Management of syncope: from evidence to clinical practice

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ABSTRACT

Syncope is defined as a transient loss of consciousness due to temporary global cerebral hypoperfusion. It is characterized by rapid onset, short duration, loss of postural tone possibly causing patient fall, and spontaneous full recovery. Syncope has a high prevalence and incidence within the general population with a relevant impact on both quality of life and health care costs. The diagnosis of syncope is often inaccurate and subject to delay, and management is greatly variable. The main objective of this monograph is to discuss a methodological diagnostic approach to signs and symptoms suggestive of syncope, aiming for a management optimization. The present work is based on a systematic review of recent international guidelines.

Introduction

Syncope is defined as a transient loss of consciousness (T-LOC) due to temporary global cerebral hypoperfusion. It is characterized by rapid onset, short duration, spontaneous full recovery and loss of postural tone, possibly causing patient fall. The post-syncopal recovery phase is typically rapid, although a retrograde amnesia can occur. The diagnosis of syncope is often inaccurate and its management is greatly variable,[1] while a correct diagnosis and risk stratification are crucial for patients' outcomes.[2]

The main objective of this monograph is to discuss the recommendations from international guidelines/guidance focusing on diagnosis and optimization of resources.

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Key words: Syncope; transient loss of consciousness; unexplained syncope; internal loop recorder.

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Epidemiology

Syncope is a frequent condition, reaching two peaks of incidence within the general population: one between 15 and 30 years and a second in patients aged 70 years or older.[3] Cohort and population studies demonstrated that about 40% of the adult population experience a T-LOC once in a life-time (sometimes described as a *weakness* or a *black-out*), with a higher incidence among women.[3] The increased incidence in older individuals is explained by the increased use of vasoactive drugs and the higher prevalence of arrhythmias.[3] Several disorders may resemble syncope and occur with either a complete or an apparent loss of consciousness,[3] but they do not recognize an underlying global cerebral hypoperfusion mechanism. With regard to the first group, the mechanism is other than global cerebral hypoperfusion: examples are epilepsy, metabolic disorders (including hypoxia and hypoglycemia), intoxication, and vertebrobasilar transient ischemic attack. The other group includes cataplexy, drop attacks, falls and the so-called psychogenic pseudosyncope (Figure 1).[2]

Syncope accounts for up to 1-3% of hospital admissions and Emergency Deparment (ED) visits and in these settings, it is associated with cardiovascular co-morbidity and cardiovascular pharmacotherapy. In older adults, syncope is a major cause of morbidity and mortality with enormous personal and wider

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health economic costs.[3] The main causes of access to the ED for syncope patients are trauma (minor injuries around 29% of cases and more to 4.7%) and carotid sinus hypersensitivity.[3]

Etiology and pathogenesis of syncope

The acute approach to a patient with syncope consists of carefully collecting personal medical history (directly from the patient or from a person who was with him/her when the syncope occurred) and an accurate physical examination for an initial differential diagnosis. Syncope recognizes different causes: however, those are identifiable in no more than two thirds of patients. Table 1[2] summarizes the causes of syncope.

ABC syncope

The initial evaluation of a patient presenting with T-LOC should answer to three key questions: i) Is it a syncopal episode or not? ii) Is the etiological diagnosis determined? iii) Is the patient at a high risk for cardiovascular events or death?

Is it a syncopal episode or not?

The differentiation between syncope and non-syncopal conditions with real or apparent LOC can be achieved with a detailed clinical history, although is often challenging. The following questions should be answered: i) Was LOC complete? ii) Was LOC transient with rapid onset and short duration? iii) Did the patient lose postural tone?

If we have positive answers, it is very likely that the episode is syncope. If we have negative answer to one or more of these questions, we must exclude other forms of LOC and then we proceed with syncope evaluation.[2]

Is the etiological diagnosis defined?

The milestones of initial evaluation of a patient presenting with syncope are three (Table 2):[2]

- *Patient medical history*, what to ask: i) circumstances just prior to syncope: position, activity, predisposing factors; ii) syncope onset: nausea, vomiting, palpitations; iii) characteristics: way of falling, skin color, duration of loss of consciousness, breathing pattern, tongue bite, movements-type, duration, onset in relation to fall); iv) syncope end: nausea, vomiting, sweating, feeling of cold, confusion, muscle aches, skin color, injury, chest pain, palpitations, urinary or fecal incontinence; v) background: family history of sudden death, previous cardiac disease, neurological history, metabolic disorders, medication, information

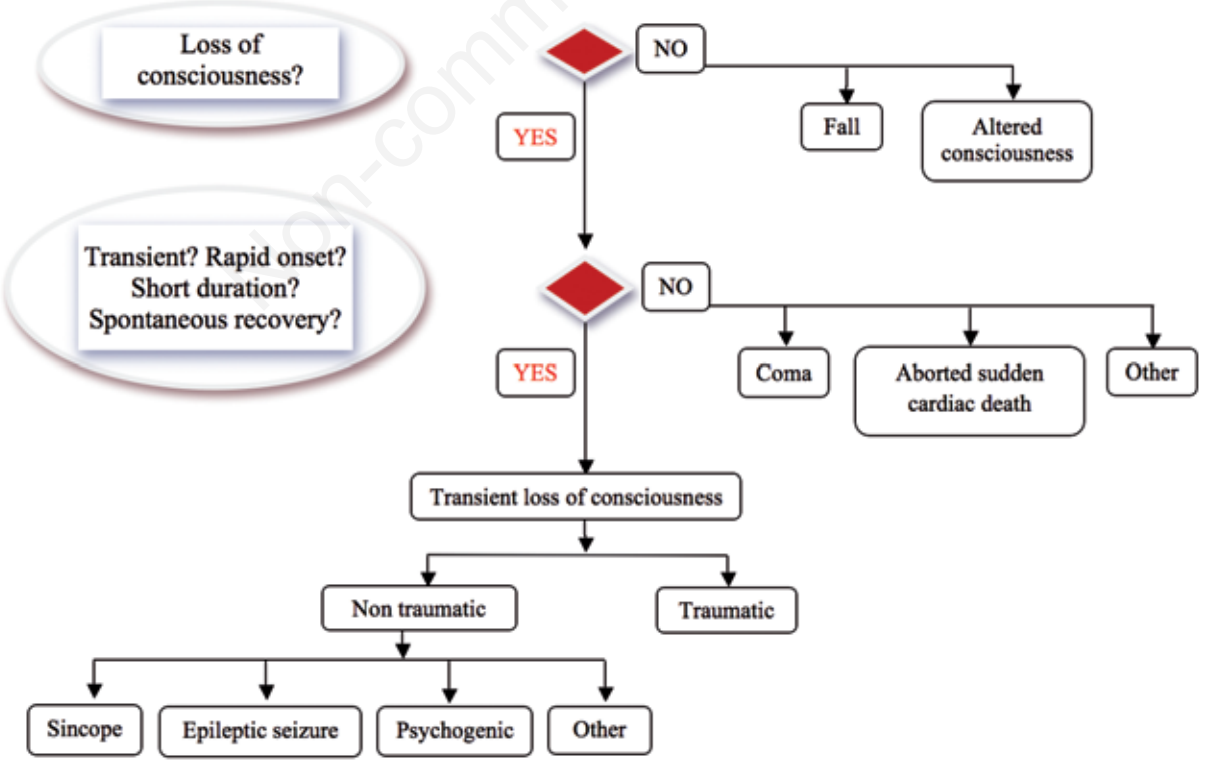

Figure 1. Type of loss of consciousness (LOC). *Modified from The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC), 2009.*[2]

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on recurrences such as the time from the first syncopal episode and on the number of spells (in the case of recurrent syncope).
- *Physical examination*: in the initial evaluation, the physical examination would better include the orthostatic challenge assessment when there is a suspicion of a reflex mechanism of orthostatic hypotension (OH).
- The electrocardiogram (ECG) is essential both for etiological diagnosis and for risk stratification.

Is the patient at a high risk for cardiovascular events or death?

The third phase of the initial evaluation of syncope is focused on the risk assessment to determine the pressing need for hospitalization or intensive care. Table 3[2] summarizes a classification of high-risk criteria for hospitalization and/or intensive evaluation. Patients with a single major risk factor must receive an urgent cardiac assessment, while patients with one or more minor risk factors could be considered for receiving an urgent cardiac assessment.

Major risk factors are: i) abnormal ECG (any bradyarrhythmia, tachyarrhythmia or conduction disease, new ischemia or old infarct); ii) history of cardiac disease; iii) hypotension; iv) heart failure (either past history or current state).

Minor risk factors are: i) age >60; ii) dyspnea; iii) anemia; iv) cerebrovascular disease; v) family history of early sudden death; vi) specific situations, such as syncope while supine, during exercise, or with no prodromal symptoms.

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Table 1. Classification of syncope.

Cardiac and cardiovascular syncope
Arrhythmia as primary cause
Bradycardia:
Sinus node dysfunction (including bradycardia/tachycardia syndrome)
Atrioventricular conduction system disease
Implanted device malfunction
Tachycardia:
Supraventricular
Ventricular (idiopathic or secondary to structural heart disease or to channelopathies)
Drug induced bradycardia and tachyarrhythmias
Structural disease
Cardiac:
Cardiac valvular disease, myocardial infarction, hypertrophic cardiomyopathy, cardiac masses (atrial myxoma, tumors, *etc*.), pericardial disease/tamponade, congenital anomalies of coronary arteries, prosthetic valves dysfunction
Others:
Pulmonary embolus, aortic dissection, pulmonary hypertension
Reflex syncope
Vasovagal:
Mediated by emotional distress: fear, pain, instrumentation, blood phobia
Mediated by orthostatic stress
Situational:
Cough, sneeze
Gastrointestinal stimulation: swallow, defecation, visceral pain
Micturition, post-micturition
Post-exercise
Post-prandial
Others (laugh, brass instrument playing, weightlifting)
Carotid sinus syndrome
Atypical forms (without apparent triggers and/or atypical presentation)
Syncope due to orthostatic hypotension (autonomic failure)
Primary autonomic failure:
Pure autonomic failure, multiple system atrophy, Parkinson's disease, Lewy body dementia, idiopathic orthostatic hypotension
Secondary autonomic failure:
Diabetes, amyloidosis, terminal uraemia, spinal cord injuries
Drug-induced orthostatic hypotension:
Alcohol, vasodilators, diuretics, phenotiazines, antidepressants
Volume depletion:
Hemorrhage, diarrhea, vomiting, *etc.*

Modified from The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC), 2009.[2]

Diagnostic approach to cardiogenic syncope

Electrocardiogram

The gold standard for the diagnosis of syncope is represented by the demonstration of likely causality between symptoms and underlying mechanism, in particular arrhythmia.[2]

There are different lengths and types of ECG analysis in front to a suspicion of etiology of syncope, the individual risk level and the expected rate of recurrent syncope.[4]

In-hospital ECG monitoring (in bed or telemetry) should be undertaken in any patient with high-risk of arrhythmic etiology. *Holter monitoring* is appropriate in patients who have frequent episodes (≥1 per week). *Implantable loop recorder* (ILR) is mainly indicated in patients without high risk but an arrhythmic suspicion of the syncope. *External loop recorder* is an alternative to ILR when symptoms occur at a rate of >2/month.

Echocardiography

Echocardiography represents an important technique to evaluate the presence of structural and functional cardiac disease involved in the etiology of cardiogenic syncope and it identifies the risk stratification.[2] The detectable conditions are: aortic stenosis, tumors or thrombi causing cardiac obstruction, pericardial tamponade, aortic dissection, congenital abnormalities of coronary arteries. Echocardiography plays also a role in hemodynamically unstable patients suspected with pulmonary embolism for whom a computed tomography pulmonary angiography is not immediately available.

Electrophysiological study

Electrophysiological study (EPS) is actually limited to a study of suspect arrhythmic syncope in patients with ischemic heart disease,[2] in order to assess the exact underlying mechanism (syncope in the pres-

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Table 2. Clinical features that may suggest the diagnosis at the time of the initial assessment.

Neurally mediated syncope
• Absence of heart disease
• Long history of recurrent syncope
• After sudden unexpected unpleasant sight, sound, smell or pain
• Prolonged standing or crowded, hot places
• Nausea and vomiting associated with syncope
• During a meal or post-prandial
• With head rotation or pressure on carotid sinus (as in tumors, shaving, tight collars)
• After exertion
Syncope due to orthostatic hypotension
• After standing up
• Temporal relationship with start or changes of dosage of vasodepressive drugs leading to hypotension
• Prolonged standing especially in crowded or hot places
• Presence of autonomic neuropathy or Parkinsonism
• Standing after exertion
Cardiovascular syncope
• Presence of definite structural heart disease
• Family history of unexplained sudden death or channelopathy
• During exertion or supine
• Abnormal ECG
• Sudden onset palpitation immediately followed by syncope
• ECG findings suggesting arrhythmic syncope
- Bifascicular block (LBBB o RBBB + LAH/LPH)
- Other intraventricular conduction abnormalities (QRS duration >120 ms)
- Mobitz 1 second degree AV block
- Asymptomatic inappropriate sinus bradycardia (<50 bpm), sinoatrial block or sinus pause ≥ 3" in the absence of negatively chronotropic medications
- Non sustained ventricular tachycardia
- Ventricular pre-excited
- Long or short QT intervals
- Early repolarization
- Right bundle branch block pattern with ST elevation in leads V1-V3 (Brugada syndrome)
- Negative T waves suggesting myocardial infarction
- Negative T waves in right precordial leads, epsilon waves and ventricular late potentials suggestive of arrhythmogenic right ventricular cardiomyopathy

ECG, electrocardiogram; LBBB, left bundle branch block; RBBB, right bundle branch block; LAH/LPH, left anterior hemiblock/left posterior hemiblock; AV, artrial ventricle.
Modified from The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC), 2009.[2]

ence of prolonged sinus bradycardia, bundle branch block, supraventricular tachycardia, sustained monomorphic tachycardia).[2] The EPS is functional to agree a specific treatment as the implantable cardioverter defibrillator (ICD) implantation or catheter ablation procedure. However, in case of severely depressed left ventricular ejection fraction (EF) the ICD should be yet indicated regardless the mechanism of syncope. Furthermore, more sensitive and non-invasive procedures are preferable to detect the syncope mechanism as the ECG continuous and ILR.

Exercise stress testing

Exercise testing is indicated in patients who had episodes of syncope during or shortly after exertion. The test is diagnostic if it reproduces syncope with ECG abnormalities or severe hypotension.[2]

Diagnostic approach to non-cardiogenic syncope

Neurogenic syncope is the most common cause of syncope. Provocative tests are aimed to reproduce the mechanism of syncope or related abnormalities in an artificial setting.

Carotid sinus massage

In some individuals, the normal carotid sinus baroreceptor reflex is damaged therefore it can be triggered by minor stimuli, causing an abnormal response of the blood pressure and heart rate controls, leading to neurally mediated syncope or symptoms related. The carotid massage is a simple test that it is able to reproduce this disorder. *Carotid sinus hypersensitivity* is diagnosed when carotid sinus massage (CSM) causes a >3 s asystole and/or lowering of the systolic blood pressure >50 mmHg.[2] *Carotid sinus syndrome* is defined when syncopal symptoms accompany these heart frequency or blood pressure changes. The massage consists in a manual light phasic rubbing lasting ten seconds on the right and on the left sides, both in supine and erect position, throughout continuous monitoring of heart rate and blood pressure. In about 30% of patients an abnormal response is present only in orthostatic position.[2] Carotid sinus hypersensitivity is quite common in older men and carotid sinus syndrome is exceptional in patients less than forty years old. In fact, after initial evaluation CSM should be performed in all patients with unexplained syncope aged >40 years. CSM is contraindicated in patients who have sustained a myocardial infarction in the last 3 months and in the presence of carotid bruits (unless Doppler studies have shown no significant arterial stenosis).[2] A panel of experts proposed a CSM cut-off change, in particular to consider positive a massage for asystole ≥6 s and drop in the mean blood pressure ≥60 lasting for ≥6 s.[5]

Orthostatic hypotension

The *active orthostatic test* is used to diagnose different types of orthostatic intolerance.[2] The classical

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Table 3. Classification of high risk criteria for hospitalization and/or intensive evaluation.

A.	**Severe structural or coronary artery disease**
	- Heart failure
	- History of cardiac disease
	- Low left ventricular ejection fraction
	- Previous myocardial infarction
B.	**Clinical or electrocardiogram features suggesting arrhythmic syncope**
	- Syncope during exertion or supine
	- Palpitations at the time of syncope
	- Family history of sudden cardiac death
	- Non-sustained ventricular tachycardia
	- Bifascicular-block: left bundle branch block or right bundle branch block (RBBB) combined with left anterior or left posterior fascicular block; other intraventricular conduction abnormalities with QRS duration > o =120 ms
	- Inadequate sinus bradycardia (<50 bpm) or sinoatrial block in absence of negative chronotropic medications or physical training
	- Pre-excited QRS complex
	- Prolonged or short QT interval
	- RBBB pattern with ST-elevation in leads V1-V3 (Brugada pattern) Negative T waves in right precordial leads, epsilon waves, and ventricular late potentials suggestive of arrhythmogenic right ventricular cardiomyopathy
C.	**Important co-morbidities:**
	- Severe anemia (HCT <30)
	- Electrolyte disturbance
	- Cerebrovascular disease
	- Dyspnea
	- Hypertension

Modified from The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC), 2009.[2]

OH is the most frequent form. In fact, the test is usually indicated in patients with syncope or dizziness that occur in the first 3 min of adopting erect position. Orthostatic hypotension is evaluated with manual intermittent blood pressure measurement with sphygmomanometer lying-to standing for at least 3 min; the diagnosis of OH is made if there is a symptomatic fall in systolic blood pressure (BP) from baseline value ≥20 mmHg or a decrease in diastolic BP ≥10 mmHg, as well as a decrease in systolic BP to <90 mmHg. If the test is doubtful, it is indicated the blood pressure continuous monitoring.[2]

Tilt table test

Tilt testing is a tool to reproduce a neurally mediated reflex triggered by prolonged standing and it shows an impaired vasoconstriction capability that can provoke a reflex syncope. The primary indications of this test are recurrent syncopes in the absence of organic heart disease or a single unexplained episode in high-risk settings. Nitroglycerine protocol is the useful tilt testing method. The response is a vasovagal reaction vasodepressive, cardioinhibitory, and mixed.[2]

Diagnostic approach to unexplained syncope

Loop recorder

Despite a complete and comprehensive diagnostic approach, approximately 30% of patients with T-LOC does not reach a conclusive diagnosis: in this case, it is defined as syncope unexplained suitably.[6] The ILR is a small device for subcutaneous implantation with retrospective memory able to retain the ECG trace for prolonged periods of time and with very prolonged duration memory (even more years). Generally, this device weighing about 17 g is positioned in the anterior chest wall in a pocket similar to the common pacemaker. Initially the ILR was used in patients with unexplained syncope at the end of a complete but unsuccessful diagnostic workup. Based on the first experiences, it became clear the ILR is a useful diagnostic tool when the arrhythmic cause of syncope is suspected but not proven with certainty from the usual diagnostic approach.

Patients' selection for the ILR-study is based on careful risk stratification and resulting pre-test probability to identify a syncopal-related arrhythmia. Relapse's rate and syncopal events' recurrence (that is to say number of T-LOC per year) and ECG-graphics alterations, such as a bundle branch block, have a high positive predictive value regarding on syncope incidence, so there are useful factors for patients' selection.[7] Conversely age, sex, positive response to the tilt test and presentation's severity of loss of consciousness have a low predictive value.[8] The ILR is a valuable weapon for the definitive diagnosis of syncope; it can be used in patients with block bundle where it is highly able to document a paroxysmal atrial ventricular (AV) block, in patients with structural heart disease but with negative cardiac evaluation, in individuals with documented carotid sinus hypersensitivity, in pediatric patients, or in patients with probable neurally mediated syncope diagnosis after initial assessment. Because of various recent evidence, the ILR appeared useful in differential diagnosis between syncope and T-LOC seizure in patients with epilepsy diagnosis that have not benefit from antiepileptic treatment, in patients with major depressive syndrome with frequent episodes of unexplained syncope, or in older individuals with recurrent unexplained falls.[9-11] Based on the results of trials conducted about unexplained syncope and use of ILR (ISSUE 1 and 2, PICTURE, EVISE and others), it is clear the high diagnostic value of the ILR to correlate the unexplained syncopal event and arrhythmia, to obtain a definitive diagnosis and to promote a decisive therapy.[12,13] For this reason, the ILR implant over time indication will be incremented in about 34 cases per million inhabitants per year compared to current use.[14,15] The question about the ILR implantation proper timing remains open entirely; if this device was initially considered a last resort option and reserve diagnostic once other investigative weapons were exhausted, now various evidence indicates a potential role of this early.[7] In conclusion, according to the European Society of Cardiology (ESC) 2009 guidelines the ILR implantation is indicated with Class 1 and evidence A: i) in patients with recurrent and uncertain origin syncope after initial assessment to exclude high risk factors presence such as severe structural heart disease and coronary important comorbidities, family history of sudden cardiac death, inadequate sinus bradycardia, BBB, abnormal QT or ventricular repolarization, preceded by palpitations or syncope occurred in the supine position or even during exercise in early stage; ii) in patients with both high likelihood of syncope recurrence (at least three syncopal episodes in the previous two years with interval between the first and the last event of at least 6 months) within the operating time of the device's battery; iii) in high-risk patients in whom complete evaluation has not led to diagnosis or did not lead to specific treatment.

The ILR diagnostic tool can also be used: i) in patients with certain or suspected neurally mediated syncope, frequent or unpredictable risk of trauma, in order to identify the role of bradycardia before a pacemaker implantation; ii) in patients with T-LOC in order to exclude the arrhythmic genesis safely.

The ECG finding provided by ILR is diagnostic when it is demonstrated the correlation between syncope and arrhythmia or in case of BAV II or III or in

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case of a ventricular pause greater than 3 s, or in case of above-ventricular paroxysmal tachycardia and rapid ventricular rhythm. Conversely, the finding ECG provided by ILR allows excluding an arrhythmic cause when there is no correlation between syncope and changes in heart rate. Finally, the ILR should be continued in case of pre-syncope, in case of asymptomatic arrhythmias or sinus bradycardia. The economic impact of the ILR for each diagnosis is lower than conventional diagnostic; it could appear superior only if it is taken individually and in the initial phase; in other words, the performance and the guaranteed rate of diagnostic efficacy compensate the high initial cost.[16,17] In conclusion, the use of ILR in selected patients remains an accurate although expensive, effective and valuable tool for the diagnosis and management of patients with recurrent unexplained syncope. Unlike many conventional monitoring available methods, the ILR provides both a high yield valuable diagnostic information and risk stratification in a single test. Based on the current evidence-based guidelines, the use of ILR should be considered an accurate and effective tool for the management of patients with syncope, but it does not replace a detailed initial assessment characterized by a careful history and a meticulous physical examination.

Neurological and psychiatric evaluations

The Neurologist is consulted for differential diagnosis both syncope and epilepsy, or to define autonomic failure in the context of neurologic ill patient. Electroencephalogram and brain scan are not recommended in the syncope study flow chart however in the differential diagnosis of other T-LOC psychiatric evaluation should be performed for a suspicion of functional attacks (*pseudo-epilepsy* and *pseudo-syncope*).

Finally, it is important to remind the concurrent multiple causes underlying a single syncopal episode, especially in the elderly population.

Therapy

The treatment of patients with syncope has the main goal to prolong survival, limit physical injuries and prevent recurrence.[2] It must be directed to the causes, which underlie the temporary global cerebral hypoperfusion[2] so it is very essential the risk stratification and the identification of specific mechanism (Figure 2).[2]

Recent guidelines on cardiac pacing[18] underline that bradyarrhythmias requiring cardiac pacing can have different etiologies and that the early identification of a potentially reversible cause represents the first step towards efficacious treatment. When a transient or reversible cause is excluded, the indication for cardiac pacing is determined by the severity of bradycardia, in particular we can recognize a *persistent bradycardia*, which is caused by an intrinsic disease of the sinus node or AV conduction system, and an *intermittent bradycardia*, whose etiology is more difficult to determine (Figure 3).[18]

Orthostatic hypotension

Lifestyle advices can improve orthostatic symptoms markedly, even if the rise in blood pressure is relatively small (10-15 mmHg). An important goal is the expansion of extracellular volume, in fact patients without hypertension should be instructed to take sufficient salt and water intake, such as 2-3 L of fluids per day and 10 g of NaCl.[19] Physical counter pressure maneuvers such as leg crossing and squatting may be indicated (Class II b, Level C).[20] In older patients, abdominal binders and/or support stockings to reduce venous pooling may be indicated (Class IIb, Level C).[21,22] Midodrine should be administered as adjunctive therapy if needed (Class IIa, Level B), such as Fludrocortisone (Class IIa, Level C).[2]

Syncope secondary to structural cardiac or cardiovascular disease

In patients with syncope secondary to structural cardiac disease, including congenital heart malformations or cardiopulmonary disease, treatments have to aim not only to prevent syncopal recurrence, but also to treat the underlying disease and to decrease the risk of sudden cardiac death (SCD).[2]

There is some evidence[23-27] supporting both short- and long-term benefits of resynchronization therapy (CRT) in patients in sinus rhythm with the New York Heart Association (NYHA) class III; moreover, CRT improves left ventricular function, decrease mortality and hospitalization rate in patients in sinus rhythm with NYHA class I and II.[28-31]

In particular in patients in sinus rhythm with: i) left bundle branch block (LBBB) and QRS duration >150 ms, CRT is recommended in chronic heart failure patients, left ventricular EF (LVEF) ≤35% and in those who remain in NYHA class II, III and IV despite adequate medical treatment (Class I, Level A); ii) LBBB and QRS duration 120-150 ms, CRT is recommended in chronic heart failure patients, LVEF ≤35% and in those who remain in NYHA class II, III and IV despite adequate medical treatment (Class I, Level B); iii) absence of LBBB and QRS duration >150 ms, CRT should be considered in chronic heart failure patients, LVEF ≤35% and in those who remain in NYHA class II, III and IV despite adequate medical treatment (Class IIa, Level B); iv) absence of LBBB and QRS duration 120-150 ms, CRT may be considered in chronic heart failure patients, LVEF ≤35% and in those who remain in NYHA class II, III and IV despite adequate medical

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treatment (Class IIb, Level B); v) CRT is not recommended in patients with chronic heart failure and QRS duration <120 ms (Class III, Level B).[18]

Biventricular pacing (BiV) is used in CRT mainly.[18]

On the other hand in patients with atrial fibrillation we have the following conditions: i) CRT should be considered in chronic heart failure patients, intrinsic QRS duration ≥120 ms and LVEF ≤35% and in those who remain in NYHA class III and IV despite adequate medical treatment (Class IIa, Level B); ii) AV junction ablation should be used in case of incomplete BiV pacing in patients with chronic heart failure, long QRS and reduced LVEF (Class IIa, level B); iii) finally CRT should be considered in patients with reduced LVEF who are candidates for AV junction ablation for rate control.[18]

When an ICD is indicated in primary or secondary prevention of sudden death, it is recommended that CRT is added to improve symptoms, exercise tolerance and cardiac function and to reduce hospitalization in symptomatic patients with chronic heart failure with adequate medical treatment, LVEF ≤35% e complete LBBB (Class I, Level A).[26,28,30,31]

Cardiac resynchronization therapy and defibrillator is used in the presence of the following factors: i) life expectancy >1 years; ii) stable heart failure (Class

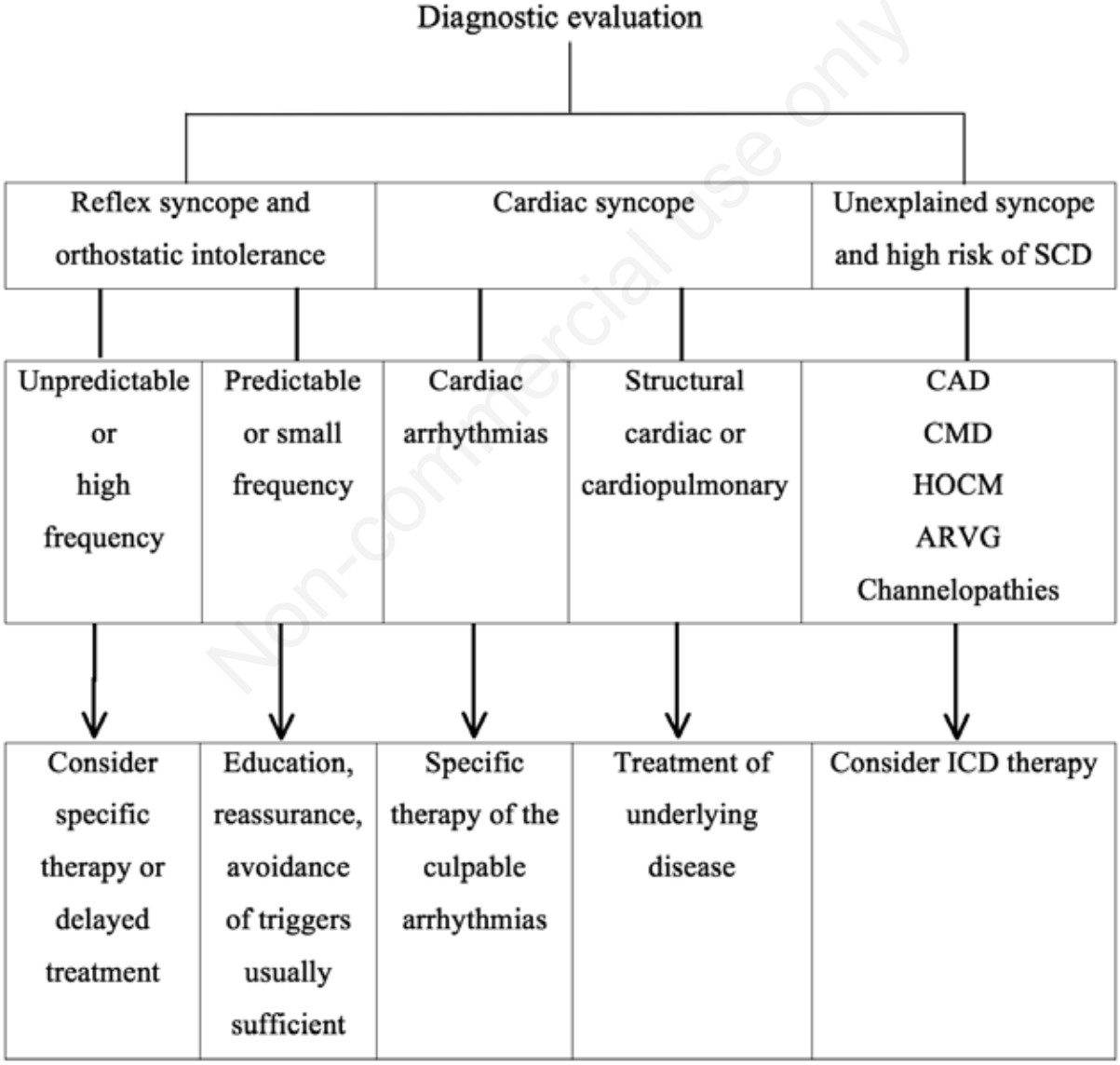

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Figure 2. Recommendation to treatment of syncope based on etiopathogenic definition. SCD, sudden cardiac death; CAD, coronary artery disease; CMD, dilated cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; ARVG, arrhythmogenic right ventricular cardiomyopathy; ICD, implantable cardioverter defibrillator. *Modified from The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC), 2009.*[2]

NYHA II); iii) ischemic heart disease and lack of comorbidities.[18]

On the other hand, cardiac resynchronization therapy and pacemaker is indicated in the presence of: i) advanced heart failure; ii) severe renal insufficiency or dialysis; iii) other major comorbidities; iv) frailty and cachexia.

Unexplained syncope in patients with high risk of sudden cardiac death

In patients at high risk of SCD it is required a specific treatment to reduce risk of mortality and of minacious events.[2] Unexplained syncope is a major risk factor for SCD in patients with hypertrophic cardiomyopathy; in these patients in whom symptoms can be caused by left ventricular outflow tract obstruction, treatment options include: negative inotropic drugs, surgical operation (septal myectomy), septal alcohol ablation and sequential AV pacing.[18] In particular sequential AV pacing with short AV interval may be considered in selected patients with left ventricular outflow tract obstruction and drug-refractory symptoms who have contraindications for septal alcohol ablation or septal myectomy (Class IIb Level B) or who are at high risk of developing heart block during septal alcohol ablation or septal myectomy (Class IIb, Level C). In conclusion for patients in whom there is an indication for ICD, a dual-chamber ICD should be considered.

The management of patient with syncope: rationale and objective

The main objective of this monograph is to define a methodological approach to the single symptom, raising awareness to the clinical management of the same in the different clinical presentations and/or in different patients, even by means of score of gravity.

The management of syncope: methodology

In order to provide evidence-based recommendations for the management of patients with syncope, we

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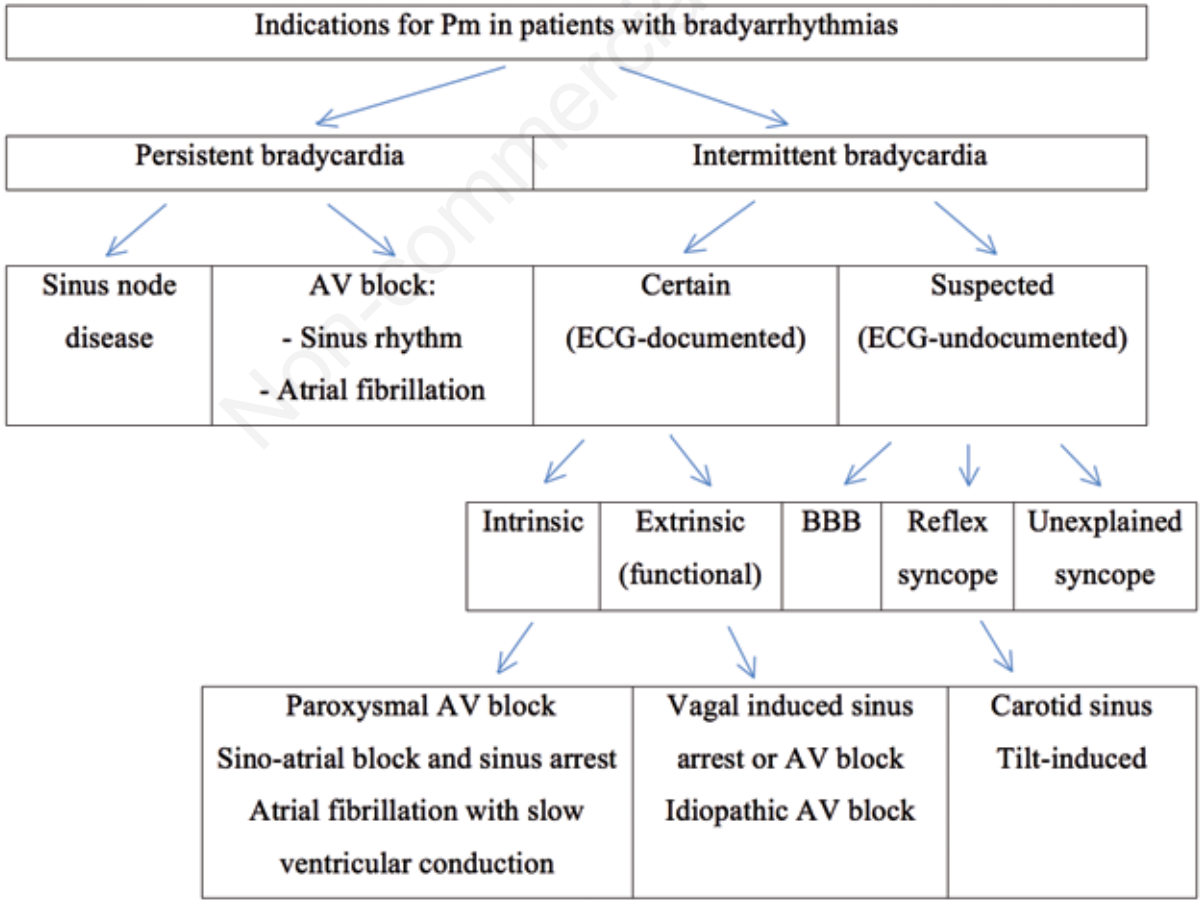

Figure 3. Classification of bradyarrhythmias based on the patient's clinical presentation. Pm, pacemaker; AV, atrioventricular; ECG, electrocardiogram; BBB, bundle branch block. *Modified from Brignole and Auricchio, 2013.*[18]

first verified the existence of guidelines on the topic. A systematic review of syncope-focused guidelines was performed accessing Medline via PubMed and the following guidelines-focused databases:

- Scottish Intercollegiate Guidelines Network (SIGN);
- Institute for Clinical Systems Improvement (ICSI);
- National Institute for Health and Care Excellence (NICE) (NHS evidence);
- National Guideline Clearinghouse; Canadian Medical Association, CMA Infobase;
- New Zealand Guidelines Group;
- National System Guidelines;
- Clinical Practice Guidelines Portal;
- eGuidelines.

The research was carried out by twelve authors independently, using the term *syncope* as key-word when the site included the search function, and in other cases we listed the last guidelines manually stored in the database or made reference to *cardiovascular*, from 2006 until 2013. The Medline literature strategy is available upon request. The inclusion process involved a two-step phase and a quality assessment. The results obtained separately were compared and discussed together subsequently.

Then obtained guidelines were evaluated using the AGREE instrument (Appraisal of Guidelines, Research and Evaluation II)[32] by 11 authors independently, in order to identify the guidelines qualitatively better. AGREE II assesses compliance with 23 requirements, meeting 6 domains as the explanation of the purpose, the clarity, the involvement of all stakeholders, the rigor of development, applicability and editorial independence of the same. Each author assessed the compliance of individual requirements with a score from 1 (disagree completely) to 7 (complete agreement). The scores assigned by each author were added within individual domains and reported with the highest and the lowest possible score within the domain based on the included requirements' and evaluators' number.

In order to update the evidence given by the guidelines, an author conducted a *post hoc* search of the available evidence in literature from 2009 to 2014 in order to obtain an elaborate updated carried out. He considered randomized controlled trials, meta-analyses and reviews, excluding case reports and case series.

In our post-hoc evaluation, given the vastness of the subject, we schematically divided randomized controlled clinical trials, meta-analyses and reviews analyzed in six different topics which are shown below: i) classification of syncope according to the action's mechanism; ii) use of diagnostic and therapeutic dedicated to syncope software with algorithms to address the work up of syncope to be used in ED; iii) novelties in the physiology of neurogenic syncope; iv) assessment of carotid sinus syndrome; v) signs of pacemaker implant according to 2013 guidelines; vi) pharmacological treatment.

The management of syncope: results

Through the databases, we identified and selected 8 guidelines for evaluation.

The overall quality of selected guidelines was assessed by 11 authors using the AGREE instrument II. The evaluation results are shown in Table 4.[1,2,4,18,33-37]

The *Guidelines for the diagnosis and management of syncope (version 2009) - The Task Force for the diagnosis and Management of Syncope of the European Society of Cardiology* (ESC)[2] was the one which has been assessed by us; it had the greatest overall score, so it was the reference guidelines for the preparation of this monograph. It was judged adoptable in 100% of cases by the group, but with modifications for an evaluator.

The 2006 *AHA/ACCF Scientific Statement on the Evaluation of Syncope*[33] was not considered to be adopted by the group; it had a very low evaluation in the third dimension (12.12%), which assessed the methodological rigor in scientific research evidence and in their assessment, and in the fifth (16.29%), which assessed their applicability.

The *Guidelines for the diagnosis and management of syncope (version 2009) the National Guidelines Clearinghouse*[4] was also judged adoptable in 100% of cases by the group, but with changes for three evaluators. It reached high score percentages especially for the first dimension (90.91%), the third (82%) and the fourth (86.36%); it showed a clear expression of goals and motivations, very good methodological rigor and application.

The 2012 Guideline *Standardized Reporting Guidelines for Emergency Department Syncope Risk Stratification Research*[34] was judged not to beeasily applicable in clinical practice.

The 2012 guideline *New Concepts in the Assessment of Syncope* by Brignole and Hamdan,[35] was evaluated non-adoptable in 55% of the evaluators. In detail the guideline in question had low scores in all dimensions.

The guideline *Transient loss of consciousness (blackouts) in adults and young people*[1] of NICE was evaluated adoptable by all evaluators (in one case with amendments), except for one. This guideline scored high percentages in all sizes and was characterized by indulging in a particular manner the point of view of the patient who had experiences of T-LOC. In fact, the guideline emphasized that the treatment and care should take on the basis of needs and preferences of patients and that people who experienced T-LOC should be able to make informed

decisions about their care and treatment with their health operators. It showed particular attention to the need of good communication between health professionals and patients, especially when it was referred to people with physical, sensory or learning disabilities.

The guideline *Standardized Approaches to the Investigation of Syncope* of Canadian Cardiovascular Society Position Paper of 2011[36] was evaluated unadoptable by 8/11 evaluators and adoptable only with modifications by the other three. The guideline scored low score percentages in all dimensions (< or around 50%), except for the first dimension where it reached 66.7%.

The guideline *The Emergency Department approach to Syncope: Evidence - based Guidelines and*

Table 4. Summary of the scores of evaluators selected on the syncope guidelines for the different sizes according to the AGREE instrument II.

Guidelines	Dimension 1 Goals and motivations Total score and percentage	Dimension 2 Stakeholder involvement Total score and percentage	Dimension 3 Methodological rigor Total score and percentage	Dimension 4 Clarity in the exposition Total score and percentage	Dimension 5 Applicability Total score and percentage	Dimension 6 Editorial independence Total score and percentage	Overall (adoptable or not) Total score and percentage
AHA/ACCF Scientific Statement on the Evaluation of Syncope, 2006 *(American College of Cardiology Foundation)*[33]	88/198 44.44%	80/198 40.40%	64/528 12.12%	68/198 34.34%	43/264 16.29%	117/132 88.63%	Unadoptable in 91% of cases (only in one case adoptable with modifications)
Guidelines for the diagnosis and management of syncope (version 2009) *(ESC)*[2]	191/198 96.16%	147/198 74.24%	415/528 78.60%	195/198 98.5%	207/264 78.41%	119/132 90.15%	Adoptable in all cases (only in one case with modifications)
Guidelines for the diagnosis and management of syncope (version 2009) *(National Guidelines Clearinghouse)*[4]	180/198 90.91%	123/198 62.12%	433/528 82%	171/198 86.36%	187/264 70.83%	107/132 75.76%	Adoptable in all cases (in 3 case with modifications)
Standardized Reporting Guidelines for Emergency Department Syncope Risk Stratification Research (*NIH Public Access; Acad Emerg Med 2013)*[34]	126/198 63.64%	123/198 62.12%	325/528 61.55%	130/198 65.56%	96/264 36.36%	107/132 81.06%	Adoptable with modifications in 8/11, unadoptable in 3/11 cases
New Concepts in the Assessment of Syncope *(Brignole M, Hamda MH, J Am Coll Cardiol 2012; 1583-91)*[35]	90/198 45.45%	68/198 34.34%	124/528 23.48%	89/198 44.94%	117/264 44.32%	35/132 26.52%	Adoptable with modifications in 5/11, unadoptable in 6/11 cases
Transient loss of consciousness (blackouts) in adults and young people *(NICE)*[1]	187/198 94.4%	180/198 90.9%	441/528 83.5%	187/198 94.4%	226/264 85.60%	86/132 65.15%	Adoptable in 10/11 cases (only in one case adoptable with modifications)
The Emergency Department Approach to Syncope: Evidence-based Guidelines and Prediction Rules *(Kessler C, Tristano JM, De Lorenzo R, 2010)*[37]	178/198 89.80%	150/198 75.76%	253/528 47.9%	110/198 55.55%	82/264 31.06%	14/132 10.60%	Unadoptable in 7/11, adoptable in 4 (3 with modifications)
The 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy *[The Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC) in collaboration with the European Heart Rhythm Association (EHRA)]*[18]	153/198 77.27%	133/198 67.17%	358/528 67.80%	182/198 91.92%	189/264 71.59%	124/132 93.93%	Adoptable in 10/11 (in 6 with modifications)

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Prediction Rules[37] of 2010 was assessed unadoptable by 7/11. The guideline achieved varying percentages score in various sizes: very high in the first (89.80%) and very low in the fifth and especially in the sixth dimension (10.60%).

The 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy[18] was evaluated adoptable by evaluators 10/11, albeit with changes in six cases; unadoptable in a single case. The guideline showed high percentage scores in the fourth and sixth dimension: respectively 91.92% and 93.93%; too high the feedback obtained in the other dimensions, at around 70%.

Conclusions

Understanding the pathophysiological cause of T-LOC is crucial for reducing patients' morbidity and mortality. An accurate initial assessment based both on clinical/imaging findings and on a careful collection of medical history appropriately selects eligible patients to further more specific diagnostic strategies.

This monograph highlights the importance of establishing: i) if a syncope really occurred; ii) if it is cardiogenic or not; iii) if it requires further evaluation; and iv) which patients would benefit from intensive monitoring and hospitalization (Figure 4).[38]

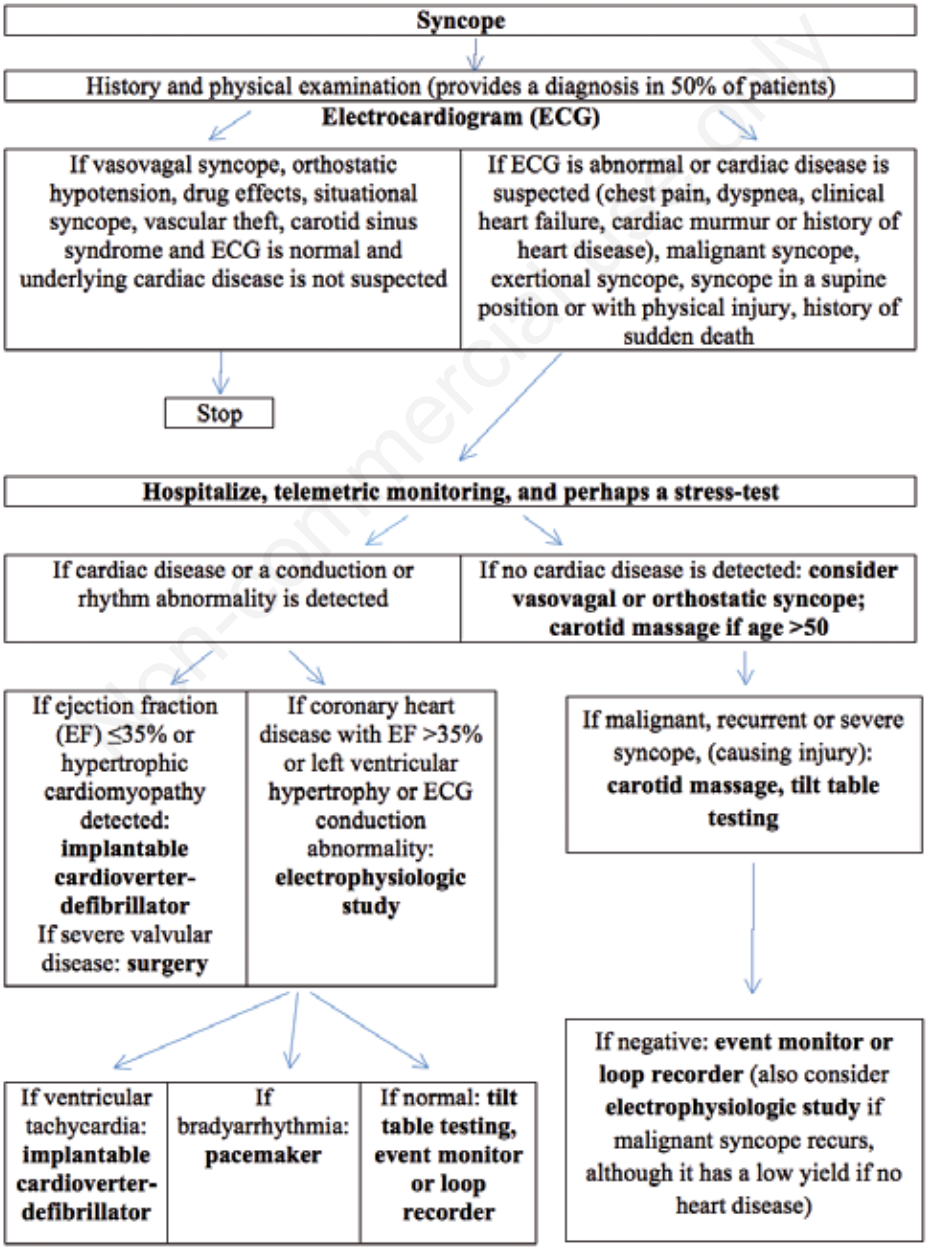

Figure 4. The management of syncope. *Modified from Hanna, 2014.*[38]

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