Mechanism-based therapy of non-cardiac syncope: a practical guide

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Abstract

The term non-cardiac syncope includes all forms of syncope, in which primary intrinsic cardiac mechanism and non-syncopal transient loss of consciousness can be ruled out. Reflex syncope and orthostatic hypotension are the most frequent aetiologies of non-cardiac syncope. As no specific therapy is effective for all types of non-cardiac syncope, identifying the underlying haemodynamic mechanism is the essential prerequisite for an effective personalized therapy and prevention of syncope recurrences. Indeed, choice of appropriate therapy and its efficacy are largely determined by the syncope mechanism rather than its aetiology and clinical presentation. The two main haemodynamic phenomena leading to non-cardiac syncope include either profound hypotension or extrinsic asystole/pronounced bradycardia, corresponding to two different haemodynamic syncope phenotypes, the hypotensive and bradycardic phenotypes. The choice of therapy—aimed at counteracting hypotension or bradycardia—depends on the given phenotype. Discontinuation of blood pressure–lowering drugs, elastic garments, and blood pressure–elevating agents such as fludrocortisone and midodrine are the most effective therapies in patients with hypotensive phenotype. Cardiac pacing, cardioneuroablation, and drugs preventing bradycardia such as theophylline are the most effective therapies in patients with bradycardic phenotype of extrinsic cause.
Graphical Abstract

Practical guide for personalized mechanism-based therapy of non-cardiac syncope

1. Identify the mechanism of non-cardiac syncope
2. Select the proper mechanism-based therapy

Keywords

Syncope • Non-cardiac syncope • Reflex syncope • Orthostatic hypotension • Arterial hypertension • Antihypertensive drugs • Central nervous system drugs • Fludrocortisone • Midodrine • Elastic garments • Theophylline • Cardioneuroablation • Cardiac pacing

What’s new?

- The term non-cardiac syncope includes all forms of syncope, in which primary intrinsic cardiac mechanism and non-syncopal transient loss of consciousness can be ruled out. Reflex syncope and orthostatic hypotension are the most frequent aetiologies of non-cardiac syncope.
- The choice of appropriate therapy and its efficacy are largely determined by the syncope mechanism rather than its aetiology and clinical presentation.
- The two main haemodynamic phenomena leading to non-cardiac syncope include either profound hypotension or extrinsic asystole/pronounced bradycardia, corresponding to two different haemodynamic syncope phenotypes, the hypotensive and bradycardic phenotypes.
- Discontinuation of blood pressure–lowering drugs, elastic garments, and blood pressure–elevating agents such as fludrocortisone and midodrine are the most effective therapies in patients with hypotensive phenotype.
- Cardiac pacing, cardioneuroablation, and drugs preventing bradycardia such as theophylline are the most effective therapies in patients with bradycardic phenotype of extrinsic cause.

Diagnostic work-up for the investigation of the mechanism of non-cardiac syncope

The term non-cardiac syncope includes forms of syncope, in which cardiac mechanism, such as primary intrinsic cardiac arrhythmia or structural flow obstruction, and non-syncopal forms of transient loss of consciousness, such as epileptic seizure or psychogenic pseudosyncope, can be ruled out. Reflex (neurally mediated) syncope and any form of orthostatic hypotension (OH) are the most frequent aetiologies of non-cardiac syncope. Identifying the haemodynamic mechanism of non-cardiac syncope is the essential prerequisite for an effective and personalized therapy aiming at preventing recurrences. While in most patients the aetiological diagnosis of non-cardiac syncope can be achieved through accurate history taking and exclusion of competing causes, the diagnosis of the underlying mechanism requires the use of diagnostic tests able to document the causal link between a specific haemodynamic mechanism and the actual moment of loss of consciousness. The possible haemodynamic mechanisms underlying non-cardiac syncope include primary hypotension and asystole/bradycardia of extrinsic cause, corresponding to two different haemodynamic phenotypes, i.e. the hypotensive and bradycardic phenotypes. The choice of therapy—aiming at counteracting hypotension or bradycardia—depends on the detected syncope phenotype. A brief autonomic diagnostic pathway including basic diagnostic tests, 24-h ambulatory blood pressure (BP) monitoring, tilt testing (TT), and carotid sinus massage (CSM) in older patients (Figure 1) may allow identification of the predominant haemodynamic mechanism of reflex syncope in most patients, leading to the diagnosis of hypotensive or bradycardic phenotype and thus guiding selection of mechanism-specific therapy. Albeit 24-h ECG monitoring and external prolonged loop ECG monitoring are widely used in clinical practice, their diagnostic value is very low in patients with syncope, and their use should be limited to selected cases in which the probability of syncope recurrence within the time duration of the test is high. Other autonomic tests (e.g. Valsalva manoeuvre or deep breathing test) may be helpful in identifying cardiovascular autonomic dysfunction as the underlying cause of syncope, but they do not determine the mechanism-specific therapy and thus are not necessary to include in the autonomic diagnostic pathway. Similarly, video-recording of spontaneous episodes is a useful tool for the identification of alternative forms of transient loss of consciousness such as psychogenic spells/pseudosyncope or epileptic seizures but cannot guide the selection of the appropriate treatment for non-cardiac syncope.

The diagnostic criteria of hypotensive phenotype are listed in Table 1. The assessment of the BP profile usually begins with BP measurement, either in-office and at home, which might reveal the presence of constitutional or drug-related hypotension (i.e. overtreated hypertensive patient). Office BP measurement should include 3 min of active standing.
test to investigate the possible presence of OH as many OH patients are asymptomatic in normal conditions. If syncope phenotype remains undetermined after the initial evaluation, the next phase of the diagnostic work-up should be a laboratory two-step strategy, which consists of (i) 24-h ambulatory BP monitoring (ABPM) and (ii) CSM, 3-min passive standing, and head-up TT performed one after another in an uninterrupted sequence as a single procedure in a tilt table laboratory. Office and home BP in the normal range should not discourage clinicians from investigating hypotensive susceptibility by means of 24-h ABPM, particularly in older patients or in the presence of symptoms of suspected hypotensive origin. Ambulatory BP monitoring may help the identification of persistent constitutional or drug-related hypotension, particularly in patients with a white coat syndrome. Moreover, ABPM might also reveal hypotensive episodes, i.e. isolated daytime systolic BP (SBP) drops <90 mmHg or SBP drops <100 mmHg. If hypotensive susceptibility is detected on ABPM, a hypotensive mechanism of syncope is likely and appropriate therapy should be considered.

Carotid sinus massage, performed according to the method of symptoms in patients aged 40 or older, and TT allow for investigation of both hypotensive and bradycardic phenotypes. Moreover, other dysautonomic syndromes, i.e. delayed OH and postural orthostatic tachycardia syndrome, can be diagnosed during TT (Tables 1 and 2). Tilt testing applicability has long been limited by time constraints that have negatively hampered its clinical use as a first-line diagnostic assessment. Recently, the ‘fast Italian protocol’ has been proposed, consisting of 10-min passive and 10-min nitroglycerine phases. The ‘fast protocol’ has been demonstrated to provide similar diagnostic yield compared to the traditional nitroglycerine protocol while being time and cost effective.

Prolonged ECG monitoring by means of implantable loop recorder (ILR) should be considered if the results of the above tests are uncertain, and an asystole/pronounced bradycardia phenotype is suspected. Although the ECG documentation of spontaneous syncope is the golden standard for the diagnosis of extrinsic arrhythmic syncope, its diagnostic value is limited by the fact that, owing to the unpredictable recurrence rate of syncope, the duration of monitoring often needs to be extended for months or even for years, thus delaying treatment and potentially exposing patients to the risk of recurrences. Moreover, even if an arrhythmic syncopal event is recorded by ILR, no information is available about BP changes associated with the event. Thus, ILR diagnosis should be completed by and combined with 24-h ABPM and short cardiovascular autonomic function assessment (SCAFA) tests to investigate all possible haemodynamic phenomena associated with syncope. Preferentially, SCAFA and 24-h ABPM should be performed prior to ILR implantation, unless pretest arrhythmic probability is very high.

It is worth noting that hypotensive and bradycardic reflexes often coexist, although being of a variable magnitude, and may both contribute to the syncopal episodes. Therefore, ILR documentation of bradycardia/asystole during a spontaneous event does not rule out the possibility that the hypotensive reflex revealed by ABPM or TT may represent the main cause of syncope, with bradycardia/asystole being a secondary late event, in some instances occurring when the patient has already fainted. Conversely, even when a hypotensive mechanism is likely, e.g. in the presence of OH, persistently low SBP, hypotensive episodes on ABPM, or a hypotensive TT response, a concomitant bradycardic reflex should be investigated. Indeed, low BP can represent both the final haemodynamic phenomenon and a trigger for reflex syncope, potentially inducing cardioinhibition that can be revealed by CSM or ILR monitoring. This reasoning implies the
need to perform a comprehensive and complete evaluation of both hypotensive and bradycardic phenotypes. An incomplete assessment will invariably increase the risk of syncope recurrences and treatment failure.

As a result of the complete syncope mechanism assessment (Figure 1), a hypotensive or bradycardic syncope phenotype can be diagnosed based on criteria detailed in Tables 1 and 2. A mixed (hypobrady) phenotype is diagnosed if criteria for both hypotensive and bradycardic phenotype, of similar magnitude, coexist in the same patient. We should bear in mind that the above-described work-up for the identification of syncope phenotype is indicated in patients with severe, unpredictable, and/or recurrent syncope episodes, as defined by ESC guidelines. 1 In contrast, in patients with mild and/or rare non-cardiac syncope, non-pharmacological treatment should be provided following the initial assessment, with no need of additional testing.

### Personalized mechanism-based therapy of non-cardiac syncope

In most patients with non-cardiac syncope, education and lifestyle measures allow to prevent syncope recurrences effectively without the need of a personalized mechanism-based therapy. These comprise reassurance about the benign nature of the disease, education regarding awareness and the possible avoidance of triggers and predisposing situations (e.g., dehydration and/or hot crowded environments), and the early recognition of pro-dromal symptoms in order to sit or lie down and activate counter-pressure manoeuvres without delay. If possible, triggers should be addressed directly, e.g., cough suppression in cough-induced syncope and micturition in the sitting position in micturition syncope. Increased daily intake and a water bolus of 500 cc in case of impending hypotensive symptoms are also advised. Salt supplementation at a dose of 120 mmol/day of sodium chloride has been proposed in non-hypertensive patients. 1 Additional interventions based on personalized mechanism-specific treatment strategies might be necessary in patients with severe, unpredictable, and recurrent syncope, if the above non-pharmacological therapies fail to prevent recurrences. In these patients, the aim of therapy is to increase BP if a predominant hypotensive phenotype is diagnosed and to counteract bradycardia if a predominant bradycardic phenotype is diagnosed. If both hypotensive and bradycardic phenotypes coexist, of similar magnitude, dual therapy is usually necessary. The flowchart of mechanism-based, evidence-based therapy is shown in Figure 2. Treatment goals are detailed in Boxes 1–3 and in Table 3.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Definition</th>
<th>Test</th>
<th>Blood pressure cut-offs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional hypotension</td>
<td>Persistently low BP in the absence of hypotensive medications, independent of triggering events</td>
<td>Office BP 24-h ABPM</td>
<td>Persistent SBP &lt;110 mmHg (males) or &lt;100 mmHg (females)</td>
</tr>
<tr>
<td>Drug-related persistent hypotension</td>
<td>SBP values persistently below the recommended target in patients receiving hypotensive medications</td>
<td>Office BP 24-h ABPM</td>
<td>Age &lt;65: persistent SBP &lt;120 mmHg</td>
</tr>
<tr>
<td>Hypotensive (intermittent) episodes</td>
<td>Orthostatic hypotension</td>
<td>Office BP and tilt testing</td>
<td>Symptomatic SBP fall ≥20 mmHg or standing SBP &lt;90 mmHg in 3 min of active standing during the initial evaluation or during passive standing while performing SCAFA. This latter includes both the classical form (during the first 3 min of the test) and the delayed form (onset after 3 min of the test). 4</td>
</tr>
<tr>
<td>Post-prandial hypotension</td>
<td></td>
<td>24-h ABPM</td>
<td>Symptomatic SBP fall ≥20 mmHg within 75 min of eating meals, compared to the mean of the last three BP measurements before the meal</td>
</tr>
<tr>
<td>Hypotensive reflex syncope</td>
<td>(1) Induction of syncope during tilt testing</td>
<td>Tilt testing</td>
<td>Typical haemodynamic pattern of mixed or vasodepressor vasovagal syncope with hypotension and bradycardia but without asystolic pauses &gt;3 s</td>
</tr>
<tr>
<td></td>
<td>(2) Reproduction of (pre)syncope during carotid sinus massage (method of symptoms)</td>
<td>Carotid sinus massage</td>
<td>Reproduction of spontaneous (pre)syncope, recognized by the patient itself, with fall in SBP &gt;50 mmHg or below 85 mmHg and the absence of asystolic pause/s &gt; 3 s</td>
</tr>
</tbody>
</table>

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

3See Fedorowski et al.1 and Torabi et al. 5

4See Solari et al. 7

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**Table 1** Hypotensive phenotype: diagnostic criteria (modified from Brignole et al.1)

**M. Brignole et al.**

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Hypotensive phenotype
Deprescribing of antihypertensive drugs

In the randomized stop-VD study,\textsuperscript{15} the reduction/withdrawal of BP therapy targeting office SBP of 140 mmHg resulted in a 63% decrease of syncopal recurrences compared to the control group. In the Discontinuation of Antihypertensive Treatment in Elderly people (DANTE) study,\textsuperscript{16} deprescribing of antihypertensive medications in older adults with mild cognitive impairment and a mean BP of 149/82 mmHg resulted in a 45% increased probability of recovery from OH.

In the SynABPM\textsuperscript{2} proof-of-concept study,\textsuperscript{17} the increase in average 24-h SBP on ABPM up to 13 mmHg, regardless of applied intervention strategy, was almost linearly correlated with the reduction of daytime SBP drops <90 and <100 mmHg. In an exploratory analysis of SynABPM\textsuperscript{2},\textsuperscript{18} an increase to an absolute 24-h SBP value of ≥134 mmHg and an increase of ≥12 mmHg of average 24-h SBP on ABPM were associated with a complete abolition of daily SBP drops <100 mmHg. Based on these data, a 24-h SBP of >134 mmHg and/or an increase of ≥12 mmHg of average 24-h SBP on ABPM can be recommended as targets for deprescribing in hypertensive patients with hypotensive phenotype. Systolic BP should not exceed 140 mmHg.\textsuperscript{15} Systolic BP values up to 160 mmHg can be accepted in individuals with severe frailty and/or disability, in view of the extremely high risk of syncope and traumatic falls, and the limited evidence supporting BP lowering in this vulnerable population.\textsuperscript{19–21} Drug withdrawal, rather than simply dose reduction, is mostly required to achieve the above targets.\textsuperscript{18} Among antihypertensive medications, α-blockers, nitrates, diuretics, β-blockers, and calcium antagonists are those at highest risk of drug-related OH and should be discontinued as much as possible. In the case that some antihypertensive medication is still needed, preference should be given to drug classes with protective effects or low

AV, atrioventricular; CSM, carotid sinus massage; ILR, implantable loop recorder; SBP, systolic blood pressure.

### Table 2  Bradycardic phenotype: diagnostic criteria according to 2018 ESC guidelines

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Definition</th>
<th>Test</th>
<th>CI cut-offs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardioinhibitory reflex syncope</td>
<td>(1) Reproduction of spontaneous symptoms during CSM (method of symptoms)</td>
<td>Supine and standing 10 s CSM</td>
<td>Induction of (pre)syncope, recognized by the patient itself, with fall in SBP &gt;50 mmHg and asystolic pause/s &gt; 3 s</td>
</tr>
<tr>
<td></td>
<td>(2) Reproduction of spontaneous syncope during tilt table test</td>
<td>Tilt testing</td>
<td>Induction of syncope with the typical ECG pattern of vasovagal syncope during hypotension and asystolic pause &gt; 3 s</td>
</tr>
<tr>
<td></td>
<td>(3) Asystolic pauses of likely reflex origin during prolonged ECG monitoring (ILR)</td>
<td>Prolonged ECG monitoring (ILR)</td>
<td>Typical ECG pattern of asystolic (&gt; 3 s) vasovagal syncope or documentation of asymptomatic asystolic pause &gt; 6 s of likely reflex origin</td>
</tr>
<tr>
<td>Idiopathic AV block (low adenosine syncope)</td>
<td>Symptomatic paroxysmal AV block</td>
<td>Prolonged ECG monitoring (ILR)</td>
<td>Typical ECG pattern of idiopathic AV block</td>
</tr>
</tbody>
</table>

AV, atrioventricular; CSM, carotid sinus massage; ILR, implantable loop recorder; SBP, systolic blood pressure.

### Figure 2  Mechanism-based first-choice therapy of patients with severe, recurrent, or unpredictable non-cardiac syncope. AV, atrioventricular; DDD-CLS, dual-chamber pacemaker with close-loop stimulation mode.


Box 1 Therapy of hypotensive phenotype

Goal: To increase average 24-h SBP and prevent SBP drops on ABPM

Interventions and target:
- In patients with drug-related hypotension, deprescribing targeted to achieve an absolute SBP value of ≥134 mmHg and/or an increase of ≥12 mmHg in 24-h ABPM. SBP should not exceed 140 mmHg, but <160 mmHg may be acceptable in frail older patients). Discontinuation rather than dose reduction is often required to reach the requested target.
- In patients with drug-unrelated hypotension or constitutional hypertension, lower body elastic garments, fludrocortisone, or midodrine, prescribed singularly or in combination, targeted to achieve an absolute average 24-h SBP of ≥116 mmHg and/or an increase of SBP ≥9 mmHg on ABPM.

Deprescribing of psychoactive drugs with hypotensive effects

Several psychoactive medications may show hypotensive effects, including levodopa, antipsychotics, tricyclic antidepressant, benzodiazepines, trazodone, and opioids.

Dopaminergic drugs may cause OH through the activation of α1-adrenergic receptors, with a higher incidence at advanced age. Hypotensive risk is higher for clozapine, chlorpromazine, and quetiapine and lower for haloperidol and olanzapine. Albeit levodopa may significantly contribute to OH associated with Parkinson disease, deprescribing is usually not possible due to worsening of motor function.

Antipsychotic drugs may cause OH through inhibition of α1-adrenergic receptors, with a higher incidence at advanced age. Hypotensive risk is higher for clozapine, chlorpromazine, and quetiapine and lower for haloperidol and olanzapine. As hypotensive effects are dose related, the lowest effective dose should be prescribed to minimize the risk of hypotension.

Orthostatic hypotension is the most common cardiovascular adverse effect of tricyclic antidepressants (with particular reference to amitriptyline and clomipramine), occurring in 10–50% of treated patients due to vasoconstriction mediated by α-adrenergic receptor blockade. Serotonin-selective reuptake inhibitors (SSRIs) are reported to have lower hypotensive effects, although impaired orthostatic BP response has been described.

Benzodiazepines have a significant hypotensive effect when administered intravenously in intensive care settings. In a recent study, users of oral benzodiazepine had lower SBP values than controls of patients with advanced age or cardiac diseases. Hypotensive effects are dose related and lower when using slow-release formulations.

Risk of OH, such as ACE inhibitors or angiotensin receptor antagonists, preferably administered at bedtime.

Although available evidence on deprescribing of antihypertensive medications mainly refers to older patients, existing data indicate it can be safely performed in patients with lower on-treatment BP values. However, the current state of knowledge claims for more evidence on the long-term benefits and safety of deprescribing.

Box 2 Therapy of bradycardic phenotype

Goal: To prevent asystolic episodes

Interventions and target:
- Dual-chamber cardiac pacing with adaptive pacing rate response (CLS probably most optimal) in patients with spontaneous or induced asystolic syncope aged >60 years.
- Cardiomechanical ablation of cardiac parasympathetic ganglia to prevent vagally induced asystolic syncope in patients aged >60 years.
- Theophylline 300 mg b.i.d., to be tailored to the maximum tolerated dose in the range 100 mg b.i.d. to 300 mg t.i.d. to be considered in patients with idiopathic paroxysmal AV block (low adenosine forms).

Blood pressure–increasing therapies

Leg compression stockings and abdominal binders

The rationale for the use of elastic compression garments is to apply external counter-pressure to capacitance vessels of the lower body, thus improving venous return to the heart. Some small, controlled trials have consistently shown the efficacy of elastic garments in preventing orthostatic SBP decrease and related symptoms. The nominal pressure of abdominal binders is set at 20–40 mmHg, and the nominal pressure of leg stocking is set at a degree of 40–60 mmHg at the level of the ankles and 30–40 mmHg at the level of the hip. The elastic stockings were well tolerated for at least 6 months in two-thirds of cases.

Fludrocortisone

The mineralocorticoid fludrocortisone expands intravascular volume by increasing renal water and sodium reabsorption, with possible long-term effects on vascular resistance. The double-blind randomized controlled Prevention of Syncope Trial (POST 2) showed a significant 49% reduction of syncope recurrences in young (median age of 30 years) vasovagal syncope patients receiving fludrocortisone at a dose of 0.2–0.3 mg/day. Moreover, some data support fludrocortisone use in young healthy subjects with constitutional hypotension and in older patients with neurogenic OH.

In an exploratory analysis of the SYNABPM2 study, fludrocortisone at a dose of 0.1–0.3 mg/day performed in patients with lower on-treatment BP values.
increased average 24-h and daytime SBP on ABPM by 9.3 mmHg (from 107 to 116 mmHg) and 9.9 mmHg (from 109–119 mmHg), respectively, reducing daytime SBP drops <90 and <100 mmHg by 73 and 50%. Based on these data, an average daytime SBP of 116 mmHg and/or an increase of SBP ≥9 mmHg on ABPM might be recommended as treatment targets.

Midodrine
In the double-blinded, placebo-controlled POST 4 trial involving young patients (median age 32 years) with vasovagal syncope, the alpha-agonist midodrine (dose range 2.5 mg b.i.d.–10 mg t.i.d.) was found to reduce recurrences from 61 to 42% (relative risk reduction of 31%) during 1 year of follow-up. In a meta-analysis of three open-label...
and two double-blind randomized trials, midodrine reduced the risk of syncopal recurrences from 55 to 34% (relative risk reduction of 51%). In an exploratory analysis of SynABPM2 study,42 intravenous midodrine was less effective than fludrocortisone. The administration of midodrine at a dose of 5–20 mg/day increased average 24-h and daytime SBP on ABPM by 2.3 mmHg (from 112.7 to 115 mmHg) and 1.7 mmHg (from 115 to 116.6 mmHg), respectively, reducing daytime SBP drops <90 and <100 mmHg by 52 and 34%. The short duration of effects of midodrine (a few hours only) likely impacted the lower observed increase in SBP features significantly lower reduced syncope recurrences compared with no active pacing treatment (relative and absolute risk reduction at 2 years: 77 and 46%, respectively; number needed to treat: 2.2). In a T7-induced vasovagal reflex study,53 CLS determined an average increase of CLS rate up to 105 ± 14 bpm during the presyncopal phase of circulatory instability, which occurred 1.7 min before the time of maximum vagal effect. Cardiac pacing with dual-chamber CLS pacemaker thus represents the treatment of choice in older patients with predominant bradycardic phenotype.

### Management of recurrences

A few general rules when syncope recurs after the above strategies have been implemented:

- If the target for effectiveness is not achieved, consider further deprescribing of hypotensive medication or higher dose of BP-increasing therapies in patients with hypotensive phenotype; consider repeating cardioneuroablation if minimal or absent heart rate increase has been achieved after the first procedure; verify pacemaker status and optimize programming.
- If a single treatment strategy is not sufficient to achieve the treatment target, a combination therapy can be considered, e.g. deprescribing of BP-lowering drugs and application of elastic garments; combined pharmacological therapy (fludrocortisone and midodrine) and application of elastic garments; cardiac pacing, if medical therapy (i.e. theophylline) or cardioneuroablation have failed.
- If a mixed phenotype has been diagnosed, a dual therapy based on a combination of antihypotensive and bradycardic measures is necessary, e.g. deprescribing of hypotensive drugs and/or elastic garments combined with cardioneuroablation or cardiac pacing.
- Alternative therapies can be considered even if there is weak evidence of efficacy on prevention of syncopal recurrences on long-term period: head-up tilt sleeping,54 tilt training,55 atomoxetine,56 and droxidopa.57
- A reappraisal of the diagnostic pathway should be considered if the above rules fail to prevent recurrences.

### Conclusions and clinical perspectives

There is no single therapy that is effective for all forms of non-cardiac syncope. Even if the diagnosis of the haemodynamic mechanism is often presumptive and, therefore, may be imperfect, a treatment approach based on the predominant syncope phenotype is likely to be more effective than a treatment approach based on aetiology. Nevertheless, since patients can still experience recurrence of syncope, the appropriate information given to the patient is very important for managing the patient’s expectations. Future large trials should be aimed to assess the efficacy of mechanism-based therapy in the long-term perspective.

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### Conflict of interest

none declared.

### Data availability

All relevant data are within the manuscript and its supporting information files.

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