other patients need an expert syncope review within two weeks and can be safely managed in an outpatient setting or, if initially evaluated in an emergency department, they could be managed in the observational unit.

Competing interests: None

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Useful information

Arrhythmia Alliance
www.heartrhythmcharity.org.uk

STARS (Syncope Trust And Reflex anoxic Seizures)
www.stars.org.uk

DVLA guidance for medical professionals
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/736938/assessing-fitness-to-drive-a-guide-for-medical-professionals.pdf