

# Syncope update 2013: diagnosis and treatment

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## INTRODUCTION

Syncope is a common problem — it occurs in up to 40% of the general population at least once during a life-time [1]. It may be caused by a benign condition, but it may also be a sign of a serious, life-threatening illness. In recent years, significant progress in the management of syncope has been

made. The year 2001 was especially important because of the publication of the first European Society of Cardiology (ESC) guidelines [1]. Experts from both sides of the Atlantic Ocean met and discussed thoroughly all aspects of syncope diagnosis and treatment. This was not an easy task because, unlike with the other guidelines on specific illnesses, syncope is a symptom and not a disease itself. Therefore it requires a multidisciplinary approach and combining data obtained by various medical specialisms.

Since the first guidelines were published, two updates have been presented: the 2009 ESC guidelines are the most recent [2]. However, during the past three years, some important data have been published. The new topics which have been extensively discussed during the past few years include: (i) differential diagnosis of transient loss of consciousness (TLOC); (ii) risk stratification; (iii) diagnostic value of implantable loop recorders (ILR); (iv) role of pacing; and (v) systematic improvements in syncope evaluation such as establishing syncope units or the introduction of interactive decision-making software. This article will summarise the new data published in the past three years, and review some of the 2009 ESC guidelines recommendations.

## DIAGNOSTIC WORK-UP SCHEME

Syncope is one of the TLOC forms and is due to global cerebral hypoperfusion with spontaneous recovery. There are four principal causes of syncope: (1) reflex syncope including the commonest – vaso-vagal faint, followed by carotid sinus syndrome; (2) orthostatic hypotension; (3) due to cardiac arrhythmia; and (4) due to structural cardiac disease. This pathophysiological classification is simple, but it does not include information

about cardiac rhythm leading to syncope. Thanks to data derived from ILR, it is now possible to elucidate the mechanism of syncope and categorise it as being due to bradycardia, tachycardia or to no rhythm abnormalities (presumed hypotension). The latter classification may best serve for the introduction of a successful mechanism-specific therapy [3].

The diagnostic algorithm introduced by the most recent ESC guidelines stresses the value of distinguishing syncope from other causes of TLOC and the need for risk stratification. This algorithm, in a very simplified version, is presented in Figure 1. Careful history taking and other parts of initial evaluation could help to distinguish syncope from other causes of TLOC such as epilepsy, metabolic disorders or neurological abnormalities. It should be stressed that initial evaluation is the most important part of the diagnostic algorithm and includes history taking, physical examination, standard ECG and blood pressure measurements in supine and standing positions. In

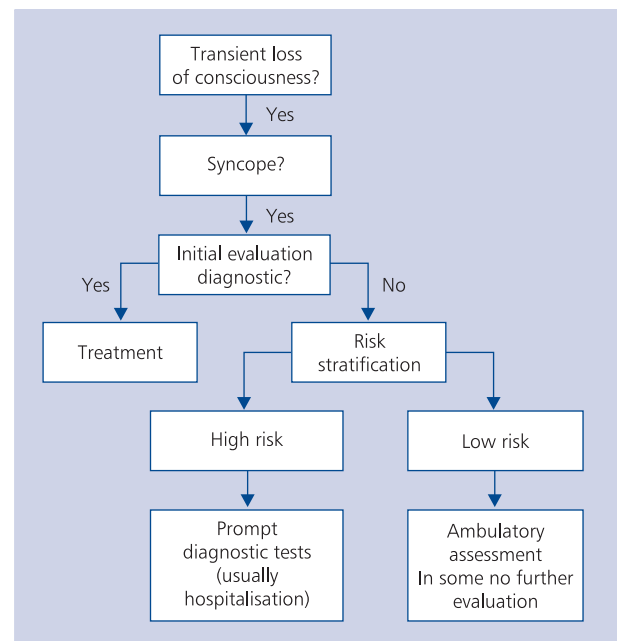


Figure 1. Simplified algorithm for syncope evaluation

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some subjects aged > 40 years carotid sinus massage should be also performed. After initial evaluation, most reflex syncope and orthostatic hypotension, as well as some cardiac causes, can be definitely diagnosed without the need for further testing.

Differentiation between syncope and other causes of TLOC can be difficult. The best example is epilepsy. It has been known for a long time that some patients with a diagnosis of epilepsy have in fact reflex syncope [4]. The differences in symptoms during TLOC in these two conditions may not be easy to appreciate by witnesses; even medical staff may interpret them incorrectly, resulting in misdiagnosis and improper treatment with anti-epileptic drugs in thousands of patients [5]. In order to distinguish syncope from seizures, Sheldon et al. [6] proposed a point score based on historical factors. This point score based on symptoms alone correctly classified 94% of patients, diagnosing seizures with 94% sensitivity and 94% specificity. The highest likelihood ratio for seizures had a cut tongue (16.46) followed by head turning (13.48) and unusual posturing (12.88).

Another attempt to distinguish syncope from seizures is ECG recording at the time of an attack. The most recent data comes from the REVISE study in which patients with a long-term treatment for misdiagnosed epilepsy received an ILR [7]. Cardiac rhythm abnormalities suggesting syncope rather than epilepsy were recorded at the time of TLOC in 67% of patients, including sinus arrest, atrio-ventricular block, tachycardia-bradycardia syndrome, and symptomatic sinus bradycardia. The authors concluded that approximately one in eight patients with syncope were misdiagnosed as having epilepsy. These findings are important also because these patients can be offered pacemaker implantation, which improves symptoms in a significant proportion of this population.

### RISK STRATIFICATION

When, after initial evaluation, the cause of syncope is unclear, risk stratification should be performed in order to avoid lengthy and ambulatory-based examinations in patients who are at risk of serious complications, including death. This is especially important because the peak of cardiovascular deaths is observed during the first month after presentation, whereas late adverse events are caused by associated cardiovascular diseases rather than by mechanisms of syncope [8]. Table 1 summarises some risk stratification scores. The OESIL [9] and EGSYS [10] scores serve to assess the risk of death and, in the case of the EGSYS score, also to predict syncope recurrence. These scores may be used in an emergency department, syncope unit, hospital ward or in an out-patient clinic. The Rose score [11] and San Francisco Syncope Rule [12] have been developed for emergency department usage and help decide whether a patient needs to be hospitalised and what is the short-term risk of serious events.

Recently, the performance of the OESIL score and the San Francisco Syncope Rule has been analysed in two systematic reviews [13, 14] which showed good sensitivity of these pre-

diction rules (ranging from 86% to 95%) and relatively poor specificity (ranging from 31% to 52%). Although the sensitivity looks good, still the adverse event rates in the low-risk groups range from 2% to 36% [13] and from 5% to 13% [14]. It seems that the weakest point is the assessment of ECG, especially when regarded as 'normal' in patients who subsequently developed a serious event due to cardiac arrhythmia (false negative classification). These findings show that prediction scores are useful, but that physicians should not solely rely on these rules and use other available information to assess the risk in individual patients. Further criticism of the prediction rules is presented by the official document of the Canadian Cardiovascular Society [15]. Although the authors listed several parameters which may be used for risk stratification (see Table 1) they state that "existing syncope decision rules do not increase diagnostic specificity or sensitivity, or reduce costs (weak recommendation, very low quality evidence)".

To summarise this issue, it is fair to say that although syncope prediction rules have several limitations which are inherent when simple risk scores are constructed, they are useful in everyday practice to estimate risk in patients with syncope.

### TESTS FOR REVEALING MECHANISM AND CAUSE OF SYNCOPE

#### *Tilt testing*

There have been no new important data published recently on tilt testing. There has been a steady move since the 1990s away from using tilt testing in almost everybody with obvious or suspected reflex syncope to patients with a problematic diagnosis, the elderly and patients with cardiovascular disorders and syncope. In patients with suspected reflex syncope, data from history and simple point scores can predict the results of tilt testing, thus obviating the need to perform the test [16]. Abnormal result of tilt testing predicts syncope recurrences in subjects with reflex syncope and no organic heart disease, whereas the prognostic role of the test in patients after myocardial infarction or with other cardiac disorders has not been well established [17].

The class I indications for tilt testing include: (i) unexplained single episode in high risk settings; (ii) recurrent episodes in the absence of organic heart disease; and (iii) in its presence when cardiac causes of syncope have been excluded; as well as (iv) when it is of clinical value to demonstrate susceptibility to reflex syncope to the patient. Tilt testing is not recommended for the assessment of efficacy of treatment (class III) [2].

The most frequent mechanism of syncope during positive tilt testing is mixed vasovagal reaction, followed by vasodepressive and cardioinhibitory mechanism [2]. In the latter form, profound bradycardia with asystole is the commonest finding, although atrio-ventricular block as well as junctional rhythm may also occur [18].

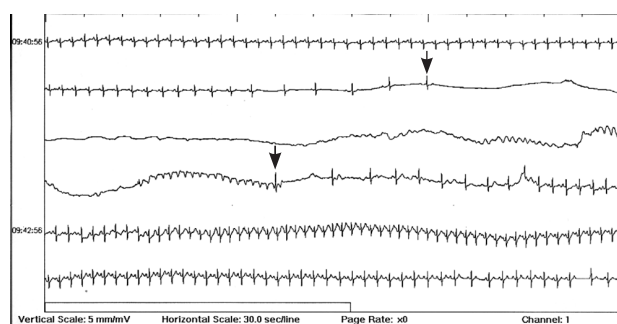
Tilt testing may be also a valuable tool for revealing vasovagal reaction or other reflexes as the cause of TLOC

**Table 1.** Some risk stratification scores which can be used in everyday practice

Score	Parameters	Points attributed	Assessed end-point	Predictive value
OESIL score [9]	Abnormal ECG	+1	1-year mortality	0 points: 0%
	History of cardiovascular disease	+1		1 point: 0.6%
	Syncope without prodromes	+1		2 points: 14%
	Age > 65 years	+1		3 points: 29%
				4 points: 53%
EGSYS score [10]	Palpitations before syncope	+4	2-year mortality	< 3 points: 2%
	Abnormal ECG or cardiac disease	+3		≥ 3 points: 21%
	Syncope during exercise	+3		
	Syncope in supine position	+2		
	'Autonomic' symptoms preceding syncope (e.g. nausea or vomiting)	-1		
	Typical triggering factors	-1		
ROSE score [11]	B-type natriuretic peptide ≥ 300 pg/mL	1 point each	Need for hospitalisation	If any parameter present — hospitalisation required
	Bradycardia ≤ 50/min			
	Per rectum — gastrointestinal haemorrhage			
	Anaemia — Hb ≤ 90 g/L			
	Chest pain associated with syncope			
	Q waves in ECG (except lead III)			
	O <sub>2</sub> saturation ≤ 94%			
San Francisco Syncope Rule [12]	History of congestive heart failure	1 point each	30-day serious events	Sensitivity: 98% Specificity: 56%
	Haematocrit < 30%	No risk: 0 points		
	Abnormal 12-lead ECG or ECG monitoring (new changes or non-sinus rhythm)	Risk: ≥ 1 points		
	History of shortness of breath			
	Systolic blood pressure < 90 mm Hg			
Canadian Cardiovascular Society Position Paper [15]	Major risk factors (7–31 day outcome):	Any item present	Urgent cardiac assessment mandatory	Not reported
	Abnormal ECG (bradyarrhythmia, tachyarrhythmia or conduction disease, new ischaemia or old infarct)			
	History of cardiac disease (ischaemic, arrhythmic, obstructive, valvular)			
	Systolic blood pressure < 90 mm Hg			
	Past or current heart failure			
	Minor risk factors (7–31 day outcome):		Urgent cardiac assessment indicated	
	Age > 60 years			
	Dyspnoea			
	Anaemia (haematocrit < 0.30)			
	Hypertension			
	Cerebrovascular disease			
	Family history of early (< 50 years) sudden death			
	Syncope while supine, during exercise or without prodromal symptoms			

in patients with other conditions such as misdiagnosed epilepsy, autonomic failure, postural orthostatic tachycardia syndrome, or chronic fatigue syndrome. An example

of original recording from tilt testing showing malignant vasovagal reaction in a patient with misdiagnosed seizures is presented in Figure 2.



**Figure 2.** Long (> 40 s) asystolic pause (start and end marked by arrows) during tilt testing in a patient with a long history of transient loss of consciousness and diagnosis of seizures not responding to antiepileptic drugs. Artifacts visible at the end of asystole are due to external cardiac massage performed by an attending physician. The patient was diagnosed with malignant vasovagal syndrome, received a pacemaker, and syncope never recurred, thus confirming that the previous diagnosis of epilepsy was incorrect. (Reproduced with permission from 'Medycyna Praktyczna', Krakow, 2012)

### **Carotid sinus massage**

This simple test is used to identify carotid sinus syndrome (CSS) as the cause of clinical syncope or carotid sinus hypersensitivity (CSH) when there is an asystole  $\geq 3$  s or/and fall in a systolic blood pressure  $\geq 50$  mm Hg, preferably associated with symptoms [2]. In spite of its simplicity, the test is severely underused in clinical practice [19]. From the practical point of view, it is worth remembering that the test should be performed both while supine and standing (increased sensitivity), the right carotid sinus should be pressed first, the massage should last for 5–10 s, and that continuous blood pressure monitoring is required in order not to miss a vasodilatory (hypotensive) type of CSS.

Recently, there has been a debate as to whether the above-mentioned cut-off criteria are not too liberal, resulting in overdiagnosis of CSS or CSH. In an excellent review on this topic, more strict criteria, of asystole  $\geq 6$  s and drop in the mean blood pressure  $\geq 60$  mm Hg lasting for  $\geq 6$  s, have been suggested [20]. These new cut-off values should be now tested in prospective studies. The prevalence of CSS increases with age, and some investigators advocate that the cut-off value of age to perform the test (class I indication) should be increased from 40 years to 50 or even 60 years [21].

### **Orthostatic stress**

The active standing test should be performed in all patients who have a history of syncope upon resuming the erect position. The test is diagnostic for orthostatic hypotension when during the first three minutes there is a drop in systolic blood pressure  $> 20$  mm Hg or to  $< 90$  mm Hg, or diastolic blood pressure drops  $> 10$  mm Hg compared to the baseline values. These criteria are diagnostic when symptoms are

reproduced (class I), and should be regarded as diagnostic when there are no accompanying symptoms (class IIa) [2].

### **Standard 12-lead ECG**

Abnormal ECG suggests a cardiac cause of syncope. The list of ECG abnormalities is presented in the ESC guidelines [2]. What has slightly changed during the past three years is increased awareness of early repolarisation as a cause of premature unexpected familiar sudden death. Thus, a J point elevation of  $> 0.1$  mV in  $\geq 2$  inferior or lateral leads in a patient with a history of syncope or malignant family history warrants further investigation since it may herald arrhythmic syncope and the risk of ventricular fibrillation. Recent data suggest that the most important ECG features are slurring or notching of the J wave in the presence of horizontal or descending ST segment elevation [22].

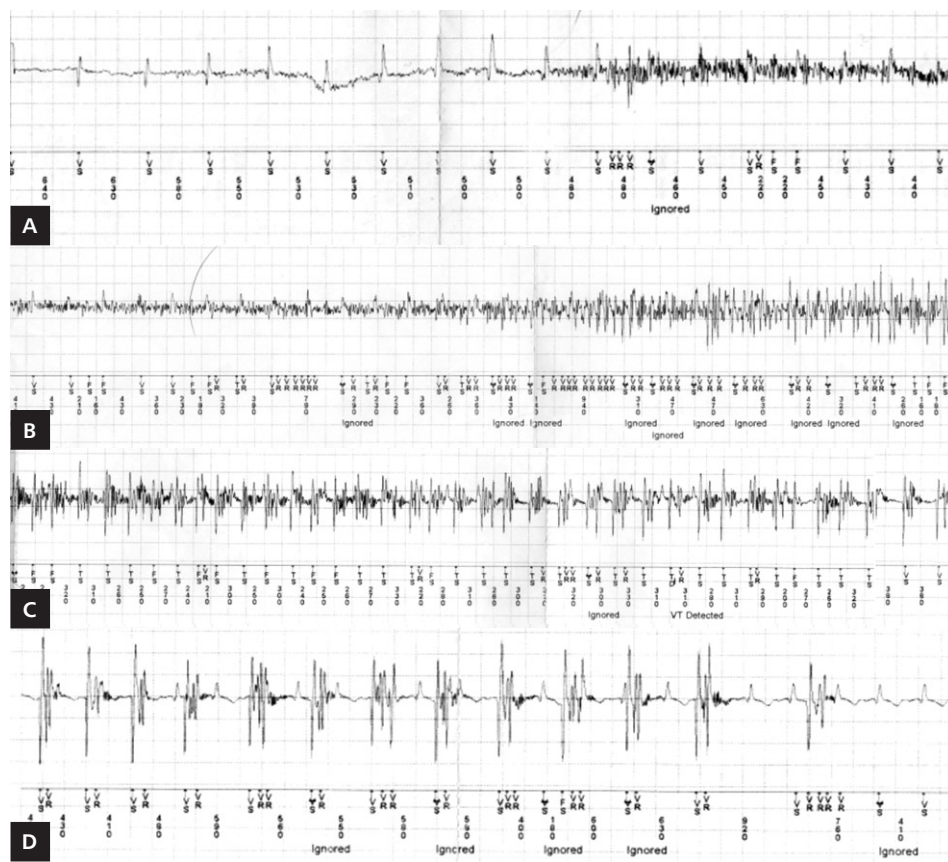
### **Prolonged ECG monitoring**

Standard 24-hour Holter ECG monitoring is usually not very helpful in establishing the cause of syncope, because in the vast majority of patients symptoms are infrequent and there is only a little chance (1–4%) that syncope will occur during monitoring [2]. Therefore, the ESC guidelines [2] advocate the use of 24-hour ECG monitoring in those who have at least one syncope per week, whereas the US guidelines are stricter and recommend Holter ECG only when syncope occurs daily [23]. In spite of these recommendations, Holter ECG remains the most overused diagnostic tool in syncope evaluation [19].

External loop recorders are recommended when syncope occurs at least once per month since the average period when a patient is compliant with the device is four weeks [2].

ECG telemetry is another tool to disclose the mechanism of syncope. It is especially useful in emergency departments while a patient with syncope is evaluated, and also in hospitals when a patient is admitted due to syncope of unknown origin. It has been shown that the optimal period of in-hospital ECG telemetry is three days. It is particularly useful in the elderly with heart failure, and the diagnostic recording can be obtained in as many as 30% of patients, with bradyarrhythmia being responsible for syncope in 63% of subjects and tachyarrhythmia in the remaining 37% [24].

Implantable loop recorders are the best tools for prolonged cardiac rhythm monitoring. These devices can record and store up to 42 (Reveal XT, Medtronic) or 48 (Confirm DJ, St. Jude) minutes of ECG over three years of battery life. The implantation procedure may be performed on an out-patient basis, is only minimally invasive, and its side effects (infection being the commonest) are very rare. According to the 2009 ESC guidelines [2], ILR are indicated: (i) in an early phase of evaluation in patients with recurrent syncope of uncertain origin, absence of high risk of serious events, and a high likelihood of recurrence within battery longevity of the device (class I, level B); (ii) high risk patients in whom evaluation did not demonstrate a cause of syncope or lead to a specific



**Figure 3.** An implantable loop recorder recording from a patient with ‘convulsive syncope’ at the time of transient loss of consciousness (TLOC). Normal sinus rhythm and artifacts due to tonic-clonic movements are seen, suggesting epilepsy as the cause of TLOC. Further evaluation confirmed epilepsy as the cause of TLOC; **A.** Recording at the onset of TLOC shows sinus rhythm (sinus tachycardia) and continuous muscle artifacts (**B, C**), suggesting tonus. Discrete muscle artifacts of clonus are seen in panel **C** and when they slow down (**D**), QRS complexes become visible again

treatment (i.e. cardioverter-defibrillator implantation) (class I, level B); and (iii) to assess the contribution of bradycardia before pacemaker implantation in patients with suspected or certain reflex syncope presenting frequent or traumatic syncopal episodes (class IIa, level B). The diagnostic yield of ILR is variable depending on the examined population, ranging from 33% in the wider patient cohort to 88% in patients with a high probability of arrhythmic syncope [2].

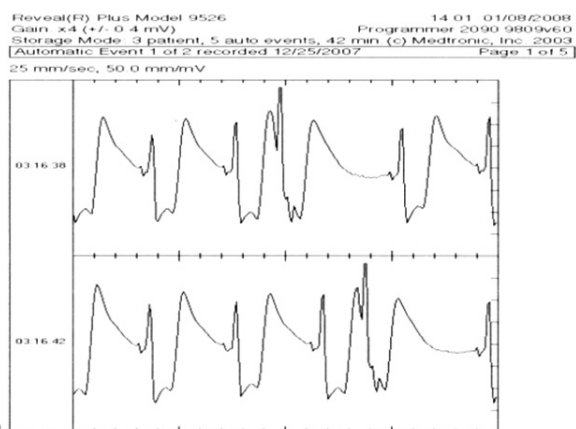
During the last three years, new data has been published which has further substantiated the role of ILR in syncope evaluation. The REVISE study (mentioned earlier in this article) showed the usefulness of ILR in detecting arrhythmic syncope in patients with a false diagnosis of epilepsy [7]. On the other hand, ILR may also disclose characteristic artifacts due to tonic-clonic movements during TLOC and normal cardiac rhythm, strongly suggesting epilepsy as the cause of TLOC. One such example of ILR recordings from our institution is presented in Figure 3.

Apart from tachy- or bradyarrhythmia, ILR may disclose other, often unexpected, causes of syncope such as marked myocardial ischaemia causing hypotension and TLOC (Fig. 4).

It has been also shown that extended ILR use gives additional diagnostic value in patients with unexplained syncope. In one study, the estimated cumulative diagnostic rates were 30%, 43%, 52% and 80% at one, two, three and four years, respectively [25]. Thus, when after three years, the end of battery life of ILR is encountered and no syncope occurred during this period, a patient should be implanted with another ILR rather than being withdrawn from further long-term ECG monitoring.

The most recent data on the everyday clinical usage of ILR comes from the prospective PICTURE registry [26]. ILR were implanted in 570 patients and the mean follow-up duration was  $10 \pm 6$  months. The registry showed that before ILR implantation, patients underwent a large number of diagnostic tests (median 13, range 9–20) which were inconclusive. This shows that ILR should be implanted early rather later in the evaluation of unexplained syncope. The registry confirmed the high diagnostic yield of ILR — 78%, of which three quarters were cardiac syncope.

Another important advantage of ILR is the possibility of remote monitoring and downloading ECG data using existing transtelephonic systems. This obviates the need for outpatient



**Figure 4.** An implantable loop recorder recording during syncope in a 43 year-old female with recurrent transient loss of consciousness. The tracings show acute myocardial ischaemia with marked ST segment depression due to ischaemic heart disease and coronary spasm which appeared to be the cause of profound hypotension and syncope. Following coronary revascularisation, syncope did not recur

visits and manual memory download, speeds up the diagnostic process, and enhances the diagnostic yield of ILR by limiting the risk of memory saturation due to the high number of false detections (mainly artifacts). Two studies found that remote monitoring is feasible and reduces physician overread time [27, 28]. Also, a recent study confirmed the cost-effectiveness of ILR in patients with suspected arrhythmic or unexplained syncope [29].

In spite of all its advantages, ILR is severely underused in clinical practice [19]. A recent study showed that the number of patients with guidelines-based indications for ILR was four times higher than the number of patients who actually received the device. On the other hand, in approximately a quarter of those who received ILR, there was no clear indication for ILR insertion [30]. Thus, there is still a need to disseminate the guidelines and improve everyday clinical practice. Another potential cause of ILR underuse is inappropriate, or even the complete absence of, reimbursement for this procedure in some countries.

There are a few limitations of ILR. First, although minor, it is an invasive procedure and not all patients can accept it. Second, there are reports showing a significant proportion of artifacts, amounting to 20% of all recorded episodes, although this was shown for patients with atrial fibrillation [31]. Third, with current technology, ILR can only detect arrhythmic syncope; syncope due to other causes, such as hypotension, can only be suspected but not definitely proved.

#### **Other tests**

No new important data on the use of echocardiography, exercise testing, electrophysiological study or coronary angiography has been published in the past three years.

### **Genetic predisposition**

Some clinical studies have suggested a familial predisposition to reflex syncope. It has been suggested that it may be gender-dependent and that female gender independently of family history increases the risk of syncope [32].

Data in the literature on genetic predisposition to syncope are conflicting. Some authors were able to identify specific gene polymorphisms predisposing to tilt-induced vasovagal syncope [33], whereas others failed to document such an association [34]. Although the concept of genetic predisposition to reflex syncope is of potential clinical importance, it is currently premature to use any genetic test for screening purposes. Studies including large populations and examining various polymorphisms are required to confirm the role of genetic screening for reflex syncope. However, reflex syncope is multifactorial and it is unlikely that it is caused by a single gene mutation. Familial history of syncope does not necessarily mean that there is a genetic predisposition; it may be also due to the high prevalence of this condition itself, or to environmental factors.

### **TREATMENT**

#### **Non-medical approaches to reflex syncope**

These methods consist of adequate fluid and salt intake, avoiding situations triggering syncope, regular exercise, isometric counter-pressure manoeuvres and orthostatic training.

**Orthostatic training.** This method, known also as passive standing or tilt training, appears attractive because of its non-invasiveness and physiological background supporting its use in reflex syncope. It has been shown in a preliminary report that orthostatic training favourably modifies autonomic tone [35]. Others have documented beneficial effects of tilt training on the renin–angiotensin–aldosterone system activity [36]. The results of clinical studies are conflicting — some have documented effectiveness of orthostatic training, whereas others have not [2]. No new important data on this topic have been recently published. It seems that the main reason for inconsistent or negative findings is poor compliance — less than one third of patients are able to continue the training for longer periods. In the ESC 2009 guidelines, the recommendation to use this method is graded as IIb ('may be considered') and is especially worth considering in highly motivated persons. However, numerous case reports and small non-randomised studies suggest some benefits of orthostatic treatment. Therefore, it is worth persuading patients to perform orthostatic training, especially the young and motivated, because it may work in approximately 30% of them. The training (passive standing by the wall) is usually started as five-minute sessions in the morning and in the evening, extending the duration of sessions by five minutes every week to achieve two 30-minute sessions per day. It has not been established how long the training should be continued.

The other non-pharmacological treatments which seem to be successful for acute prevention of reflex syncope are

isometric counter-pressure manoeuvres such as arm tensing, leg crossing and lower body muscle tensing [37]. These methods may work in patients who have prodromal symptoms prior to syncopal attack. One study documented the efficacy of this treatment: syncope burden was significantly reduced in the active arm of the trial compared to controls (32% vs. 51%,  $p < 0.004$ ) [38]. The ESC 2009 guidelines strongly recommend the use of counter-pressure manoeuvres (class I, level B) [2].

There is one recent study which prospectively addressed non-pharmacological treatment in reflex syncope [39]. The effects of assuring an adequate fluid and salt intake, regular exercise and application of physical counter-pressure manoeuvres were assessed in 100 patients with frequent episodes of reflex syncope. During the first year of therapy, the number of syncopal recurrences significantly decreased compared to the last year before treatment (median 0 vs. 3), although almost half of the patients still experienced syncopal recurrences.

### Pharmacological therapy

Therapeutic options include alpha agonists (midodrine), beta blockers, selective serotonin uptake inhibitors, and fludrocortisone. In the recent ESC guidelines, only midodrine received IIb recommendation ('may be used') whereas other drugs, including beta blockers, are not recommended [2].

Since the 2009 ESC guidelines, only a few new studies regarding drug therapy have been published. Sheldon et al. [40] studied the effects of beta blockers on syncope recurrences in different age groups. Using the population from the POST trial and another observational cohort study, they found that metoprolol had beneficial effects in patients aged  $> 42$  years (hazard ratio: 0.52, CI 0.27–1.01). There are also case reports and small studies suggesting that beta blockers may be effective in preventing reflex syncope in those in whom vasovagal reaction is preceded by a marked sinus tachycardia [41]. If beta blockers can stop the pathological reflex at this point, it may prevent syncope. However, it should be remembered that when the drug fails to do so, asystolic pause may be prolonged due to beta blocker effects.

New data concerning midodrine have also been published [42]. The STAND trial investigated whether the institution of midodrine therapy in patients with vasovagal syncope who are on full non-pharmacological treatment and still experience symptoms, decreases syncope recurrences. Twenty-three patients received midodrine and placebo treatment in a cross-over fashion. The proportion of patients who experienced syncopal and pre-syncopal recurrences did not differ significantly between midodrine and placebo treatment (syncope: 48% vs. 65%,  $p = 0.22$ ). The median number of syncopal episodes was also not different during midodrine and placebo treatment (0 vs. 1,  $p = 0.57$ ). These findings indicate that additional midodrine treatment is not very effective in patients with vasovagal syncope not responding to non-pharmacological treatment.

The role of midodrine in reflex syncope will be investigated in the multicentre, randomised, placebo-controlled POST 4 trial [43]. This study promises to be the first adequately powered trial to determine whether midodrine is effective in preventing vasovagal syncope.

Another potentially interesting agent is ivabradine — a selective sinus node blocker. This has been shown to be useful in some patients with postural orthostatic tachycardia syndrome [44]. Whether it could be useful in some forms of reflex syncope remains to be determined.

### Pacing

The role of pacing in patients with atrio-ventricular conduction abnormalities and syncope has been relatively well established for many years. Usually these patients require permanent pacing, especially when distal atrio-ventricular conduction disturbances are present [2]. However, these patients may also have syncope due to other causes. Moya et al. [45] in the B4 study elegantly showed that in patients with prolonged QRS duration, syncope and preserved left ventricular ejection fraction, a systematic stepwise diagnostic approach enables a high rate (82.7%) of correct diagnosis and allows specific treatment. Of the 267 patients with established aetiology of syncope, diagnosis was made at initial evaluation in 102 subjects, in a further 113 upon electrophysiological study, and in the remaining 52 by the use of ILR. Pacemakers were implanted in 68% of patients. Of note, in as much as 17.6% of this population other aetiologies of syncope such as CSS, reflex, drug-related or cardiac (arrhythmic or structural) were detected, showing that not all patients with conduction abnormalities and syncope need permanent pacing.

In patients with reflex syncope, pacing should be considered in those who have documented spontaneous cardioinhibitory reaction during syncope, frequent episodes and are  $> 40$  years (class IIa recommendation) [2]. The ISSUE-2 study showed that asystolic syncope accounts for approximately half of all syncopal events and that ILR-guided pacemaker implantation resulted in a  $> 80\%$  relative risk reduction in syncope recurrences [3].

However, the ISSUE-2 study was not a controlled, double-blind study. Moreover, previous double-blind studies on pacing in vasovagal syncope, which gave negative results, were small, underpowered and included also patients with vasodepressive (hypotensive) reaction which clearly cannot be prevented by pacing. Therefore, the ISSUE-3 study was conducted and the results published in 2012 [46]. The study group consisted of patients aged  $\geq 40$  years with  $\geq 3$  syncopes during the previous two years with ILR-confirmed syncope due to asystole  $> 3$  s or with asystole  $> 6$  s not associated with syncope. Out of 511 screened patients, 77 patients were eligible for the study and received a DDDR pacemaker with a rate drop response function. In 38 patients, the pacemaker was turned on, and in 39 it was turned off. The intention to

treat analysis showed that pacemaker therapy reduced significantly syncope recurrences during a two-year follow-up (57% vs. 25%,  $p < 0.04$ ) which corresponds to a 57% reduction of the recurrence rate. Thus, the ISSUE-3 study demonstrated that pacing may offer significant benefit in asystolic reflex syncope in a well-defined group of patients. However, it should be kept in mind that the study was relatively small and the difference in outcome between patients with pacing turned on and off was of borderline significance. In addition, there were eight patients from the group with no pacing who had their pacemaker turned on during the study not because of syncope but for other reasons, and that might have influenced results. The study also showed that a significant proportion (25%) of patients with active pacemaker continued to have syncope recurrences. This probably shows the importance of the vasodepressive component in neurally mediated syncope. Lastly, the ISSUE-3 diagnostic and therapeutic approach is applicable to only 9% of patients with reflex syncope referred for evaluation. Based on the patients' flowchart, the authors calculated that 1,255 patients need to have ILR implanted in order to identify 38 subjects with indications for pacing, of whom in 11 pacing really prevents syncope. In summary, the ISSUE-3 was a next step in substantiating the use of pacing in spontaneous asystolic reflex syncope; however, even in such 'ideal' candidates as those with the ISSUE-3 characteristics, pacing does not prevent syncope in one in four patients.

There are ongoing trials which should further clarify which subgroups of patients with reflex syncope benefit the most from permanent pacing [47]. Also an issue of pacing vs. monitoring only in patients with syncope and bifascicular conduction block is being investigated in an ongoing trial [48].

### **Surgery**

There is interesting data regarding surgical carotid sinus denervation in patients with CSS. Surgical carotid sinus denervation has been used for many years in some centres as the last resort treatment of CSS [49, 50]. However, this method was not mentioned in the guidelines. Recently, new data were presented from a centre in the Netherlands. A total of 39 carotid denervation procedures were performed in 27 patients. At 30-day follow up, 25 of the 27 patients (93%) were free of syncope, and 24 were free of a pacemaker (89%). The authors concluded that carotid denervation by adventitial stripping of the proximal carotid internal artery is effective, safe and may offer a valid alternative to pacemaker treatment in patients with CSS, especially for those with vasodilatory reaction [51].

## **IMPROVEMENTS IN MANAGEMENT OF SYNCOPE**

### **Syncope facilities**

In recent years, so-called 'syncope units' have been introduced in several hospitals in order to speed up and improve evaluation of patients with syncope [2]. These facilities are usually conducted by a specialist in syncope management

or a team of such specialists. There is easy and fast access to other specialists for consultations, which enables more accurate diagnostics and therapy. It has been shown that such an approach leads to a high rate of establishing a definite diagnosis at reasonable cost [52].

### **Interactive decision-making software**

In spite of the publication of the guidelines on syncope management, the number of inappropriate hospital discharges and admissions in patients presenting with syncope in the emergency department is still high. It has been shown that implementation of guideline-based algorithms may result in a 52% reduction in admission rate without increasing the risk of serious events [53]. Thus, these algorithms, coupled with online decision-making software, may increase the rate of proper discharges and admissions of patients presenting to the emergency departments with syncope. However, this has to be documented by prospective validation studies.

**Conflict of interest:** none declared

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