New insights in diagnostics and therapies in syncope: a novel approach to non-cardiac syncope

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ABSTRACT

This article aims to give advice on how to identify and manage patients with syncope who are at risk of severe outcomes, that is, at risk of trauma, potentially life-threatening episodes or frequent recurrences reducing quality of life. The first step of syncope diagnostic assessment is to identify patients with cardiac syncope, and once established, these patients must receive the adequate mechanism-specific treatment. If cardiac syncope is unlikely, reflex (neurally mediated) syncope and orthostatic hypotension are the most frequent causes of transient loss of consciousness. For these presentations, efficacy of therapy is largely determined by the mechanism of syncope rather than its aetiology or clinical features. The identified mechanism of syncope should be carefully assessed and assigned either to hypotensive or bradycardic phenotype, which will determine the choice of therapy (counteracting hypotension or counteracting bradycardia). The results of recent trials indicate that 'mechanism-specific therapy' is highly effective in preventing recurrences. Established mechanism-specific treatment strategies include withdrawal of hypotensive drugs, applying fludrocortisone and midodrine for the hypotensive phenotype and cardiac pacing in the bradycardic phenotype.

INTRODUCTION

Transient loss of consciousness of suspected syncopal nature is a common event in the general population. Overall, it is estimated that approximately half of the whole population will have one episode during their lifetime. Most patients do not seek medical help, and only a small fraction sees a specialist or presents to the emergency department.[1] As a consequence, in most cases, syncope is perceived as a benign transient condition constituting a minor clinical problem and deserving of less attention than other life-threatening conditions. Nevertheless, it has been estimated that about 14% of the syncope population are at risk of severe outcomes, that is, at risk of trauma, potentially life-threatening episodes or frequent recurrences reducing quality of life.[1] The patients with such *severe forms* deserve careful investigations aimed to find an effective mechanism-specific therapy. How to identify and manage such patients is the aim of this article, which is summarised in figure 1.

WHY AND WHO TO TREAT

Syncope is a clinical and social problem especially in older patients as it is usually more severe than in younger people and significantly impact individuals' functional autonomy and prognosis (figure 2).

Avoiding severe injuries due to syncopal falls, such as fractures and intracranial haemorrhages, is probably the most important goal of treatment. The risk of injuries is higher in patients with recurrent episodes and when warning symptoms are absent or very short preventing the patient from performing any measure to avoid a fall and its adverse consequences. In a pooled analysis of 16 studies of patients seeking for specialistic assessment for a syncopal episode, the weighted mean injury rate was 35% (range 12%–71%); the rate of major injuries, as fractures and/or concussion and/or hospital admission and surgical treatment was 10% (range 3%–53%) (online supplemental table 1). In a Danish cohort study,[2] adults hospitalised for their first syncope had an 80% higher risk of fall-related injuries within the year following discharge. The risk increased steeply with advancing age starting from the age of 70 years: 46% of falls caused fractures and 7% caused major head injury. Falls in older patients frequently result in fractures or other major injuries leading to hospitalisation, functional decline and nursing home admission, with worse functional outcomes in those with prefall disability.[3 4] In elderly adults with dementia, Ungar *et al*[5] reported any injury in 48.6% and major injuries in 14.6% due to syncope and falls.

Syncope may also have detrimental effects on quality of life, which mainly concern patients with very frequent or unpredictable syncopes[6] (figure 2). Quality of life impact of syncope has been estimated to be comparable with that of chronic diseases such as arthritis, low back pain and depressive disorders, in terms of psychosocial impairment.[6 7] Indeed, syncope may also cause disruption of school and working activities, with syncope patients having a twofold higher risk of termination of employment compared with the general employed population.[8] Regarding older patients, activity restriction due to fear of falling may lead to dependency and social isolation, thus affecting individuals' well-being and quality of life.[9 10] Mobility restriction may be the start of a vicious circle leading to an immobility syndrome with muscle atrophy, deconditioning and poor balance, thereby, contributing to functional decline and future falls.[9 10] Finally, falls can be an indirect cause of mortality, for example, approximately 20% of hip fractures lead to death within 6 months.[11]

In conclusion, syncope and falls, especially in older people, may be a devastating event. In this context, an effective syncope treatment plays a major role in preventing functional decline.

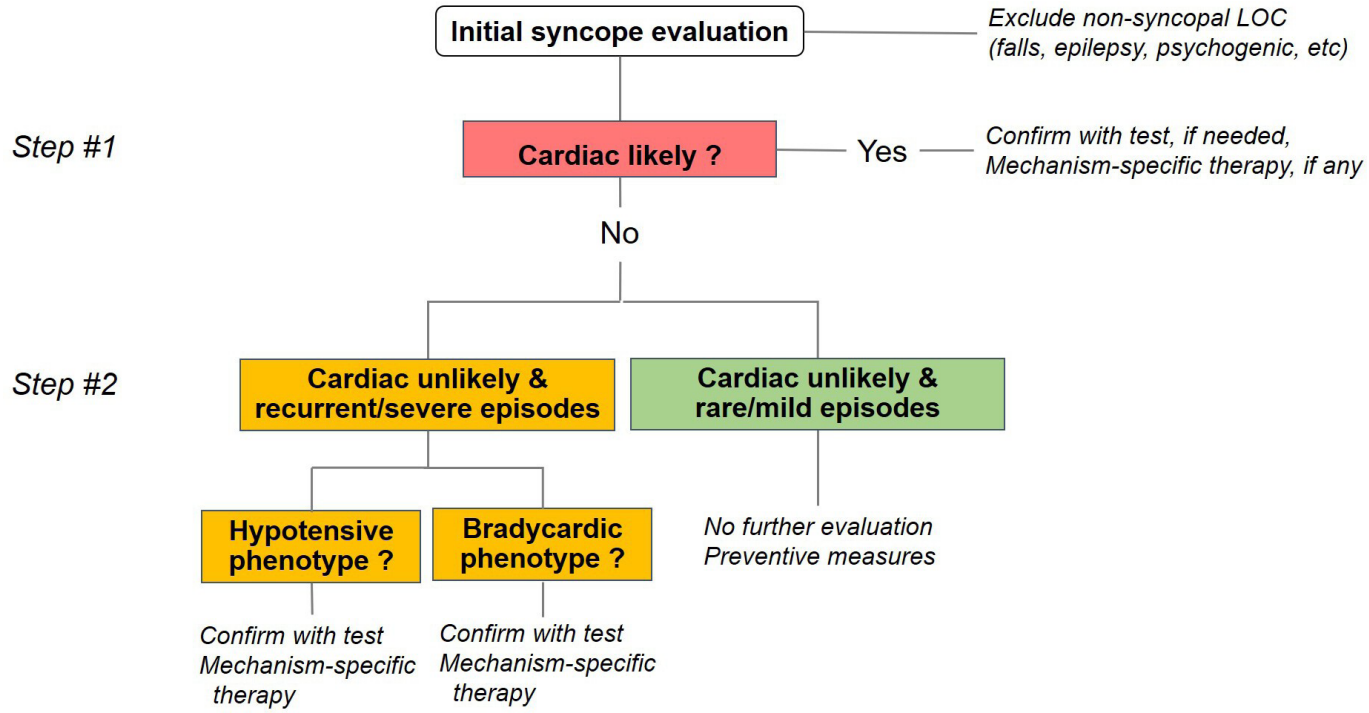

Figure 1 The management of a patient with syncope based on risk stratification. LOC, loss of consciousness.

FIRST STEP: IS THERE A CARDIAC SYNCOPE?

Sudden death caused by the same mechanism that had led to syncope is rare. Typically, this is the case when cardiac arrhythmia is the cause. An additional, indirect risk of death in syncope patients stems from underlying diseases, being more relevant in presence of structural cardiac diseases.[12 13] Consequently, the first step of the diagnostic work-up of syncope should aim to identify patients with cardiac syncope in order to offer appropriate treatment.

The frequency of cardiac syncope depends on the setting, accounting for 1% of episodes in the general population aged <40 years, 9.5% in the adult general population aged >40 years, 5%–11% in the emergency department, 6%–13% in syncope units and 23%–37% in cardiology departments.[12] In about half of the cases the diagnosis is established during the initial evaluation including standard 12-lead ECG[1] (table 1). In other cases, a cardiac diagnosis may be suspected during the initial evaluation

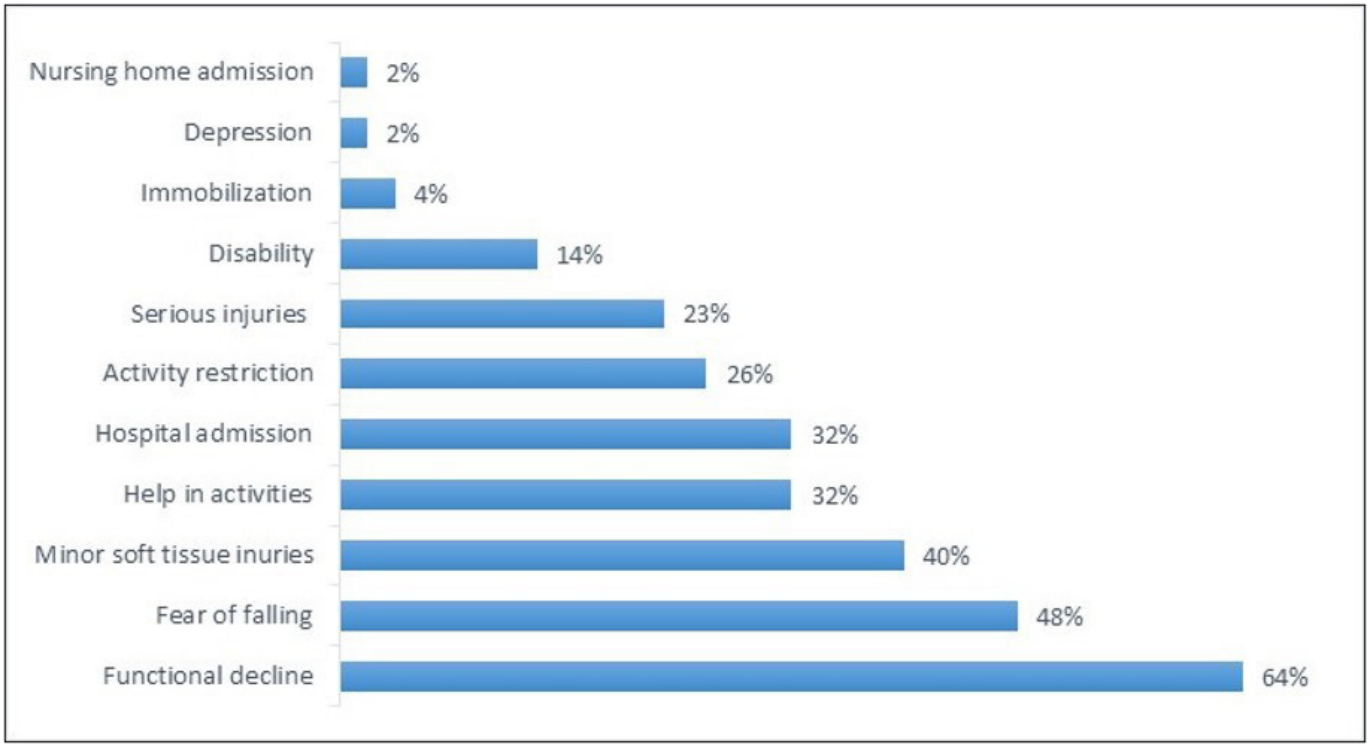

Figure 2 Rates of fall-related adverse events in older people (data from refs[3 11]).

Table 1 Role of the initial evaluation (history taking, physical examination and standard 12-lead ECG) for the diagnosis of cardiac syncope (modified from 2018 ESC guidelines, with permission)

Cardiac syncope established	Cardiac syncope possible (to be confirmed by further investigations)
Arrhythmic syncope is highly probable when the ECG shows: ► Persistent sinus bradycardia <40 bpm or sinus pause >3 s. ► Mobitz II second-degree and third-degree AV block. ► Alternating left and right BBB. ► VT or rapid paroxysmal SVT. ► Non-sustained episodes of polymorphic VT and long or short QT interval. ► Pacemaker or ICD malfunction with cardiac pauses. Cardiac ischaemia-related syncope is highly probable when syncope presents with evidence of acute myocardial ischaemia with or without myocardial infarction. Syncope due to structural cardiopulmonary disorders is highly probable when syncope presents in patients with prolapsing atrial myxoma, left atrial ball thrombus, severe aortic stenosis, pulmonary embolus or acute aortic dissection.	**ECG findings suggesting arrhythmic syncope:** ► Bifascicular block. ► Other intraventricular conduction abnormalities (QRS duration ≥0.12 s) ► Mobitz I second-degree AV block and one-degree AV block with markedly prolonged PR interval. ► Asymptomatic mild inappropriate sinus bradycardia (40–50 bpm) or slow atrial fibrillation (40–50 bpm). ► Non-sustained VT. ► Pre-excited QRS complexes. ► Long or short QT intervals. ► ST-segment elevation with type 1 Brugada pattern. ► Negative T waves in right precordial leads, epsilon waves suggestive of ARVC. ► Left ventricular hypertrophy suggesting hypertrophic cardiomyopathy. **Historical findings suggesting cardiac syncope:** ► Syncope during exertion or when supine. ► Sudden onset palpitation immediately followed by syncope. ► Family history of unexplained sudden death at young age. ► Presence of structural heart disease or coronary artery disease.

ARVC, arrhythmogenic right ventricular cardiomyopathy; AV, atrioventricular; BBB, bundle branch block; bpm, beats per minute; ESC, European Society of Cardiology; ICD, impantable cardioverter difibrillator; SVT, supraventricualr tachycardia; VT, ventricular tachycardia.

and confirmed by prolonged ECG monitoring and, less frequently, by electrophysiological study or stress test. Echocardiography and coronary angiography play a role in the diagnosis of syncope due to structural cardiac causes.[1]

Once the diagnosis has been established, cardiac syncope must always receive the best mechanism-specific treatment: cardiac pacing in symptomatic bradycardia, catheter ablation in supraventricular tachycardia, ablation or ICD in ventricular tachycardias, coronary revascularisation in ischaemic coronary syndromes, cardiac surgery/transarterial catheter valve replacement in aortic stenosis and cardiac surgery for masses (atrial myxoma, ball thrombus and so on), pericardial disease/tamponade or acute aortic dissection.[1]

SECOND STEP: DIAGNOSIS AND THERAPY OF NON-CARDIAC SYNCOPE

Reflex (neurally mediated) syncope and orthostatic hypotension are the most frequent causes of transient loss of consciousness when cardiac syncope is ruled out. Non-syncopal causes of real or apparent loss of consciousness that may be incorrectly diagnosed as syncope (eg, unexplained falls, epilepsy, psychogenic pseudosyncope and other rare causes) must be excluded at the initial evaluation, but the diagnostic process is beyond the scope of this article.

Traditionally, reflex syncope and orthostatic hypotension are classified by their aetiology and clinical presentation. Figure 3, left panel, shows the classification of syncope proposed by the European Society of Cardiology (ESC) guidelines.[1] Because of recent advances in technology, our ability to make a diagnosis based on the documentation of spontaneous events has increased. This resulted in a new classification of syncope based on the underlying mechanism (figure 3, right panel). Each clinical form can cause syncope by different mechanisms. Diagnostic tests are aimed to document the causal correlation between underlying mechanism and syncope.

The efficacy of therapy is largely determined by the mechanism of syncope rather than its aetiology or clinical presentation. The dominant mechanism of syncope should be carefully assessed and assigned to hypotensive or to bradycardic phenotype, the choice of therapy (counteracting hypotension or bradycardia) depending on the given phenotype (figure 1). A typical dominant hypotensive phenotype is that of syncope due to classical orthostatic hypotension and a typical dominant bradycardic phenotype is that of syncope due to low adenosine paroxysmal idiopathic atrioventricular (AV) block.[14] In many other cases, the final mechanism is often a combination of hypotension and bradycardia, although of variable magnitude, and therapy should often be aimed to counteract both mechanisms. For example, in patients with delayed orthostatic hypotension, when syncope occurs, a vagally reflex bradycardia is often present, triggered by orthostatic hypotension itself, making the distinction between reflex and orthostatic hypotension somehow arbitrary. Conversely, some patients with ECG documentation of a long asystolic pause at the time of a spontaneous syncope have syncopal recurrence despite cardiac pacing. In such cases, syncope is often due to an associated vasodepressor reflex that can be unmasked by tilt testing.[15 16] Finally, a compensatory sinus tachycardia may be present during the presyncopal phase of reflex syncope and in postural orthostatic tachycardia syndrome.

Hypotensive phenotype

Diagnosis

Non-cardiac syncope due to hypotensive phenotype is likely when syncope occurs in patients who have constitutional or drug-related persistent hypotension, or inappropriately low blood pressure (BP) during ambulatory blood pressure monitoring (ABPM), or have hypotensive symptoms induced by tilt testing (figure 4).

Hypotensive phenotype is the most common mechanism underlying syncope. Recent data suggest that the patients with hypotensive phenotype have a different cardiovascular physiology which predisposes to syncope, characterised by lower systolic BP, and higher diastolic BP and heart rate than the general population.[17] Moreover, tilt-positive patients have lower systolic and diastolic BP values than tilt-negative patients[18] These haemodynamic features suggest reduced venous return and lower stroke volume, which prompt a compensatory increase in heart rate and vascular resistance. Therefore, in individuals with hypotensive susceptibility, cardiovascular homeostasis and organ perfusion are maintained at the expenses of chronic activation of compensatory mechanisms. This peculiar haemodynamic profile makes these individuals more prone to develop hypotension and syncope in the presence of stress conditions, for example, orthostatic stress, that overcome the

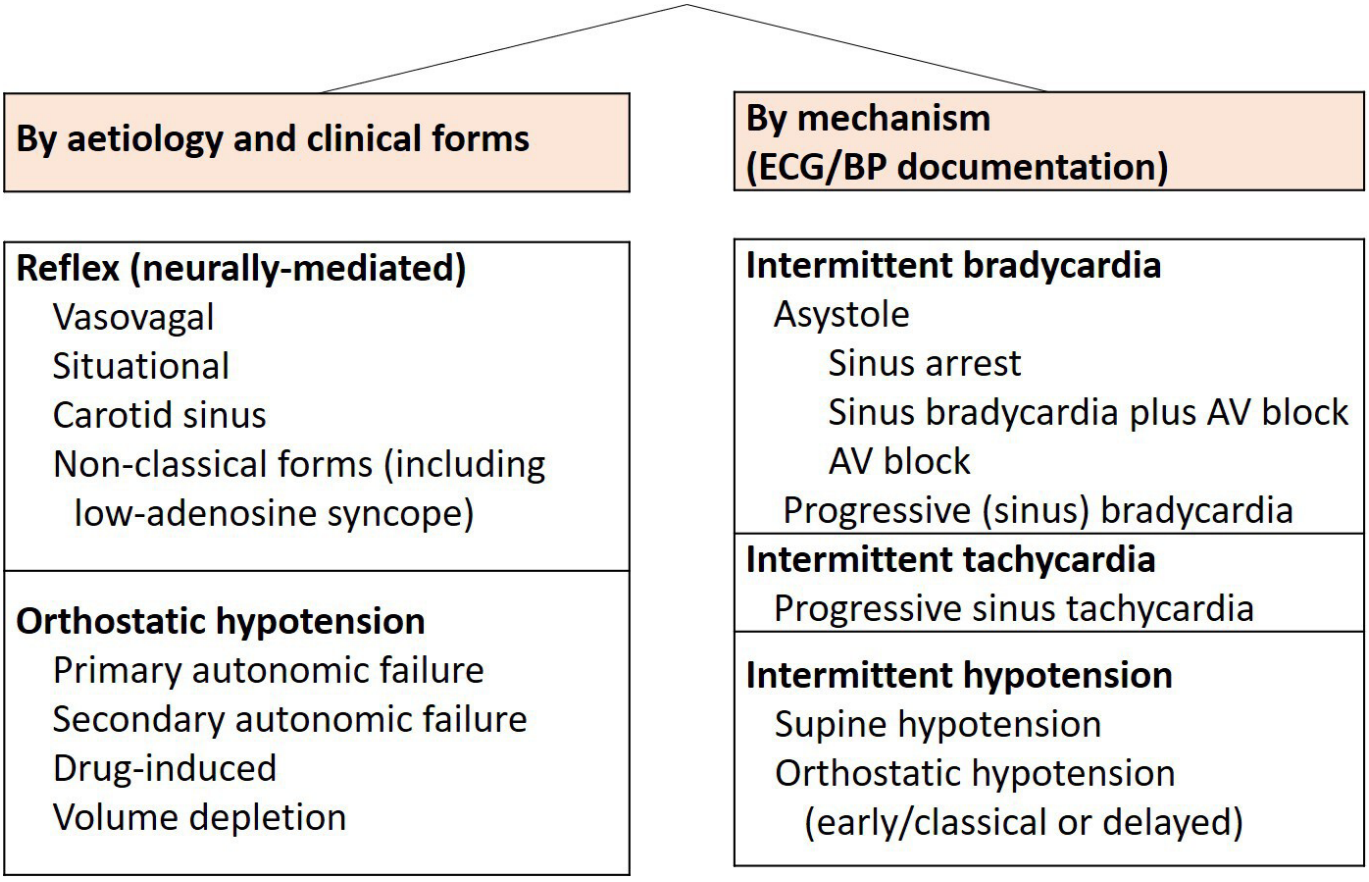

Figure 3 Classification of non-cardiac syncope according its aetiology (left panel) and mechanism (right panel). AV, atrioventricular; BP, blood pressure.

compensatory capacity of these adaptative mechanisms.[17] Hypotensive susceptibility may be exacerbated by hypotensive drugs, which interfere with cardiovascular homeostasis leading to a drug-related hypotensive phenotype.

Constitutional hypotension is characterised by inappropriately low BP independent of the presence of further pathological conditions.[19] It is defined by systolic BP below 110 mm Hg in men and 100 mm Hg in women, regardless of diastolic BP.[20] Its prevalence ranges from 1% to 4%, mostly observed in women.[21] Although constitutional hypotension may be a protective factor against cardiovascular risk, there is evidence that it may be associated with recurrent orthostatic symptoms including syncope, leading to substantial quality of life impairment.[21 22] Alterations in autonomic cardiovascular regulation are assumed to be involved in the aetiology of this condition, particularly increased baroreflex sensitivity and reduced sympathetic vascular tone, which may result in stabilising BP at a lower level.[22] Reduced cardiac output and higher renin and aldosterone levels have also been reported, suggesting presence of hypovolaemia.[22 23]

Drug-related persistent hypotension can be defined as persistent low BP below the target range in hypertensive patients receiving antihypertensive therapy. Drug-related hypotension may also result from non-cardiovascular hypotensive medications (figure 5). Indeed, psychoactive drugs such as antipsychotics, tricyclic antidepressants, trazodone and benzodiazepines may significantly impair the BP response to standing and enhance hypotensive susceptibility, particularly at old age.[24]

ABPM provides an overview of BP values throughout the day, thus representing a valuable tool to detect hypotension.[1] In general, in a patient with non-cardiac syncope, systolic BP <100 mm Hg is considered inappropriately low.[25 26] The probability of a causal relationship with the mechanism of syncope increases with its lower value and the number of times detected. For example, the presence of at least 1 hour time systolic BP values lower than 90 mm Hg showed a positive predictive value of 78% and a specificity of 87% in identifying patients with reflex syncope; its specificity increased to 97% if two episodes were detected during the same daytime (*Rivasi G, personal communication*).

Tilt testing should be performed according to the Italian protocol,[12] which requires reproduction of symptoms along with the characteristic circulatory pattern of reflex hypotension/bradycardia in patients with suspected reflex syncope, progressive BP fall in patients with suspected orthostatic hypotension and excessive heart rate increase in patients with suspected postural orthostatic tachycardia syndrome.[1]

Mechanism-specific treatment

A medication review is recommended as a first-line treatment strategy. In recent years, increasing evidence from randomised controlled trial and metanalyses has become available supporting a pharmacological treatment approach in patients with severe, recurrent hypotensive syncope (table 2 and online supplemental table 2).

Deprescribing

In patients with syncope receiving hypotensive medications (figure 5), it is advisable to reconsider treatment targets adopting a more cautious approach to BP lowering, particularly at advanced age. In the stop-VD study, the reduction/withdrawal of BP therapy targeting systolic blood pressure (SBP)

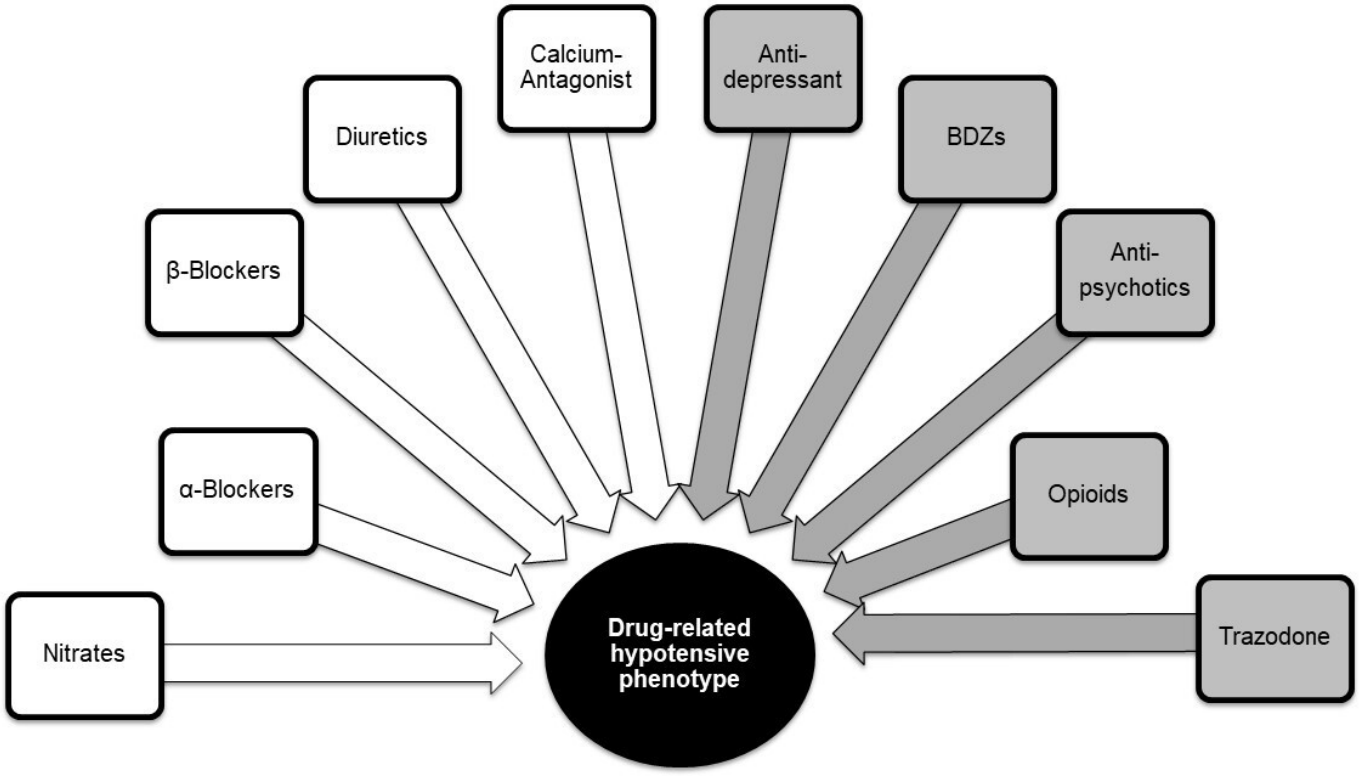

Figure 4 Diagnostic flow for the identification of patients with hypotensive phenotype. ABPM, ambulatory blood pressure monitoring; BDZs, benzodiazepines; BP, blood pressure.

of 140 mm Hg resulted in a 63% decrease in syncopal recurrences.[27] In the Discontinuation of Antihypertensive Treatment in Elderly people (DANTE) study, deprescribing of antihypertensive medications in older adults with mild cognitive impairment and a mean BP of 149/82 mm Hg resulted in a 45% increased probability of recovery from orthostatic hypotension.[28] Discontinuation of antihypertensives medications was found to be safe, with no increase in risk of mortality and cardiovascular

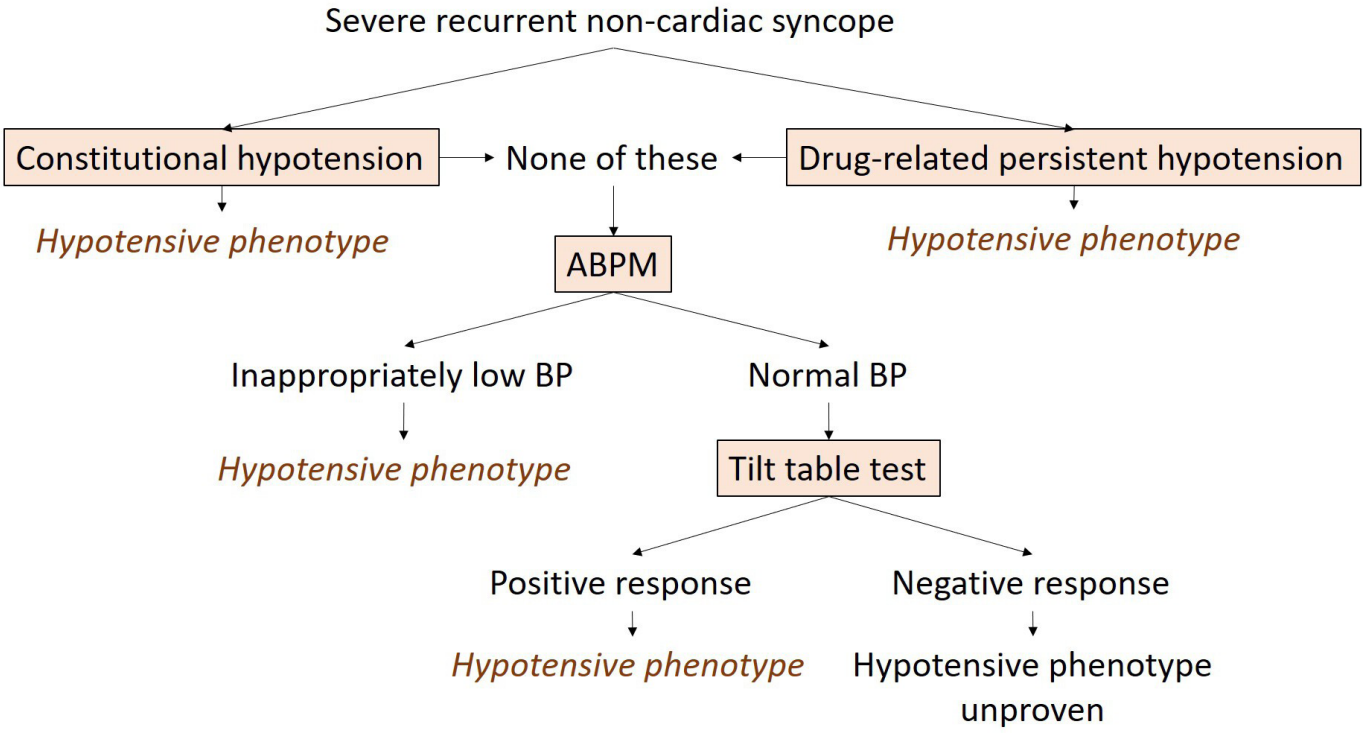

Figure 5 Drug-related hypotensive phenotype. Modified from Rivasi *et al* with permission[24] ABPM, ambulatory blood pressure monitoring; BDZs, benzodiazepines; BP, blood pressure.

Table 2 Pharmacological treatment strategies for patients with severe recurrent syncope[24 34 36 39 64]

	Indication	Mechanism of action	Dosage	Side effects	Contraindications
Midodrine	Hypotensive phenotype.	Selective alpha-receptor agonist inducing arterial and venous vasoconstriction.	2.5–5 mg twice daily to three times a day, to be titrated (max 15/day).	Pilomotor reactions, chills, urinary retention and supine hypertension.	Heart failure/CAD, urinary retention, glaucoma and PAD.
Fludrocortisone	Hypotensive phenotype.	Mineralocorticoid-inducing renal water and sodium reabsorption and volume expansion.	Initial dose 0.1–0.2 mg daily, to be titrated (max 0.3 mg daily).	Hypokalaemia, supine hypertension, volume overload and headache.	Heart failure and severe renal impairment.
Atomoxetine,	Hypotensive phenotype.	Norepinephrine transporter inhibition.	Initial dose 20 mg daily. Max dose 40 mg daily.	Palpitations and insomnia.	Cardiac diseases.
Droxidopa	Hypotensive phenotype.	Synthetic norepinephrine prodrug promoting vasoconstriction.	Initial dose 100 mg three times a day. Max dose 600 mg three times a day.	Supine hypertension, headache, dizziness and nausea.	Cardiac diseases, patients receiving drugs increasing NE levels.
Theophylline	Bradycardic phenotype.	Non-selective xanthine antagonist block adenosine cardiac and vascular receptors.	Initial dose 300 mg twice daily, to be titrated (max 900 mg day).	Tachycardia, headache, insomnia, irritability, diarrhoea, nausea and tremors.	Cardiac arrhythmias, thyrotoxicosis and epilepsy.

CAD, coronary artery disease; PAD, peripheral artery disease; NE, norepinephrine.

events.[28 29] Based on these data, a systolic BP target of 140 mm Hg is recommended in older people with hypotensive susceptibility[30] (figure 6). SBP values up to 160 mm Hg can be accepted in individuals with severe frailty and/or disability, in view of the extremely high risk of syncope and falls and the limited evidence supporting BP lowering in this vulnerable population.[30 31] In younger adults, hypotensive risk increases significantly at SBP values <120 mm Hg[32]; a less intensive BP control seems to be appropriate in patients with severe/recurrent syncope, targeting an SBP of 130–140 mm Hg.[30]

Among antihypertensive medications, preference should be given to drug classes with protective effects or low risk of orthostatic hypotension, such as ACE inhibitors or angiotensin receptor antagonists.[24] Additionally, bedtime administration can be considered to minimise the risk of daytime hypotension.[30] In patients with prostatic hyperplasia, α-blockers should only be prescribed in the presence of bladder outflow obstruction and uroselective molecules should be preferred given their limited hypotensive effects.[24]

As regards non-cardiovascular hypotensive medications, treatment optimisation is recommended to achieve the lowest effective dose. Use of prolonged release formulations or fractioned doses may be considered for medications with dose-related hypotensive effects, such as antipsychotics and trazodone.[24]

Fludrocortisone

There is moderate evidence that fludrocortisone may be effective in reducing syncopal recurrences in young patients with low normal values of arterial BP and without comorbidities.[1] The double-blind randomised controlled Prevention of Syncope Trial (POST 2)[33] showed a significant 49% reduction of recurrences

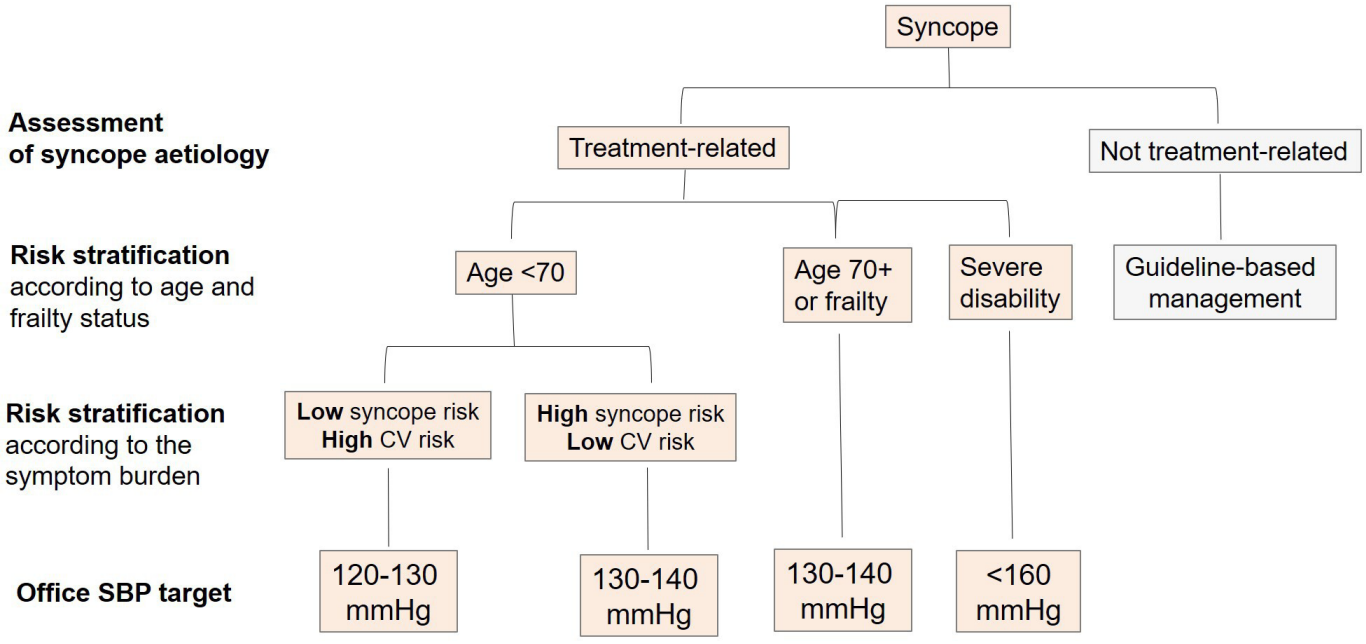

Figure 6 BP targets in patients with hypertension and syncope. In hypertensive patients with treatment-related hypotensive phenotype, BP targets should be modulated based on cardiovascular and hypotensive risk. Patients at high risk of syncope include those with severe, recurrent episodes. Moreover, hypotensive risk can be expected to be more relevant in older patients with frailty or disability. Modified from Rivasi *et al*[30] with permission. BP, blood pressure; CV, cardiovascular; SBP, systolic blood pressure.

in young (median age of 30 years) vasovagal syncope patients receiving the mineralocorticoid fludrocortisone at a dose of 0.2 mg/day (table 2 and online supplemental table 2). Additionally, fludrocortisone was found to improve standing BP in small-sized, open-label studies including patients with neurogenic orthostatic hypotension.[24]

Midodrine

There is modest evidence from multiple trials that alpha agonists may be effective in reducing syncopal recurrences in patients with the hypotensive phenotype[1] (table 2 and online supplemental table 2). Midodrine was found to elevate BP in patients with constitutional hypotension.[23] A systematic review by Izcovich *et al*[34] evaluated the efficacy of midodrine in symptomatic orthostatic hypotension and recurrent reflex syncope. In patients with orthostatic hypotension, midodrine improved symptoms (risk difference 32.8%) and in patients with reflex syncope midodrine reduced syncope recurrences (risk difference 37%). More recently, in the double-blind, placebo-controlled POST 4 trial,[35] midodrine was found to reduce recurrences from 57% to 43% during 1 year of follow-up in young patients with vasovagal syncope.

New area of scientific inquiry: atomoxetine

As norepinephrine transporter (NET) is responsible for removing about 90% of released cardiac synaptic norepinephrine, NET inhibitors are particularly suitable to selectively increase adrenergic drive to the heart in stress conditions[36] (table 2 and online supplemental table 2). Atomoxetine, a selective NET inhibitor, reduced the risk of tilt-induced syncope mainly by increasing heart rate during the vagal syncopal phase.[37] In a small placebo-controlled trial,[38] atomoxetine reduced (pre)syncopal rate and prolonged the time to syncope at 3 months. Moreover, atomoxetine was found to increase seated and standing systolic BP in patients with central autonomic failure and orthostatic hypotension.[24]

New area of scientific inquiry: droxidopa

Moderate quality of evidence from four small short-term randomised controlled trials[39] supports the use of droxidopa in neurogenic orthostatic hypotension, showing an increase in standing systolic BP of approximately 10 mm Hg and improvement in orthostatic tolerance and symptom impact on daily activities (table 2 and online supplemental table 2).

Bradycardic phenotype

Diagnosis

Non-cardiac (reflex) syncope due to bradycardic phenotype is likely when syncope occurs at the time of an asystolic pause >3 s recorded during a spontaneous event or induced by carotid sinus massage or by tilt testing.

In a meta-analysis[16] of 383 patients who had an ECG diagnostic event documented by an implantable loop recorder, 52% had an asystolic event of 12.8±11.0 s duration compatible with a reflex mechanism. The mechanism of the index asystolic event was sinus arrest in 52%, AV block in 20%, sinus arrest plus AV block in 11% and remained undefined in 16% of cases. This AV block is reflex in origin rather than revealing covert ventricular conduction tissue disease.[40]

Tilt testing and carotid sinus massage protocols require complete loss of consciousness to define positive responses. As presyncope symptoms may develop before heart rate decreases resulting in asystole, an earlier interruption of tilt testing and carotid sinus massage before complete loss of consciousness may lead to underappreciation of the cardioinhibitory response. The prevalence of cardioinhibitory response during tilt testing is 18% in younger patients until the age of 50 years and then decreases progressively across age decades until a value of 3% in patients older than 80 years.[41] In patients over 40 years, the prevalence of cardioinhibitory responses during carotid sinus massage is 8%.[42] The overlap of cardioinhibitory responses between the two tests is minimal, and both tests contribute to identifying patients with cardioinhibitory phenotype.[42]

Mechanism-specific treatment

Cardiac pacing

Cardiac pacing is the only therapy of proven efficacy for dominant bradycardic phenotype. The evidence of efficacy of cardiac pacing comes from several trials[43–50] (table 3), consistently showing superiority of active pacing compared with not paced controls. In the most recent multicentre, randomised, placebo-controlled BIOSync trial,[50] dual-chamber pacemaker with closed loop stimulation features highly significantly reduced syncope recurrences compared with no active pacing treatment: the relative and absolute risk reduction at 2 years were 77% and 46%, respectively, and the number needed to treat was 2.2. Conversely, cardiac pacing is not indicated in the absence of a documented cardioinhibitory reflex.[51 52]

Table 3 Results of randomised controlled trials on cardiac pacing in patients with the bradycardic phenotype of reflex syncope

	Diagnostic test	Pacing mode	Mean age, years	Follow-up length, months	Recurrence of syncope in the pacing group	Recurrence of syncope in the control group	1-year recurrence active/control	P value/OR
ISSUE 3[43]	ILR	DDD-RDR versus Pm Off	63	12	8/38 (21%)	19/39 (49%)	25%/37%	0.039/0.43
Claesson[44]	CSS	DDD versus no Pm	75	12	3/30 (10%)	12/30 (40%)	10% /40%	0.008/na
Brignole[45]	CSS	DDD versus no Pm	70	35	3/32 (9%)	16/28 (57%)	0%/36%	0.001/na
VASIS PM[46]	HUT	DDI hysteresis versus no Pm	63	44	1/19 (5%)	14/23 (61%)	0%/39%	0.0006/na
SYDIT[47]	HUT	DDD-RDR versus no Pm	58	36	2/46 (4%)	12/47 (25%)	3%/24%	0.004/0.13
SPAIN[48]	HUT	DDD-CLS vs DDI 40	56	11	4/46 (9%)	21/46 (46%)	9%/46%	0.0001/0.11
Russo[49]	HUT	DDD-CLS versus no Pm	43	41	9/50 (18%)	10/18 (54%)	na	0.005/0.25
BIOSync CLS[50]	HUT	DDD-CLS versus Pm Off	62	11	10/63 (16%)	34/64 (53%)	19%/53%	0.00005/0.44

.CSS, carotid sinus syndrome; DDD-CLS, dual-chamber pacemaker with close-loop stimulation; DDD-RDR, dual-chamber pacemaker with rate-drop response; HUT, head-up tilt testing; ILR, Implantable loop recorder; Pm, pacemaker.

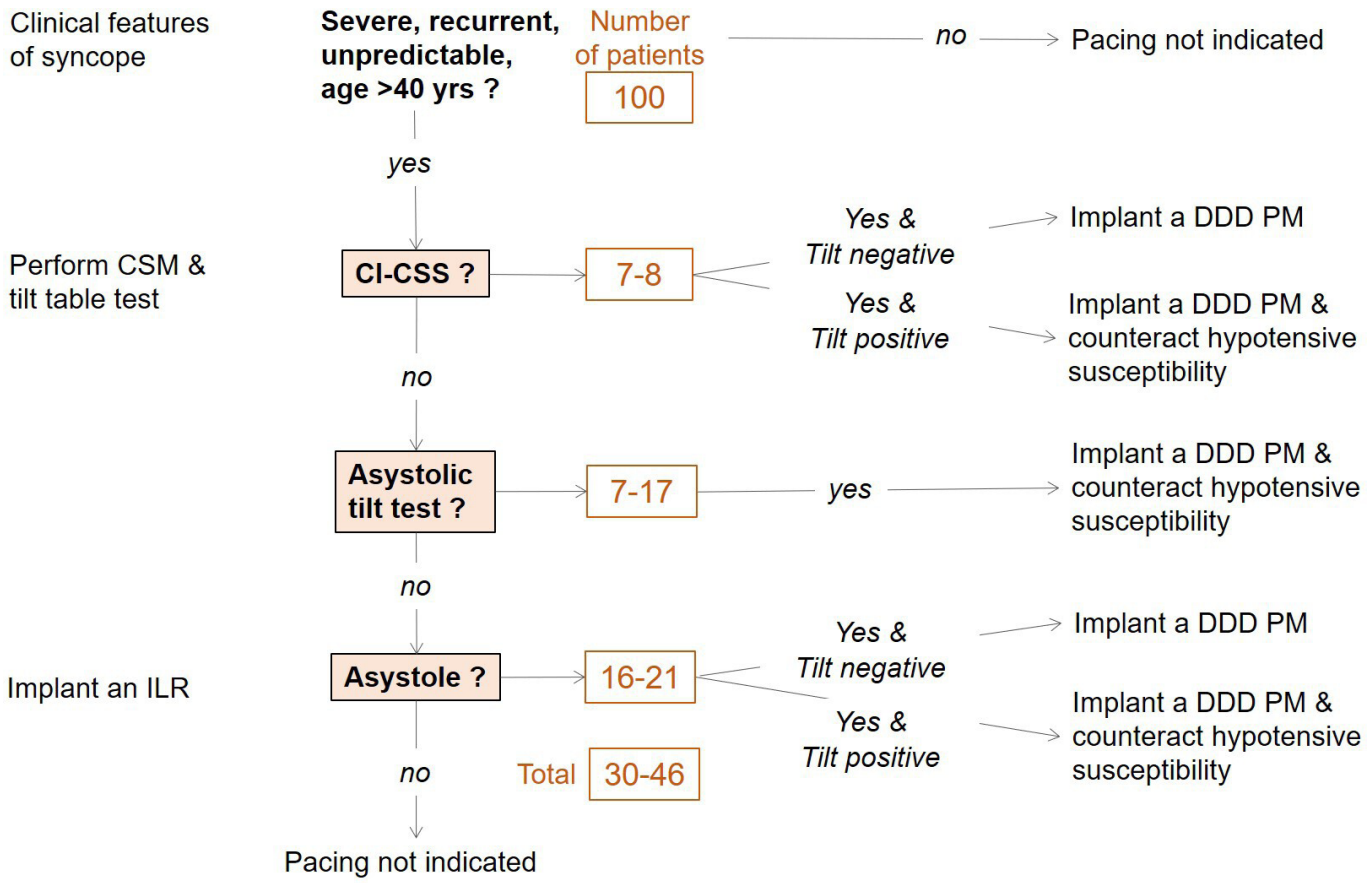

Figure 7 Diagnostic flow for the identification of patients with bradycardic phenotype who can benefit from cardiac pacing. In orange, the relative frequency of positive findings with each test compared with 100 patients with severe, recurrent unpredictable syncope with an age >40 years (see text for explanation). Modified from 2018 ESC guidelines on syncope,[1] with permission. ESC, European Society of Cardiology; CSM, carotid sinus massage; CSS, carotid sinus syndrome; CI, cardioinhibitory; DDD, dual-chamber; ILR, implantable loop recorder; PM, pacemaker.

Cardiac pacing should be considered in patients with severe, frequent, unpredictable syncopes with an age >40 years. ESC guidelines[1] have proposed a diagnostic flow for the identification of patients with bradycardic phenotype who may benefit from cardiac pacing (figure 7). This algorithm has been prospectively validated in a multicentre pragmatic study, which showed a lower syncope recurrence rate at 2 years in paced patients than untreated controls (15% vs 37%).[53] The 3-year recurrence rate was similar in patients with cardioinhibitory carotid sinus syndrome (16 %), asystolic tilt response (23%) and spontaneous asystole documented by implantable loop recorder (24%), thus suggesting similar indications and similar benefits for the three forms of reflex syncope.[54] Overall, a bradycardic phenotype accounts for 30%–46% of patients aged >40 years with severe unpredictable syncope. The contribution to the above figures is 7%–8% by carotid sinus syndrome,[55] 8%–18% by tilt testing[41 53 56] and 22%–25% by implantable loop recorder.[16 57]

In a minority of patients, syncope recurs despite cardiac pacing due to a coexistent hypotensive susceptibility.[58–60] In a meta-analysis,[16] the estimated 3-year recurrence rate of syncope was 2% in tilt-negative patients and 33% in tilt-positive patients; a positive tilt test response was the only significant predictor of syncope recurrence with an HR of 4.3. Therefore, specific treatment for hypotensive susceptibility should be provided in these patients, in addition to cardiac pacing.

New area of scientific inquiry: theophylline and low adenosine syncope

Patients affected by unexplained syncope without or with very short (≤5 s) prodromes, normal heart and normal ECG (ie, absence of structural heart disease) usually show low values of plasma adenosine (≤0.36 mmol/L).[61] Conversely, patients with typical vasovagal syncope show normal-to-high values.[62] The most typical mechanisms of syncope in patients with low adenosine are sudden onset idiopathic paroxysmal AV block[14] and sinus arrest. Overall, syncope due to long asystolic pauses accounts for 66% of episodes,[63] while the remaining show progressive sinus bradycardia or no rhythm variations, suggesting an overlap with other forms of reflex syncope.

When plasma adenosine is low, a high number of free high-affinity A1 receptors are available on the AV node and the sinoatrial node. In such circumstance, a transient release of endogenous adenosine may be sufficient to block AV node and sinoatrial conduction. Conversely, when adenosine levels are high, for example, in patients with vasovagal syncope, most A1 receptors are saturated, and AV block or bradycardia is less likely to occur.

Theophylline, a non-selective adenosine receptor antagonist, was effective in reducing syncope burden (from 2.6 to 0.4 per year) and asystole burden (from 9.6 to 1.1 per year) compared with no treatment in an intrapatient comparison of 16 patients with low adenosine syncope and implantable loop recorder[64]

(table 2). Thus, in patients with low adenosine values and asystolic syncope, theophylline may be a valid alternative to cardiac pacing.

New area of scientific inquiry: cardioneuroablation

Cardioneuroablation in patients affected by cardioinhibitory vasovagal syncope aims to decrease the vagal outflow by ablating epicardial intrinsic cardiac ganglia, which results in partial parasympathetic denervation.

A periprocedural modification of electrophysiological parameters (increase in heart rate, lengthening of AH interval and shortening of Wenckebach cycle length) is usually observed after ganglia ablation.[65–72] Compared with baseline data before ablation, several authors[65 70–72] observed a significant increase in mean, minimum and maximum heart rate at 24-hour Holter monitoring performed up to 30 months after ablation, even if this effect tended to decline after 12 months. Similarly, Debruyne *et al*[69] showed a significant decrease in the number of P–P intervals >1000 ms at 1 and 6 months of follow-up. Overall, the above findings denote a partial parasympathetic denervation of the sinoatrial and AV nodes and provide the pathophysiological prerequisite for efficacy of cardioneuroablation in preventing syncopal recurrences.

Nevertheless, several issues still need to be clarified before this technique can be introduced in the clinical practice:

1. Which ganglia should be ablated is uncertain. Some authors performed extensive ablation of up to six ganglia in the left and right atrium,[65–68] while some others limited ablation to the left[71] or to the right atrium only,[69 70 72] with apparently similar electrophysiological and clinical results.
2. The method for identification of the site for ablation and the end points are not yet clearly established and vary in different studies.
3. Nerves are known to be capable of regeneration after injury, but neural regeneration and remodelling after cardioneuroablation are still unclear. While a transient effect of parasympathetic ablation favours resumption of syncopal events or, conversely, a permanent tachycardia has potential long-term adverse effects, it remains to be elucidated.
4. Current evidence in favour of cardioneuroablation derives from observational studies and case series, thus caution is needed in interpreting the reported results. The lack of a control group and absence of blinding of both patients and investigators raises the possibility of bias and placebo effect. Well-designed randomised controlled studies are mandatory.

CONCLUSIONS

The most recent 2018 Guidelines on Syncope of the ESC[1] identified the urgent need for new therapies of proven efficacy for the prevention of syncope as an area of future research. We propose a mechanism-specific diagnostic approach (in parallel with the classical aetiological approach) as the basis for personalised treatment. After these guidelines, several controlled trials have been published, showing that mechanism-specific therapy is highly effective in preventing syncope recurrences and, hopefully, severe complications secondary to recurrences. Finally, new promising 'mechanism-specific therapies' are currently under evaluation.

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Supplemental data

Supplemental Table 1. Prevalence of syncope-related injuries in different settings and aetiologies

	Number of pts	Avg age	Minor injuries	Major injuries (fractures, concussion)	Remark
Bartoletti et al., 2008 (1)	1114	60.7	329 (29.5)	54 (4.8)	Patients with any syncope referred to Emergency department
Ungar et al., 2006 (2)	295	77	64 (21.7)	26 (11.2)	Patients with any syncope referred to Emergency department
Furukawa et al., 2013 (3)	273	61	61 (22)	9 (3) *	Patients hospitalized for suspected arrhythmic syncope *Only concussion
Brignole et al 2002 (4)	52	71	34 (65)	10 (19)	Suspected cardiac syncope (patients with bifascicular block and implantable loop recorder)
Menozzi et al 2002 (5)	35	66	25 (71)	2 (6)	Suspected cardiac syncope (patients with structural heart disease).
Moya et al 2011 (6)	323	73	96 (29.7)	44 (13.6)	Suspected cardiac syncope (patients with bifascicular block)
Alboni et al 2004 (7)	280	56	112 (40)	8 (3)	Reflex syncope referred to Syncope Unit.
Ammirati et al., 2001 (8)	346	42	94 (27.2)	31 (8.9) *	Reflex syncope referred to Syncope Unit *Hospital admission and surgical treatment due to trauma severity
Graham et al 2001 (9)	62	50	39 (62.9)	33 (53.2)	Unexplained syncope referred to Syncope Unit
Ventura et al 2002 (10)	56	44	36 (64.3)	18 (32.1)	Vasovagal syncope
Sheldon et al 2020 (11)	459	45	56 (30)	4 (4)	Vasovagal syncopes and unexplained syncopes
Wenzke et al 2017 (12)	218	45	-	17 (7.8)	Reflex syncope referred to Syncope Unit
Brignole et al 2006 (13)	392	66	230 (54.8)	82 (21)	Suspected reflex syncope undergoing loop recorder implantation
Ungar et al 2013 (14)	504	65	313 (62)	83 (16)	Severe suspected reflex syncope undergoing ILR (57% without prodromes)
Connolly et al 2003 (15)	100	49	60 (60)	10 (10)	Recurrent vasovagal syncopes undergoing pacemaker implantation
Raviele et al 2004 (16)	29	53	19 (65.5)	9 (31)	Recurrent vasovagal syncopes undergoing pacemaker implantation
Total	**4538**	**59**	**1568 (35)**	**440 (10)**	

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Supplemental Table 2. Randomized placebo-controlled evidence supporting pharmacological treatment in patients with hypotensive phenotypes

	Drug therapy	Study population (No., mean age)	Study period	Study group	Placebo group	P value
POST 2 Sheldon et al., 2016, (17)	Fludrocortisone, targeting 0.2 mg daily (efficacy analysis)	VVS patients (n=210, 30 yrs)	Follow-up: 364 days	35/101 (35%)	52/104 (50%)	0.029, HR 0.62 (p=0.019), HR 0.51 for 0.2 mg dose
POST 4 Sheldon et al., 2019 (18)	Midodrine 5 to 30 mg (individual dose-adjusted)	Recurrent VVS patients (n=134, 32 yrs)	Follow-up:12 months	29/67 (43%)	38/67 (57%)	0.12
Ward et al., 1998 (19)	Midodrine 5 mg tid	TT positive, recurrent syncope (n=16, 56 yrs)	Cross-over study (treatment period: 1-month)	6/16 (37%) +7.3 symptom free days	14/16 (87%)	0.01 <0.001 (95% CI 4.6-9.9)
Kaufmann et al., 2002 (20)	Midodrine 5 mg daily	Reflex syncope (n=12, 42 yrs)	Acute cross-over tilt test study	17%	67%	<0.02
Perez-Lugones et al., 2001 (21)	Midodrine 5-15 mg tid vs salt and fluid therapy	VVS patients (n=61, 42 yrs)	Follow-up: 6 months	6/31 (19%)	18/30 (60%)	<0.001
POST 6 Sheldon et al., 2019 (22)	Atomoxetine 40 mg x2	VVS patients (n=56, 35 yrs)	Acute tilt test RCT	10/29 (35%)	19/27 (70%)	0.003 RR 0.49
Schroeder et al. 2006 (23)	Sibutramine or reboxetine	Healthy subjects (n=51)	Acute cross-over tilt test study,	Tolerated tilt test duration: 35 ± 1 min	Tolerated tilt test duration: 29 ± 2 min	0.001 OR 0.22
Tajdine et al., 2020 (24)	Atomoxetine	VVS patients (n=46, 33 yrs)	RCT, 3 months of FU	2.3 ± 1.3 (pre)syncopes	4.3 ± 1.7 (pre)syncopes	0.001
Kaufmann et al., 2003 (25)	Droxidopa 200-2000 mg (as determined in a dose-ranging study)	Severe symptomatic OH (n=19, 64 yrs)	3-day cross-over study	Ability to stand for 3 minutes: 94% of the time	Ability to stand for 3 minutes: 84% of the time	<0.001
Kaufmann et al., 2014 (26)	Droxidopa 100–600 mg 3 times daily	Neurogenic OH (n=162, 57 yrs)	7 days	Symptom composite score: 21.68 (SD 2.13)	Symptom composite score: 20.95 (SD 1.90)	0.01
Hauser et al., 2015 (27)	Droxidopa 100-600 mg tid	Subjects with neurogenic OH (n=147, 72 yrs)	1 week	Improvement on Symptom Score: 2.3 (SD 2.95)	Improvement on Symptom Score: 1.3 (SD 3.16)	0.018

VVS=vasovagal syncope; TT=Tilt Testing; OH= orthostatic hypotension; SD=standard deviation

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