



Review

Syncope in adults: Systematic review and proposal of a diagnostic and therapeutic algorithm

Salvatore Rosanio ^{a,*}, Ernst R. Schwarz ^b, David L. Ware ^c, Antonio Vitarelli ^d^a University of North Texas Health Science Center (UNTHSC) Department of Internal Medicine, Division of Cardiology 855 Montgomery Street 76107 Fort Worth, TX, United States^b Cardiology Division, Cedars Sinai Medical Center, Los Angeles, CA, United States^c Cardiology Division, University of Texas Medical Branch, Galveston, TX, United States^d Cardio-Respiratory Department, La Sapienza University, Rome, Italy

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ABSTRACT

This review aims to provide a practical and up-to-date description on the relevance and classification of syncope in adults as well as a guidance on the optimal evaluation, management and treatment of this very common clinical and socioeconomic medical problem. We have summarized recent active research and emphasized the value for physicians to adhere current guidelines. A modern management of syncope should take into account 1) use of risk stratification algorithms and implementation of syncope management units to increase the diagnostic yield and reduce costs; 2) early implantable loop recorders rather than late in the evaluation of unexplained syncope; and 3) isometric physical counter-pressure maneuvers as first-line treatment for patients with neurally-mediated reflex syncope and prodromal symptoms.

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1. Introduction

Syncope is a transient loss of consciousness often unwitnessed and accompanied by loss of postural tone, with rapid onset and full and typically quick recovery. A brief and abrupt decrease in or cessation of global cerebral blood flow is the basic mechanism.

Syncope is known to affect quality-of-life, to cause physical injuries, be challenging to manage and can be a harbinger of sudden death.

We present a systematic review on its relevance, classification and evidence-based management strategies and therapeutic approaches. New aspects presented in current guidelines are covered and we also propose a practical diagnostic and therapeutic algorithm.

2. Relevance

Syncope has a considerable medical and socioeconomic burden on the adult population. Its prevalence rises with advancing years: from 6.2 per 1000 person-years in middle age to 11 per 1000 person-years in 70–79 year olds, and to 19 per 1000 person-years in those over 80 years [1–3]. The age-adjusted incidence rate among patients with structural heart disease is about twice that among subjects without (10.6 vs. 6.4 per 1000 patient-years). The overall mortality and morbidity associated with syncope is 7.5%, with one-year mortality of 18% to 33% for cardiac syncope, which is noticeably greater than syncope of unknown

origin and cerebrovascular syncope (less than 10%); whereas neurally-mediated reflex syncope is associated with the same mortality of comparably aged healthy individuals [1–3].

Syncope accounts for 1% of emergency department (ED) and urgent care clinic referrals; of these, ≈40% are hospitalized, resulting in excess of 200,000 hospital admissions annually in the U.S. [4–6]. The estimated costs for syncope-related hospitalizations in the year 2000 approached \$2.5 billion, with a mean cost of \$5400 per hospitalization [5]. The cost per-reliable diagnosis can be as high as \$78,000, depending on the tests performed and their diagnostic accuracy. The average syncope patient visits a physician 10 times per-year and sees an average of 3.2 specialists [6–8].

Recurrences are frequent after an initial syncopal episode and the number of them during life is the strongest predictor. Indeed, a history of 1 or 2 episodes predicted a recurrence rate of 15% and 20% after one and two years, respectively; whereas 3 episodes predicted a recurrence of 36% and 42%, respectively [9]. Conversely, gender, severity of presentation, and presence or absence of structural heart disease have poor predictive value [9]. Recurrences have a substantial impact on patients' quality-of-life. They may develop excessive fear of dying and have difficulty returning to previous level of activities. Up to 76% of patients will change activities of daily living, 64% will limit their driving, and 39% will change employment. The functional impairment matches that of chronic low back pain, rheumatoid arthritis, chronic obstructive lung disease and depressive disorders [10,11].

Physical injuries are frequent complications of syncope occurring in ≈30% of patients admitted to EDs, of whom 5% experience severe trauma causing 1) skull or major bone segments fracture; 2) intracranial hemorrhage; 3) internal organ lesions requiring urgent treatment;

* Corresponding author at: University of North Texas Health Science Center (UNTHSC) Department of Internal Medicine, Division of Cardiology 855 Montgomery Street 76107 Fort Worth, TX, United States. Tel.: +1 817 735 2072; fax: +1 817 735 2748.

E-mail address: Salvatore.Rosanio@unthsc.edu (S. Rosanio).

and 4) retrograde amnesia or focal neurological defect [6,12]. Approximately 10% of falls in the elderly are caused by syncope and the cost to treat them exceeds \$7 billion per-year in the U.S. [13,14].

3. Pathophysiological classification

Despite general elusiveness in the medical literature, syncope is and should be unquestionably classified on the origin of its pathophysiological mechanisms as shown in Table 1.

4. Neurally-mediated reflex syncopal syndromes

They refer to a diversity of clinical scenarios, generally described as vasovagal and situational, in which the triggers of abnormal neural reflexes are 1) fear of bodily injury; 2) painful or noxious stimuli; 3) venipuncture; 4) prolonged standing (e.g., soldiers fainting on parade); 5) heat exposure; 6) exertion; and 7) coughing, swallowing or straining while urinating or defecating. Patients frequently experience warmth, nausea, lightheadedness and pallor before syncope. However, they may not occasionally exhibit any symptom at all [15].

Three responses are generally seen: 1) cardioinhibitory; 2) vaso-depressor; and 3) mixed response with features of both. The former results from increased parasympathetic tone and may be manifested by any or all of the following ECG findings 1) sinus bradycardia; 2) PR interval prolongation; and 3) advanced atrioventricular block.

The vasodepressor-hypotensive response is caused by “hypersensitivity” of the autonomic nervous system, which over-responds to

different stimuli with orthostatic stress being one of the most common triggers seen in clinical practice.

Finally, reduced cardiopulmonary baroreceptor sensitivity may be a contributing factor for both cardioinhibitory and vasodepressor responses.

4.1. Carotid sinus syndrome

It is an unusual type of neurally-mediated syncope. It is due to hypersensitivity of the afferent or efferent limbs of the carotid sinus reflex arc resulting in vagal activation and/or sympathetic inhibition, which leads to bradycardia and/or vasodilation. It rarely occurs in adults under 50 years and increases in prevalence with advancing age and in close relationship with accidental mechanical manipulation of carotid sinuses and can be reproduced by carotid sinus massage [16]. The test is considered positive if symptoms are produced immediately after the massage in the presence of asystole > 3 s and/or a fall in systolic blood pressure ≥ 50 mm Hg [16].

5. Orthostatic syncope and associated autonomic disorders

Orthostatic syncope occurs when the autonomic sympathetic vasomotor system is incapacitated and fails to respond to challenges imposed by the upright position causing hypotension. As Andresen D. pointed out, it is diagnosed when there is documentation of orthostatic hypotension associated with total loss of consciousness [17]. An asymptomatic decrease in systolic blood pressure of ≥ 20 mm Hg and decrease in diastolic blood pressure ≥ 10 mm Hg within 3 min of standing, defined as classical orthostatic hypotension, should not be taken as evidence for a cause of syncope if the medical history is inconsistent with such a diagnosis [17,18].

Orthostatic syncope may be due to primary or secondary autonomic disturbances. Primary forms include 1) pure autonomic failure; 2) multiple system atrophy; and 3) parkinsonian dysautonomia. The former is characterized by autonomic system dysfunction alone, while multiple system atrophy is characterized by both autonomic and somatic nervous system involvement, and finally parkinsonian dysautonomia develops over time in patients with Parkinson's disease.

Among the secondary forms, alcohol, diabetes, and amyloidosis are common causes as well as volume depletion in which the autonomic nervous system is not itself unbalanced, but is unable of maintaining adequate blood pressure due to reduced circulating volume.

Orthostatic syncope might also occur due to the effects of many drugs, mainly in the elderly, such as anti-depressives, phenothiazines, diuretics, β - and α -adrenergic blockers, vasodilators and nitroglycerin.

6. Cardiac syncope

The most common causes are arrhythmias, such as 1) severe sinus bradycardia (<40 bpm) while awake; 2) sinoatrial block or sinus pause ≥ 3 s; 3) third-degree atrioventricular block; 4) intermittent atrioventricular block (i.e., high-grade, Mobitz type II or type I in elderly); 5) sustained ventricular tachycardia; and 6) supraventricular tachycardia.

Other causes include 1) long- and short-QT syndromes; 2) Brugada syndrome; 3) arrhythmogenic right ventricular dysplasia/cardiomyopathy; 4) malfunction of implantable pacing and defibrillator systems; and 5) drug-induced pro-arrhythmias. However, we recommend, especially in men with a history of unexplained syncope and/or a familial incidence of sudden death at a young age, to assess the presence of early repolarization on ECG, particularly a J-point elevation of ≥ 0.1 mV in ≥ 2 leads in either the inferior (II, III, aVF) or lateral (I, aVL, V₄₋₆) territory or both. Indeed, strong evidence from recent literature suggests a significant link between this ECG pattern and occurrence of syncope and sudden death due to life-threatening ventricular arrhythmias as well as a heritable basis in the general population [19–21].

Table 1
Pathophysiological classification of syncope.

Neurally-mediated reflex syncope
Vasovagal
Situational (e.g., coughing, swallowing or straining while urinating or defecating, excessive heat, pain, prolonged standing, exertion, venipuncture, fear of bodily injury)
Carotid sinus syndrome
Orthostatic syncope and associated autonomic disorders
Primary autonomic failure syndromes (e.g., pure autonomic failure, multiple system atrophy, Parkinsonian dysautonomia)
Secondary autonomic failure disturbances (e.g., alcohol, diabetes, amyloidosis, volume depletion)
Drugs (e.g., anti-depressives, phenothiazines, diuretics, β - and α -adrenergic blockers, vasodilators, nitroglycerin)
Cardiac syncope
Arrhythmias (e.g., sinus bradycardia <40 bpm while awake, sinoatrial block or pauses ≥ 3 s, third-degree or high-grade or Mobitz type II atrioventricular block, VT, SVT)
Genetic disorders (e.g., long- and short-QT syndromes, ARVD/C, HOCM, Brugada syndrome, ECG early repolarization in infero-lateral leads)
Pacemaker or ICD malfunction with cardiac pauses
Structural heart or cardiopulmonary diseases (e.g., aortic stenosis, ischemic and non-ischemic or dilated cardiomyopathies, HOCM, pulmonary embolus, pulmonary hypertension, atrial myxoma, pericardial tamponade, MI/ischemia, aortic dissection)
Drug-induced pro-arrhythmias (e.g., antiarrhythmics, antipsychotics, antidepressants, antihistamines, antiinfectives, gastrointestinal agents)
Cerebrovascular syncope
Migraines
Steal syndromes (e.g., subclavian artery steal syndrome)
Vertebrobasilar transient ischemic attacks
Non-syncopal attacks
Disorders with partial or complete loss of consciousness (e.g., epileptic seizures, metabolic disorders, intoxications)
Disorders without loss of consciousness (e.g., falls, psychogenic pseudosyncope, cataplexy)

VT, ventricular tachycardia; SVT, supraventricular tachycardia; ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; ICD, implantable cardioverter defibrillator; MI, myocardial infarction.

Both ischemic and non-ischemic or dilated cardiomyopathies are responsible for cardiac arrhythmic syncope. The risk of sudden death is considerably high when the left ventricular ejection fraction is $\leq 35\%$ [22].

Finally, structural heart or cardiopulmonary diseases that may lead to syncope due to poor cardiac output include 1) aortic stenosis; 2) hypertrophic obstructive cardiomyopathy; 3) atrial myxoma; 4) pulmonary embolus; 5) pulmonary hypertension; 6) pericardial tamponade; 7) myocardial infarction/ischemia; and 8) aortic dissection.

7. Cerebrovascular syncope

Causes are 1) migraines, in which the loss of consciousness can be due to either cerebral vascular spasm or vasovagal reflexes triggered by pain and/or nausea; 2) steal syndromes, in which syncope may occur when blood supply is rerouted from the brain to another organ (the most common example is the so-called “subclavian steal syndrome” caused by stenosis or occlusion of the proximal subclavian artery with retrograde filling of it via the vertebral artery and subsequent diversion of blood flow from the brain to the upper extremity of the affected side); and 3) vertebrobasilar transient ischemic attacks, which are usually accompanied by other posterior circulation symptoms, such as vertigo, paresis, ataxia and/or evidence of brainstem dysfunction (e.g., diplopia, dysphagia, dysarthria).

8. Non-syncope attacks

They are not the result of global cerebral hypoperfusion and are often misdiagnosed as syncope. They include situations without loss of consciousness, such as accidental falls and psychiatric disorders, and conditions with partial or complete loss of consciousness, such as intoxication and metabolic causes (e.g., hypoglycemia, hypoxia or hyperventilation with hypocapnia).

Psychogenic pseudosyncope is a group of psychiatric disorders such as conversion and factitious disorders or malingering. Usually the state of “pseudo-unconsciousness” lasts longer than true syncope and upon physical examination there is no gross neurological abnormality. Instead, cataplexy refers to the loss of muscle tone due to emotions, particularly laughter. The attacks look like syncope in which patients can't respond at all, although they are completely aware of the surroundings.

Seizures are primary electrical disturbances of brain function and suspected cause in ≈ 5 to 15% of patients presenting with apparent syncope [23–26]. They can mimic syncope, especially in patients with atypical seizures with no tonic-clonic activity. In contrast to many types of syncope, seizures are not generally related to definite circumstances or triggers. If the jerks are unilateral during the attack, seizure is more likely. If the jerks start before loss of consciousness, seizure is fairly likely. The post-ictal phase with the absence of complete recovery is a feature of seizure not present in syncope.

Epileptic seizures should be distinguished from convulsive syncope, which is usually the result of cardiac arrhythmias followed by seizure-like movements due to cerebral hypoperfusion. These episodes may be clinically impossible to discriminate from seizures. Of note, collaborative studies by neurologists and cardiologists using long-term ECG monitoring by implantable loop recorders (ILRs) found cardiac arrhythmias as cause of sudden unexplained death and seizure symptoms in $\approx 40\%$ of patients with an epilepsy diagnosis who were treatment-resistant or had atypical seizures [23–26]. Therefore, clinicians should consider a wary cardiac evaluation in addition to a full neurological assessment for these subjects.

9. Management

Although syncope is such an everyday clinical problem, its management remains disorganized and often marked by the undertaking of

costly and time consuming diagnostic tests, such as cardiac enzymes, prolonged inpatient telemetry monitoring, cardiac catheterization, electroencephalography, CT and MRI brain scans, carotid Doppler sonography and pulmonary scintigraphy [5–8].

An accurate appraisal is crucial for an effective treatment aimed at preventing recurrences, avoiding trauma and death. Discriminating true syncope from non-syncope attacks is the first challenge for physicians and influences the subsequent management strategy. From time to time it is not possible to assign a solo etiology to syncope. Comorbidities and interacting factors are common and may act together (e.g., diabetic neuropathy and drug-induced orthostatic hypotension; diuretics in older patients already vulnerable to orthostasis; myocardial ischemia in the setting of moderate aortic stenosis; and patients with structural cardiovascular disease might faint due to arrhythmias or overmedication). Therefore, the clinician should not too hurriedly believe an observed abnormality to be the only cause of syncope.

According to the 2009 guidelines by the European Society of Cardiology and 2011 recommendations by the National Institute for Health and Clinical Excellence in the UK, the initial evaluation of patients presenting with transient loss of consciousness consists of 1) taking a structured medical history investigating: a) circumstances just prior to the attack; b) onset of attack; c) attack itself, including input from witnesses; d) ending of attack; e) clinical background and comorbidities; 2) complete physical exam with orthostatic blood pressure measurements; 3) 12-lead standard ECG; 4) carotid sinus massage in patients over 50 years with recurrences and falls; 5) echocardiogram to find out whether structural heart disease is present or there is a suspicion of pulmonary hypertension; and 6) psychological/psychiatric consultation in patients with recurrences who have other somatic complaints, and when there are concerns about stress, anxiety and other mental disorders [27,28].

The steps depicted above will provide a diagnosis in 23–50% of patients without need for superfluous tests [29,30]. Only then should physicians consider further investigations for the cases that are categorized as having syncope of unknown origin (unexplained), making this a considerably large patient population.

10. Diagnostic tools: yield and indications

10.1. Holter monitoring

In current practice 24–48 h ECG monitoring via 3–12 surface electrodes is still the most common initial investigation in patients who present with syncope. However, since in the vast majority of patients symptoms do not recur during the monitoring period the overall diagnostic yield of Holter is low: 4% in 2612 patients with symptoms of syncope or near-syncope in a pooled analysis of Linzer et al. [31].

In large studies using Holter monitoring the correlation between arrhythmias and symptoms, including syncope, was less than 5% [32,33].

The only reason to consider this diagnostic test is when a patient has daily single or multiple episodes of loss of consciousness over a short period of time. In such a context, true negative findings by Holter may be very useful, for example, in confirming cases of psychogenic pseudosyncope.

10.2. Head-up tilt-table testing

It has been the diagnostic groundwork for reflex and unexplained syncope in the last two decades since its first description in 1986 by Kenny et al. [34]. Despite its broad acceptance as a diagnostic procedure, many questions concerning the precise pathophysiology of neurally-mediated syncope and the most optimal provocative agent during tilt testing remain unanswered.

Central to tilt-table testing is the concept that orthostatic stress contributes to venous pooling in the lower extremities, which provokes

syncope via von Bezold–Jarisch mechanisms [35]. However, neurally-mediated reflex syncope cannot only be provoked by increased sympathetic nerve tone due to stressful stimuli or by hypovolemia or orthostatism, but can also be initiated and/or exaggerated by an increased responsiveness of the central serotonergic neural system to afferent inputs [36]. This complexity may explain why different drugs, such as isoproterenol, adenosine, nitroglycerin, or clomipramine, acting at very different levels, can trigger a neurally-mediated reflex during tilt testing [37,38].

In the face of many studies published, there is still no unanimously accepted tilt testing protocol and many patients still remain undiagnosed. A divergence of opinion exists regarding the angle (45°, 60°, 75° or 90°), duration (20 to 45 min), type of drug challenge, and number of head-up phases. Additionally, patients' age and hydration status may affect test's outcome. Tilt testing doesn't always faithfully reproduce patients' symptoms and the hemodynamic responses are so variable and rarely based on evidence [37,38]. Notably, tilt testing has not been validated against “gold standard” populations, and diverse test protocols identify patients that don't have common characteristics. In fact, one of the most confusing findings is the large difference in the diagnostic yield of tilt testing ranging from 11% to 87%, and the pretest likelihood of a positive response may explicate this [37–39]. Thus, a large amount of syncope patients will have a negative tilt-table test underlining the shortcomings of its clinical value. Consistent with these findings, data obtained from ILRs in patients with recurrent neurally-mediated or unexplained syncope revealed that patients with or without a positive tilt testing response can have similar clinical features and outcome, suggesting they are clinically similar [40,41]. Regardless of tilt-table test response, these patients have analogous ECG findings during recurrent syncope. Hence, in both tilt-table test positive and negative patients, an asystolic syncope preceded by sinus bradycardia can be recorded, consistent with a neurally-mediated mechanism having a dominant cardioinhibitory reflex with prolonged pauses. These data confirm that the sensitivity of tilt testing is probably lower than expected and that its use for assessing the exact mechanism, and eventually for selecting therapy in patients with severe or recurrent syncopal episodes, has limitations [38].

10.3. Prolonged ECG monitoring

External loop recorders (ELRs) and ILRs have shown satisfactory diagnostic yield [9]. These devices are designed to correlate transient symptoms with ECG rhythms. They have a retrospective (loop) memory, which continuously records and deletes ECGs, an activation function that allows patients to activate ECG storage as result of symptoms, and finally, auto-activation features allowing capture of arrhythmic events without relying on patients' compliance or perception of symptoms. A randomized trial has shown cost-effective diagnostic superiority of ELR to Holter monitoring (22% for Holter vs. 56% for ELR, $P < 0.01$) [42].

Since patients must continuously wear external electrodes in order to activate the loop memory, they usually are not compliant for more than a few weeks and symptom–ECG correlation cannot be achieved when recurrences are infrequent. Consequently, ELRs are most fruitful in motivated patients with inter-symptom intervals of ≤ 4 weeks [9].

In contrast, current ILRs can record events and store-up to 49.5 min of ECG data over 3 years' battery life. Recently, remote automatic recording and wireless transmission of data detected by ILRs have become available, enhancing the diagnostic yield, limiting the risk of memory saturation due to the high number of false detections, and reducing the time to diagnosis [43,44]. A recent report has shown that in a consecutive cohort of 50 patients with unexplained syncope receiving a novel wireless ILR, which automatically transfer ECG data to a central monitoring center within minutes to hours virtually eliminating the possibility of data loss, a diagnosis (most commonly significant bradycardia) was made in 32% within a median time of

71 days from ILR implant, thus greatly facilitating the clinical decision making [44].

Two randomized controlled trials, RAST (Randomized Assessment of Syncope Trial) and EaSyAS (Eastbourne Syncope Assessment Study), between a primary ILR strategy versus conventional testing in unselected patients with recurrent unexplained syncope, demonstrated that ILR was twice as effective as ELR, tilt testing and electrophysiological (EP) study, with substantial cost/diagnosis benefits [45–47].

In RAST, the ILR monitoring strategy followed by conventional testing in patients with recurrent or a single episode of unexplained syncope with injury warranting cardiovascular investigation was associated with a diagnostic yield of 50% at a cost of $\$2937 \pm \579 per-patient and $\$5875 \pm \1159 per-diagnosis. Conventional testing followed by ILR was associated with a diagnostic yield of 47% at a significant greater cost of $\$3683 \pm \1490 per-patient and greater costs per-diagnosis ($\$7891 \pm \3193). The authors concluded that the cost per-diagnosis using ILRs was significantly less than the cost of conventional work-up ($\$5852$ vs. $\$8414$) despite higher initial costs ($\$2731$ vs. $\$1683$) [45,46].

By EaSyAS census, 33% of 103 patients in the ILR group had an ECG diagnosis (usually a form of bradyarrhythmias) compared to 4% of 98 subjects in the non-ILR group (hazard ratio 8.93, 95%CI 3.17–25.2, $P \leq 0.0001$). By the study follow-up date, post-randomization investigations and hospital days were both fewer for ILR patients, resulting in a saving of costs (£406 vs. £1210 [mean difference £809, 95%CI £123–£2770]). This overall cost difference of £809 was equivalent to 60% of the purchase price of the ILR device [47].

In addition, the multicenter observational International Study on Syncope of Uncertain Etiology-2 (ISSUE-2) prospectively investigated the efficacy of therapies based on ILR diagnosis of recurrent suspected neurally-mediated syncope [48]. Patients without structural heart disease were included in the study if they experienced ≥ 3 syncopal episodes over 2 years. Patients with orthostatic or carotid-sinus syncope were excluded. One-year recurrence rate among the 53 patients assigned to ILR-specific therapy (pacing [mostly], ICD or ablation) was 10% (burden of 0.07 ± 0.2 episodes per-patient/year) compared with 41% in patients who received education and reassurance, (0.83 ± 1.57 episodes per-patient/year; 80% relative risk [RR] reduction per-patient, $P = 0.002$, and 92% for burden, $P = 0.002$). One-year recurrence rates in patients who received pacemakers and in those with bradyarrhythmias but no pacing were 5% and 31%, respectively (90% RR reduction, $P = 0.002$). The investigators concluded that early ILR implant with therapy delayed until documentation of syncope is a safe and effective treatment for recurrent neurally-mediated syncope [48].

Recently, the PICTURE registry (Place of reveal In the Care pathway and Treatment of patients with Unexplained REcurrent syncope), the largest observational study to date to evaluate the value of ILRs in everyday diagnostic work-up for syncope of unknown origin, provided two important findings 1) large number of tests patients underwent before ILR implant (median of 13, range 9–20), as well as great diversity and number of physicians consulted (an average of 3 different specialists); and 2) high yield with ILRs, which guided the diagnosis in 78% of patients and provided useful information in another 6% [8].

Overall, all the above findings support current guidelines recommending that ILRs should be implanted early rather than late in the evaluation of patients with syncope of unknown origin [27,28].

10.4. Electrophysiological study

The expected yield from an EP study to determine the cause of syncope is variable, dependent upon anticipated abnormalities and patient risk factors [49]. Of note, nowadays in clinical practice only 2% of patients with unexplained syncope assessed by cardiologists undergo EP study and even fewer if they are evaluated by other specialists [27,50]. Nonetheless, this diagnostic test still can be helpful to ascertain the necessity for pacing therapy in syncope patients with no structural heart

disease but with ECG abnormalities, such as 1) asymptomatic sinus bradycardia in the absence of negatively chronotropic drugs; 2) second-degree atrioventricular block Mobitz type I; and 3) bifascicular block [either left bundle branch block or right bundle branch block with left anterior or posterior fascicular block]. The EP study protocol includes evaluation of sinus node function, measurement of atrioventricular intervals, progressive atrial pacing and intravenous administration of class Ic or Ia antiarrhythmic drugs. However, a negative EP study doesn't rule out an arrhythmic etiology of syncope as demonstrated by RAST, EaSyAS, and ISSUE trials [45–48,51,52]. Of note, in a subgroup of patients with bifascicular block, negative EP study and normal ejection fraction, enrolled in the ISSUE trial, paroxysmal atrioventricular block was recorded in up to 50% of those who had recurrent syncope [52]. Additionally, 25% of the patients showed asystolic pauses preceded by sinus bradycardia suggestive of neurally-mediated reflexes [52]. Moreover, Fujimura et al. demonstrated that in 21 patients who had documented intermittent atrioventricular block (n=13) or sinus pauses (n=8) causing syncope, but by the time of referral their cardiac rhythm had reverted to normal, the EP study showed poor sensitivity values [53]. It correctly identified only 3 of the patients with sinus pauses (sensitivity 37.5%) and only 2 of those with atrioventricular block (sensitivity 15.4%). On the contrary, other abnormalities (i.e., sinus node dysfunction and atrial flutter or atrial fibrillation causing hypotension) not known to have occurred spontaneously in these subjects were often induced during EP study [53]. In summary, a negative EP study in syncopal patients with normal ECG doesn't rule out transient bradyarrhythmias as cause of syncope and may seldom reveal rhythm disturbances that may wrongly be elected as the cause of syncope.

Finally, an EP study with premature ventricular stimulation still can be useful in syncope patients with structural heart disease without severely depressed left ventricular ejection fraction and established implantable cardioverter defibrillator (ICD) indications by current guidelines when the likelihood of ventricular tachyarrhythmias is high, such as in the presence of sustained palpitations, prolonged QRS duration (≥ 120 ms) and/or non-sustained ventricular tachycardia, and in whom a comprehensive evaluation and non-invasive diagnostic studies did not demonstrate a cause or lead to specific treatment [54–59].

As Telfer E.A. and Olshansky B. pointed out, the yield of EP study for sustained monomorphic ventricular tachycardia is higher in patients with ischemic cardiomyopathy and lower (but not zero) in those with non-ischemic or dilated cardiomyopathy [60]. The potential for inducible sustained monomorphic ventricular tachycardia cannot be dismissed in patients with non-ischemic or dilated cardiomyopathy. However, an EP study may be negative in a patient with dilated cardiomyopathy and unexplained syncope but the risk of death and recurrent syncope resulting from a ventricular arrhythmia can remain high [60].

11. Syncope of unknown origin: evidence-based algorithm

The published diagnostic yield of ILR, tilt testing and EP study along with the accumulation of data in the last two decades have led us, authors of the present article, to generate a diagnostic and therapeutic algorithmic tool approach for patients with unexplained syncope, representing our current practice at our Institutions (Fig. 1).

In patients with no structural heart disease, normal ECG and ejection fraction, we recommend no further investigations for those who have sustained a single episode and are not having syncope in high-risk settings (e.g., driving, machine operation, flying, competitive athletics, etc.); whereas, we advise ILR in subjects with ≥ 3 syncopal episodes over 2 years or if a single syncopal episode is associated with secondary trauma.

In patients with ECG abnormalities, as listed in the text, in whom the likelihood of bradyarrhythmias as cause of syncope is high, we

propose an EP study to determine the need for pacemaker therapy otherwise if the EP study is negative we recommend ILR implant.

An EP study is proposed in unexplained syncope patients with structural heart disease without severely depressed left ventricular function (ejection fraction $> 35\%$ and $< 55\%$), when the probability of ventricular tachyarrhythmias is high, such as in the presence of sustained palpitations, QRS ≥ 120 ms and/or non-sustained ventricular tachycardia. An ICD is recommended in those with inducible sustained monomorphic ventricular tachycardia; whereas ILR is considered in not-inducible patients to help define the nature of syncope.

In patients with supraventricular tachycardia, idiopathic ventricular tachycardia and Wolff–Parkinson–White syndrome, radiofrequency ablation is recommended.

In patients with unexplained syncope and high-risk genetic disorders for sudden death (e.g., hypertrophic obstructive cardiomyopathy, arrhythmogenic right ventricular dysplasia/cardiomyopathy, long-QT syndrome and Brugada syndrome with spontaneous type I ECG pattern) ICDs are usually implanted.

We also consider ICD therapy in subjects with syncope and ECG early repolarization in infero-lateral leads, once all ischemic and non-ischemic causes, including the high-risk genetic disorders listed above, have been ruled out.

Finally, in patients with cardiomyopathy and ejection fraction $\leq 35\%$ the evidence-based recommendation is ICD [61].

12. Risk stratification and syncope management unit

Of paramount importance is to know the prognosis in the light of data showing major differences in one-year prospective death rates between cardiac (24%) and non-cardiac syncope (4%) [1]. It is critical for ED and urgent care physicians to discriminate those patients at high- or intermediate risk who require immediate hospital care from the much larger portion that can be managed safely and at substantially lesser cost outside of hospital in the so-called “blackout” clinics [6,62].

A number of studies derived and validated risk classification systems and point scores for envisaging short- and long-term risk of death with high sensitivity and good specificity. For example, SEEDS (Syncope Evaluation in the Emergency Department Study), OESIL (Osservatorio Epidemiologico sulla Sincope nel Lazio), SFSR (San Francisco Syncope Rule), STePs (Short Term Prognosis of Syncope), EGSYS (Evaluation of Guidelines in Syncope Study), and recently ROSE (Risk stratification Of Syncope in the Emergency department), each provide recommendations readily accessible to ED physicians or general practitioners [63–69].

Markers found by almost all these investigators that predict unfavorable outcomes include 1) age ≥ 65 years; 2) ECG abnormalities; 3) history of heart failure or ischemic heart disease or ventricular arrhythmias; 4) lack of warning symptoms/signs before syncope; and 5) B-type natriuretic peptide ≥ 300 pg/ml.

Moreover, SEEDS and EGSYS from U.S. and Europe, respectively, introduced the concept of dedicated syncope management units equipped with diagnostic tests for common causes of syncope and immediate consultations from electrophysiologists, cardiologists, neurologists or internists [63,68]. Both studies tested the hypothesis that prospective systematic standardized guidelines-based evaluation and management would provide more resourceful and effective triage of patients with syncope referred to general hospitals or EDs. The authors demonstrated that the vast majority of syncope management unit-managed patients had, when compared with those receiving usual care, significantly lower hospitalization rate, shorter length of hospital stay, and fewer diagnostic tests performed per-patient without negatively affect patients' survival and syncope recurrence rate. In addition, EGSYS showed that in the syncope management units the mean cost per-patient was 19% lower (€1127 vs. €1394) as well as the mean cost per-diagnosis, which was 29% lesser (€1240 vs. €1753) [68].

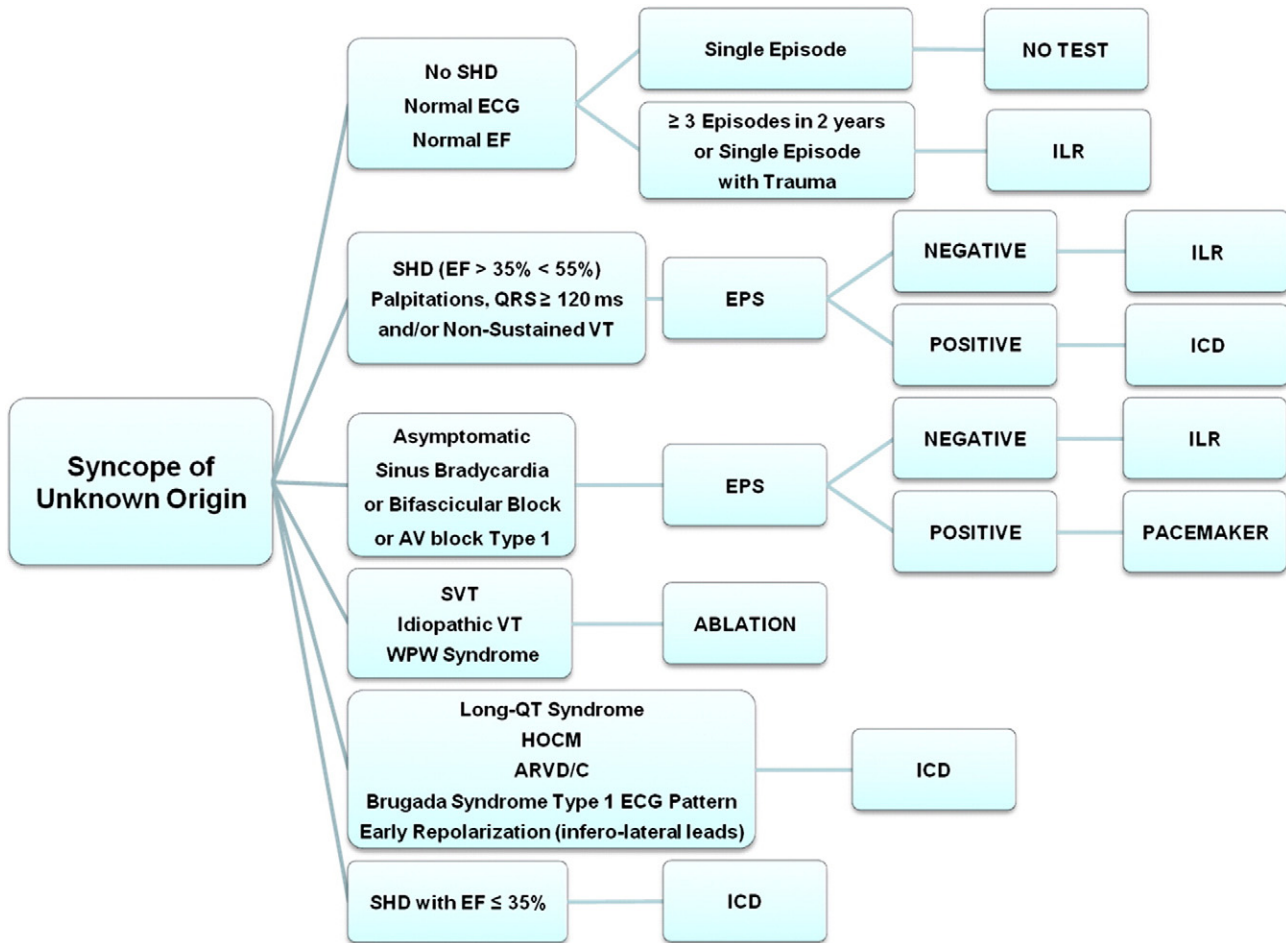


Fig. 1. An evidence-based algorithm for the management of syncope of unknown origin utilized at the authors' current Institutions. SHD, structural heart disease; EF, ejection fraction; ILR, implantable loop recorder; VT, ventricular tachycardia; EPS, electrophysiological study; ICD, implantable cardioverter-defibrillator; AV, atrioventricular; SVT, supraventricular tachycardia; WPW, Wolff–Parkinson–White; HOCM, hypertrophic obstructive cardiomyopathy, ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy.

Although, EGSYS and SEEDS data cannot be applied to the general population of patients with syncope, we predict that the concept of syncope management unit will continue to move forward with further evidence-based data to finally provide the best possible care for our patients.

13. Treatment

The therapeutic approaches for neurally-mediated reflex syncope and orthostatic intolerance/syncope are not uniform and for the most part based on case series, observational/cohort studies, or retrospective analyses. Their impact on preventing recurrences, limiting injuries, and improving quality-of-life is hard to determine without large randomized controlled trials.

The first strategy due the benign nature of these conditions includes reassurance and education concerning 1) nature of the disease; 2) prompt recognition of premonitory symptoms; and 3) prevention of triggering situations. Watchful use of agents that lower blood pressure, including β - and α -blockers, diuretics, vasodilators and alcohol is essential as well.

It is also noteworthy to recognize and treat psychological and/or psychiatric issues that might contribute to loss of consciousness vulnerability. Indeed, a high frequency of psychiatric disorders has been described in syncope patients [70].

14. Physical maneuvers and techniques

Prescription of non-pharmacological physical therapies is increasingly recommended and emerging as a new front-line treatment. Being aware of situations and warning symptoms preceding syncope can allow patients to take protective action, such as certain physical countermaneuvers (PCMs), which may avert loss of consciousness.

Squatting, arm-tensing, leg-crossing, and leg-crossing with lower body muscles tensing, which induce a significant blood pressure increase during the phase of imminent loss of consciousness, allow patients who are aware of prodromal symptoms to abort and/or delay syncope or improve orthostatic tolerance [71,72]. Recently, the Physical Counter-pressure maneuvers Trial tested the efficacy of isometric PCMs: 117 patients were randomized to conventional therapy alone and 106 received conventional therapy plus training in PCMs. The median yearly syncope burden during follow-up was significantly lower in the PCM-trained patients than controls (32% vs. 51%, $P < 0.004$). Recurrence-free survival was better with PCMs (39% relative risk reduction) [73]. Thus, isometric PCMs are recommended as class I by guidelines in recurrent neurally-mediated reflex syncope with warning symptoms.

Another approach that has been well studied is that of tilt or standing training. Nonrandomized observations demonstrated that progressively prolonged periods of forced upright posture reduce significantly syncope vulnerability in patients with recurrent vasovagal

symptoms triggered by orthostatic stress [74,75]. However, limitations of orthostatic training are 1) patients' low compliance to continue the training program for long periods even if this therapy is beneficial; and 2) durability of its effectiveness once treatment is discontinued [76]. In addition, randomized controlled trials didn't confirm tilt training's short term efficacy in reducing the positive response rate to tilt-table test [76–78]. Although more data are needed, tilt training appears to be a feasible treatment only for highly motivated patients, but not for the majority of those with recurrent neurally-mediated syncope.

15. Pharmacological therapy

A number of drugs have been and are still used in everyday practice for treatment and prevention of vasovagal and orthostatic syncope. Plasma volume expansion by increased salt and fluid intake is commonly advised, but this strategy has not been validated by clinical trials [79]. In this regard, a synthetic mineralocorticoid, fludrocortisone, is also widely prescribed in clinical practice, particularly in younger patients. However, its evidence-based efficacy is poor. Two small randomized trials, one in pediatric patients and the other in children, showed no benefit of this agent over atenolol or placebo, respectively, in preventing the recurrence of syncope [80,81]. Nevertheless, clinical experience still favors fludrocortisone, suggesting that additional evaluation of this approach remains warranted (the Prevention Of Syncope Trial II [POST-II] is currently ongoing to test fludrocortisone in a double-blind randomized controlled fashion) [82].

Among other prescription drugs proposed the most commonly used in the real world are β -blockers, selective serotonin reuptake inhibitors and α -agonist vasoconstrictors.

β -blockers have been supposed to decrease loss of consciousness susceptibility by diminishing the impact of the adrenergic surge and ventricular mechanoreceptor activation that commonly precedes and might be part of the trigger in reflex syncope [15,33]. Encouraging evidence is derived mainly from observational experiences and one small randomized trial [83–85]. However, POST, a large randomized placebo-controlled double-blind trial, showed no clear β -blocker benefit in terms of syncope recurrence prevention [86]. A total of 208 patients with a median of 9 syncopal spells over a median of 11 years were randomized, 108 to receive metoprolol and 100 to the placebo group. The likelihood of recurrent syncope was not significantly different between groups. Neither the age of the patient nor the need for isoproterenol to produce a positive tilt test predicted subsequent significant benefit from metoprolol [86].

Selective serotonin reuptake inhibitors have been thought to blunt an abnormal hypersensitive serotonin response in the central nervous system contributing to triggering neurally-mediated syncope. However, although paroxetine was shown to reduce syncope recurrence in 30 patients taking active medication compared with placebo, a next study demonstrated no benefit in preventing the vasovagal reaction associated with carotid sinus massage and/or lower body negative pressure in healthy volunteers [87,88].

Among the α -agonist vasoconstrictors, midodrine is recommended in patients with orthostatic hypotension and recurrent vasovagal syncope [27]. It constricts both arterial and venous beds, thus increases peripheral blood pressure, improves venous return and diminishes venous pooling. It showed positive results in three randomized controlled trials enrolling patients with very frequent reflex syncope mainly due to orthostatic intolerance [89–91]. Its major limitations are 1) frequent dosing, limiting long-term compliance; 2) hypertension; and 3) urinary retention or urgency in older men. Therefore, chronic treatment with midodrine may be of little use in neurally-mediated syncope. However, one dose of midodrine 1 h before to protracted standing or performing an activity that typically triggers syncope (pill in the pocket strategy), might be useful in selected patients in addition to lifestyle measures and physical therapies.

16. Cardiac pacing

With the exception of carotid-sinus syncope, for which early initiation of dual-chamber cardiac pacing is considered an essential part of the treatment [92,93], the role of pacemaker therapy for refractory neurally-mediated reflex syncope is controversial and not yet fully established.

Non-placebo randomized controlled trials, such as the North American Vasovagal Pacemaker Study (VPS), VASovagal Syncope International Study (VASIS) and SYNcope Diagnosis and Treatment study (SYDIT), showed a significant reduction in syncope recurrences with dual-chamber pacing [94–96]. However, placebo randomized controlled trials, such as VPS-II and vasovagal SYNcope and PACING (SYNPACE), in which all patients received dual-chamber pacemakers and randomly assigned to being “ON” (DDD mode) or “OFF” (ODO; sensing without pacing), could not reproduce this favorable outcome [97,98]. A recent meta-analysis suggested a non-significant 17% reduction in recurrences from the double-blinded studies, and an 84% reduction in the studies where the control group did not receive pacing [99]. Thus, VPS, VASIS and SYDIT have overestimated the efficacy of pacemaker therapy due to a lack of blinding of physicians and patients and, on the other hand, VPS-II and SYNPACE suggest that the apparent beneficial results are due to a strong expectation response to pacing [99]. Finally, the pre-implant patients' selection in these trials was based on a positive tilt-table test response, which has been clearly shown not to be predictive of spontaneous syncope [40,41]. As a result, the controversial results from these studies are not surprising if we consider that pacing is effective for the cardioinhibitory component of reflex syncope but has no effect on its vasodepressor component, which is often the dominant reflex. Cardiac pacing should be recommended only for patients with spontaneous symptomatic bradycardia and/or asystolic pauses detected during prolonged ECG monitoring as emerged from the results of the ISSUE-2 study (summarized in earlier text), which have given “birth” to the ISSUE-3. This large ongoing placebo-controlled randomized trial is testing the value of pacing in patients with reflex syncope and asystole documented by ILR [100].

17. Conclusions

The management and treatment of syncope in adults are in continuous growth. Much has been done in the last decade thanks to the efforts of professional medical societies. Our review has summarized evidence-based management strategies and therapeutic recommendations and emphasized the importance for physicians to adhere to current guidelines. A modern approach to syncope should take into account 1) use of risk stratification algorithms and implementation of syncope management units to increase the diagnostic yield and reduce costs; 2) early ILR implantation rather than late in the evaluation of syncope of unknown origin; and 3) isometric PCMs as first-line treatment for patients with neurally-mediated syncope and recognizable prodromal symptoms.

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References

- [1] Kapoor WN, Karpf M, Wienad S, Peterson JR, Levey GS. A prospective evaluation and follow-up of patients with syncope. *N Engl J Med* 1983;309:197–204.
- [2] Savage DD, Corwin L, McGee DL, Kannel WB, Wolf PA. Epidemiologic features of isolated syncope. *Stroke* 1985;16:626–9.
- [3] Soteriades ES, Evans JC, Larson MG, et al. Incidence and prognosis of syncope. *N Engl J Med* 2002;347:878–85.
- [4] Sarasin FP, Louis-Simonet M, Carballo D, et al. Prospective evaluation of patients with syncope: a population-based study. *Am J Med* 2001;111:177–84.

- [5] Sun BC, Emond JA, Camargo Jr CA, Sun BC, Emond JA, Camargo Jr CA. Direct medical costs of syncope-related hospitalizations in the United States. *Am J Cardiol* 2005;95:668–71.
- [6] Brignole M, Alboni P, Benditt DG, et al. Task Force on Syncope, European Society of Cardiology. Guidelines on management (diagnosis and treatment) of syncope—update 2004. *Europace* 2004;6:467–537.
- [7] Calkins H, Byrne M, el-Atassi R, Kalbfleisch S, Langberg JJ, Morady F. The economic burden of unrecognized vasodepressor syncope. *Am J Med* 1993;95:473–9.
- [8] Edvardsson N, Frykman V, van Mechelen R, et al. On behalf of the PICTURE study investigators. Use of an implantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry. *Europace* 2011;13:262–9.
- [9] Brignole M, Vardas P, Hoffman E, et al. Indications for the use of diagnostic implantable and external ECG loop recorders. *Europace* 2009;11:671–87.
- [10] Linzer M, Pontinen M, Gold DT, Divine GW, Felder A, Brooks WB. Impairment of physical and psychosocial function in recurrent syncope. *J Clin Epidemiol* 1991;44:1037–43.
- [11] van Dijk N, Sprangers M, Colman N, Boer K, Wieling W, Linzer M. Clinical factors associated with quality of life in patients with transient loss of consciousness. *J Cardiovasc Electrophysiol* 2006;17:998–1003.
- [12] Bartoletti A, Fabiani P, Bagnoli L, et al. Physical injuries caused by a transient loss of consciousness: main clinical characteristics of patients and diagnostic contribution of carotid sinus massage. *Eur Heart J* 2008;29:618–24.
- [13] Campbell AJ, Reinken J, Allan BC, Martinez GS. Falls in old age: a study of frequency and related clinical factors. *Age Ageing* 1981;110:264–70.
- [14] Davies AJ, Kenny RA. Falls presenting to the accident and emergency department: types of presentation and risk factor profile. *Age Ageing* 1996;25:362–6.
- [15] Grubb BP. Clinical practice: neurocardiogenic syncope. *N Engl J Med* 2005;352:1004–10.
- [16] Brignole M, Alboni P, Benditt D, et al. Task Force on Syncope, European Society of Cardiology. Guidelines on management (diagnosis and treatment) of syncope—update 2004. Executive summary. *Eur Heart J* 2004;25:2054–72.
- [17] Andresen D. Recording ambulatory blood pressure in the syncope and TLOC evaluation. In: Benditt DG, Brignole M, Wieling W, editors. *Syncope and transient loss of consciousness: multidisciplinary management*. Malden, MA: Blackwell Futura; 2007. p. 56–60.
- [18] Consensus statement on the definition of orthostatic hypotension pure autonomic failure, and multiple system atrophy. *J Neurol Sci* 1996;144:218–9.
- [19] Haissaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. *N Engl J Med* 2008;358:2016–23.
- [20] Tikkanen JT, Anttonen O, Juhani Juntila M, et al. Long-term outcome associated with early repolarization on electrocardiography. *N Engl J Med* 2009;361:2529–37.
- [21] Noseworthy PA, Tikkanen JT, Porthan K, et al. The early repolarization pattern in the general population. Clinical correlates and heritability. *J Am Coll Cardiol* 2011;57:2284–9.
- [22] Bardy GH, Lee KL, Mark DB, et al. For the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225–37.
- [23] Linzer M, Grubb B, Ho S, Ramakrishnan L, Bromfield E, Estes M. Cardiovascular causes of loss of consciousness in patients with presumed epilepsy: a cause of the increased sudden death rate in people with epilepsy? *Am J Med* 1994;96:146–54.
- [24] Zaidi A, Clough P, Cooper P, Scheepers B, Fitzpatrick A. Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. *J Am Coll Cardiol* 2000;36:181–4.
- [25] Rugg-Gunn FJ, Simister RJ, Squirrell M, Holdright DR, Duncan JS. Cardiac arrhythmias in focal epilepsy: a prospective long-term study. *Lancet* 2004;2212–9.
- [26] McKeon A, Vaughan C, Delanty N. Seizure versus syncope. *Lancet Neurol* 2006;5:171–80.
- [27] Moya AR, Sutton R, Ammirati F, et al. 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). *Eur Heart J* 2009;30:2631–71.
- [28] Cooper PN, Westby M, Pitcher DW, Bullock I. Synopsis of the national institute for health and clinical excellence guideline for management of transient loss of consciousness. *Ann Intern Med* 2011;155:543–9.
- [29] Crane SD. Risk stratification of patients with syncope in an accident and emergency department. *Emerg Med J* 2002;19:23–7.
- [30] Croci F, Brignole M, Alboni P, et al. The application of a standardized strategy of evaluation in patients with syncope referred to three syncope units. *Europace* 2002;4:351–6.
- [31] Linzer M, Yang EH, Estes NA, Wang P, Vorperian VR, Kapoor WN. Diagnosing syncope. Part 2: unexplained syncope. Clinical efficacy assessment project of the American College of Physician (see comments). *Ann Intern Med* 1997;127:76–86.
- [32] Clark PI, Glasser SP, Spoto Jr E. Arrhythmias detected by ambulatory monitoring: lack of correlation with symptoms of dizziness and syncope. *Chest* 1980;77:722–5.
- [33] Lacroix D, Dubuc M, Kus T, Savard P, Shenasa M, Nadeau R. Evaluation of arrhythmic causes of syncope: correlation between Holter monitoring, electrophysiologic testing, and body surface potential mapping. *Am Heart J* 1991;122:1346–54.
- [34] Kenny RA, Bayliss J, Ingram A, Sutton R. Head-up tilt: a useful test for investigating unexplained syncope. *Lancet* 1986;327:1352–5.
- [35] Mark AL. The Bezold–Jarisch reflex revisited: clinical implications of inhibitory reflexes originating in the heart. *J Am Coll Cardiol* 1983;1:90–102.
- [36] Flevari P, Leftheriotis D, Komborozos C, et al. Recurrent vasovagal syncope: comparison between clomipramine and nitroglycerin as drug challenges during head-up tilt testing. *Eur Heart J* 2009;30:2249–53.
- [37] Mittal S, Lerman BB. Tilt testing: on the road to obsolescence? *J Cardiovasc Electrophysiol* 2003;14:925–6.
- [38] Moya A. Tilt testing and neurally mediated syncope: too many protocols for one condition or specific protocols for different situations. *Eur Heart J* 2009;30:2174–6.
- [39] Kapoor W. Evaluation and management of the patient with syncope. *JAMA* 1992;268:2553–60.
- [40] Moya A, Brignole M, Menozzi C, et al. Mechanism of syncope in patients with isolated syncope and in patients with tilt-positive syncope. *Circulation* 2001;104:1261–7.
- [41] Dehara JC, Jeco C, Lanteaume A, Djiane P. An implantable loop recorder study of highly symptomatic vasovagal patients. *J Am Coll Cardiol* 2006;47:587–93.
- [42] Sivakumaran S, Krahn AD, Klein GJ, et al. A prospective randomized comparison of loop recorders versus Holter monitors in patients with syncope or presyncope. *Am J Med* 2003;115:1–5.
- [43] Furukawa T, Maggi R, Bertolone C, et al. Effectiveness of remote monitoring in the management of syncope and palpitations. *Europace* 2011;13:431–7.
- [44] Paruchuri V, Adhaduk M, Gankipati N, Steinberg JS, Mittal S. Clinical utility of a novel wireless implantable loop recorder in the evaluation of patients with unexplained syncope. *Heart Rhythm* 2011;8:858–63.
- [45] Krahn AD, Klein GY, Yee R, Skanes AC. Randomized assessment of syncope trial: conventional diagnostic testing versus a prolonged monitoring strategy. *Circulation* 2001;104:46–51.
- [46] Krahn AD, Klein GJ, Yee R, Hoch JS, Skanes AC. Cost implications of testing strategy in patients with syncope: randomized assessment of syncope trial. *J Am Coll Cardiol* 2003;42:495–501.
- [47] Farwell DJ, Freemantle N, Sulke AN. The clinical impact of implantable loop recorders in patients with syncope. *Eur Heart J* 2006;27:351–6.
- [48] Brignole M, Sutton R, Menozzi C, et al. International Study on Syncope of Uncertain Etiology 2 (ISSUE 2) Group. Lack of correlation between the responses to tilt testing and adenosine triphosphate test and the mechanism of spontaneous neurally-mediated syncope. *Eur Heart J* 2006;27:2232–9.
- [49] Klein GJ, Gersh BJ, Yee R. Electrophysiological testing: the court of final appeal for the diagnosis of syncope? *Circulation* 1995;92:1332–5.
- [50] Brignole M, Ungar A, Bartoletti A, et al. Evaluation of Guidelines in Syncope Study 2 (EGSYS-2) GROUP. Standardized-care pathway vs. usual management of syncope patients presenting as emergencies at general hospitals. *Europace* 2006;8:644–50.
- [51] Menozzi C, Brignole M, Garcia-Civera R, et al. International Study on Syncope of Uncertain Etiology (ISSUE) investigators. Mechanism of syncope in patients with heart disease and negative electrophysiologic test. *Circulation* 2002;105:2741–5.
- [52] Brignole M, Menozzi C, Moya A, et al. International Study on Syncope of Uncertain Etiology (ISSUE) investigators. Mechanism of syncope in patients with bundle branch block and negative electrophysiologic test. *Circulation* 2001;104:2045–50.
- [53] Fujimura O, Yee R, Klein GJ, Sharma AD, Boahene KA. The diagnostic sensitivity of electrophysiologic testing in patients with syncope caused by transient bradycardia. *N Engl J Med* 1989;332:1703–7.
- [54] Zecchin M, Di Lenarda A, Gregori D, et al. Are nonsustained ventricular tachycardias predictive of major arrhythmias in patients with dilated cardiomyopathy on optimal medical treatment? *Pacing Clin Electrophysiol* 2008;31:290–9.
- [55] de Sousa MR, Morillo CA, Rabelo FT, Nogueira Filho AM, Ribeiro ALP. Nonsustained ventricular tachycardia as a predictor of sudden cardiac death in patients with left ventricular dysfunction: a meta-analysis. *Eur J Heart Fail* 2008;10:1007–14.
- [56] Horwich T, Lee SJ, Saxon L. Usefulness of QRS prolongation in predicting risk of inducible monomorphic ventricular tachycardia in patients referred for electrophysiologic studies. *Am J Cardiol* 2003;92:804–9.
- [57] Stecker EC, Zargarian M, Dogra V, et al. Native QRS duration predicts the occurrence of arrhythmic events in ICD recipients. *Europace* 2006;8:859–62.
- [58] ACC/AHA/ESC Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death—executive summary. *Circulation* 2006;114:1088–132.
- [59] AHA/ACC scientific statement on the evaluation of syncope. *Circulation* 2006;113:316–27.
- [60] Telfer EA, Olshansky B. Use of electrophysiology studies in syncope: practical aspects for diagnosis and treatment. In: Grubb BP, Olshansky B, editors. *Syncope, mechanisms and management*. Second edition. Malden, MA: Blackwell Futura; 2005. p. 126–58.
- [61] ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. *J Am Coll Cardiol* 2008;51:1–62.
- [62] Petkar S, Bell W, Rice N, Iddon P, Cooper P, Fitzpatrick A. Rationale for a rapid access blackouts triage clinic. *Br J Cardiac Nursing* 2008;10:468–74.
- [63] Shen WK, Decker WW, Smars PA, et al. Syncope Evaluation in the Emergency Department Study (SEEDS): a multidisciplinary approach to syncope management. *Circulation* 2004;110:3636–45.
- [64] Colivicchi F, Ammirati F, Melina D, Guido V, Imperoli G, Santini M. 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;24:811–9.
- [65] Birnbaum A, Esses D, Bijur P, Wollowitz A, Gallagher EJ. Failure to validate the San Francisco Syncope Rule in an independent emergency department population. *Ann Emerg Med* 2008;52:151–9.

- [66] Quinn V, Stiell IG, McDermott DA, Sellers KL, Kohn MA, Wells GA. Derivation of the San Francisco Syncope Rule to predict patients with short-term serious outcomes. *Ann Emerg Med* 2004;43:224–32.
- [67] Costantino G, Perego F, Dipaola F, et al. Short- and long-term prognosis of syncope, risk factors, and role of hospital admission: results from the STePS (Short-Term Prognosis of Syncope) study. *J Am Coll Cardiol* 2008;51:276–83.
- [68] Del Rosso A, Ungar AR, Maggi R, et al. Clinical predictors of cardiac syncope at initial evaluation in patients referred urgently to a general hospital: the EGSYS score. *Heart* 2008;94:1620–6.
- [69] Reed MJ, Newby DE, Coull AJ, Prescott RJ, Jacques KG, Gray AJ. The ROSE (Risk stratification Of Syncope in the Emergency department) study. *J Am Coll Cardiol* 2010;55:713–21.
- [70] Pezawas T, Stix G, Kastner J, Schneider B, Wolz M, Schmidinger H. Implantable loop recorder in unexplained syncope: classification, mechanism, transient loss of consciousness and role of major depressive disorder in patients with and without structural heart disease. *Heart* 2008;94:e17.
- [71] Brignole M, Croci F, Menozzi C, et al. Isometric arm counter-pressure maneuvers to abort impending vasovagal syncope. *J Am Coll Cardiol* 2002;40:2053–9.
- [72] Krediet CT, van Dijk N, Linzer M, van Lieshout JJ, Wieling. Management of vasovagal syncope: controlling or aborting faints by leg crossing and muscle tensing. *Circulation* 2002;106:1684–9.
- [73] van Dijk N, Quartieri F, Blanc JJ, et al. PC-Trial investigators. Effectiveness of physical counterpressure maneuvers in preventing vasovagal syncope: the Physical Counterpressure Maneuvers Trial (PC-Trial). *J Am Coll Cardiol* 2006;48:1652–7.
- [74] Di Girolamo E, Di Iorio C, Leonzio L, Sabatini P, Barsotti A. Usefulness of a tilt training program for the prevention of refractory neurocardiogenic syncope in adolescents: a controlled study. *Circulation* 1999;100:1798–801.
- [75] Reybrouck T, Heidbuchel H, Van De Werf F, Ector H. Long-term follow-up results of tilt training therapy in patients with recurrent neurocardiogenic syncope. *Pacing Clin Electrophysiol* 2002;25:1441–6.
- [76] Gurevitz O, Barsheshet A, Bar-Lev D, et al. Tilt training: does it have a role in preventing vasovagal syncope? *Pacing Clin Electrophysiol* 2007;30:1499–505.
- [77] Foglia Manzillo G, Giada F, Gaggioli G, et al. Efficacy of tilt training in the treatment of neurally mediated syncope. A randomized study. *Europace* 2004;6:199–204.
- [78] Duygu H, Zoghi M, Turk U, et al. The role of tilt training in preventing syncope in patients with vasovagal syncope: a prospective and randomized study. *Pacing Clin Electrophysiol* 2008;31:592–6.
- [79] El-Sayed H, Hainsworth R. Salt supplement increases plasma volume and orthostatic tolerance in patients with unexplained syncope. *Heart* 1996;75:134–40.
- [80] Scott WA, Pongiglione G, Bromberg BI, et al. Randomized comparison of atenolol and fludrocortisone acetate in the treatment of pediatric neurally mediated syncope. *Am J Cardiol* 1995;76:400–2.
- [81] Salim MA, Di Sessa TG. Effectiveness of fludrocortisone and salt in preventing syncope recurrence in children: a double-blind, placebo-controlled, randomized trial. *J Am Coll Cardiol* 2005;45:484–8.
- [82] Raj SR, Rose S, Ritchie D, Sheldon RS. POST II Investigators The Second Prevention of Syncope Trial (POST II)—a randomized clinical trial of fludrocortisone for the prevention of neurally mediated syncope: rationale and study design. *Am Heart J* 2006;151:1186.e1–7.
- [83] Muller G, Deal BJ, Strasburger JF, Benson Jr DW. Usefulness of metoprolol for unexplained syncope and positive response to tilt testing in young persons. *Am J Cardiol* 1993;71:592–5.
- [84] Iskos D, Dutton J, Scheinman MM, Lurie KG. Usefulness of pindolol in neurocardiogenic syncope. *Am J Cardiol* 1998;82:1121–4.
- [85] Mahanonda N, Bhuripanyo K, Kangkagate C, et al. Randomized double-blind, placebo-controlled trial of oral atenolol in patients with unexplained syncope and positive upright tilt table test results. *Am Heart J* 1995;130:1250–3.
- [86] Sheldon R, Connolly S, Rose S, et al. Prevention of Syncope Trial (POST): a randomized, placebo-controlled study of metoprolol in the prevention of vasovagal syncope. *Circulation* 2006;113:1164–70.
- [87] Di Girolamo E, Di Iorio C, Leonzio L, Sabatini P, Ranalli G, Barsotti A. Effectiveness of paroxetine in the treatment of refractory vasovagal syncope in young patients. *G Ital Cardiol* 1999;29:1472–7.
- [88] Takata TS, Wasmund SL, Smith ML, et al. Serotonin reuptake inhibitor (Paxil) does not prevent the vasovagal reaction associated with carotid sinus massage and/or lower body negative pressure in healthy volunteers. *Circulation* 2002;106:1500–4.
- [89] Ward CR, Gray JC, Gilroy JJ, Kenny RA. Midodrine: a role in the management of neurocardiogenic syncope. *Heart* 1998;79:45–9.
- [90] Samniah N, Sakaguchi S, Lurie KG, Iskos D, Benditt DG. Efficacy and safety of midodrine hydrochloride in patients with refractory vasovagal syncope. *Am J Cardiol* 2001;88:80–3.
- [91] Perez-Lugones A, Schweikert R, Pavia S, et al. Usefulness of midodrine in patients with severely symptomatic neurocardiogenic syncope: a randomized control study. *J Cardiovasc Electrophysiol* 2001;12:935–8.
- [92] Brignole M, Menozzi C, Lolli G, Bottoni N, Gaggioli G. Long-term outcome of paced and non paced patients with severe carotid sinus syndrome. *Am J Cardiol* 1992;69:1039–43.
- [93] Claesson JE, Kristensson BE, Edvardsson N, Wahrborg P. Less syncope and milder symptoms in patients treated with pacing for induced cardioinhibitory carotid sinus syndrome: a randomized study. *Europace* 2007;9:932–6.
- [94] Connolly SJ, Sheldon R, Roberts RS, Gent M. The North American Vasovagal Pacemaker Study (VPS). A randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. *J Am Coll Cardiol* 1999;33:16–20.
- [95] Sutton R, Brignole M, Menozzi C, et al. Vasovagal Syncope International Study (VASIS) investigators dual-chamber pacing in the treatment of neurally mediated tilt-positive cardioinhibitory syncope: pacemaker versus no therapy. *Circulation* 2000;102:294–9.
- [96] Ammirati F, Colivicchi F, Santini M, et al. Permanent cardiac pacing versus medical treatment for the prevention of recurrent vasovagal syncope: a multicenter, randomized, controlled trial. *Circulation* 2001;104:52–7.
- [97] Connolly SJ, Sheldon R, Thorpe KE, et al. Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: Second Vasovagal Pacemaker Study (VPS-II): a randomized trial. *JAMA* 2003;289:2224–9.
- [98] Raviele A, Giada F, Menozzi C, et al. A randomized, double-blind, placebo-controlled study of permanent cardiac pacing for the treatment of recurrent tilt-induced vasovagal syncope. The vasovagal syncope and pacing trial (SYN-PACE). *Eur Heart J* 2004;25:1741–8.
- [99] Sud S, Massel D, Klein GJ, et al. The expectation effect and cardiac pacing for refractory vasovagal syncope. *Am J Med* 2007;120:54–62.
- [100] Brignole M. International study on syncope of uncertain aetiology 3 (ISSUE 3): pacemaker therapy for patients with asystolic neurally-mediated syncope: rationale and study design. *Europace* 2007;9:25–30.