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

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[1]IRCCS Istituto Auxologico Italiano, Faint and Fall Research Centre, Department of Cardiology, S. Luca Hospital, Piazzale Brescia 20, 20149 Milano, Italy; [2]Division of Geriatric and Intensive Care Medicine, University of Florence and Azienda Ospedaliero Universitaria Careggi, Florence, Italy; [3]Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden; and [4]Department of Medicine, Karolinska Institute, Stockholm, Sweden

**Abstract**

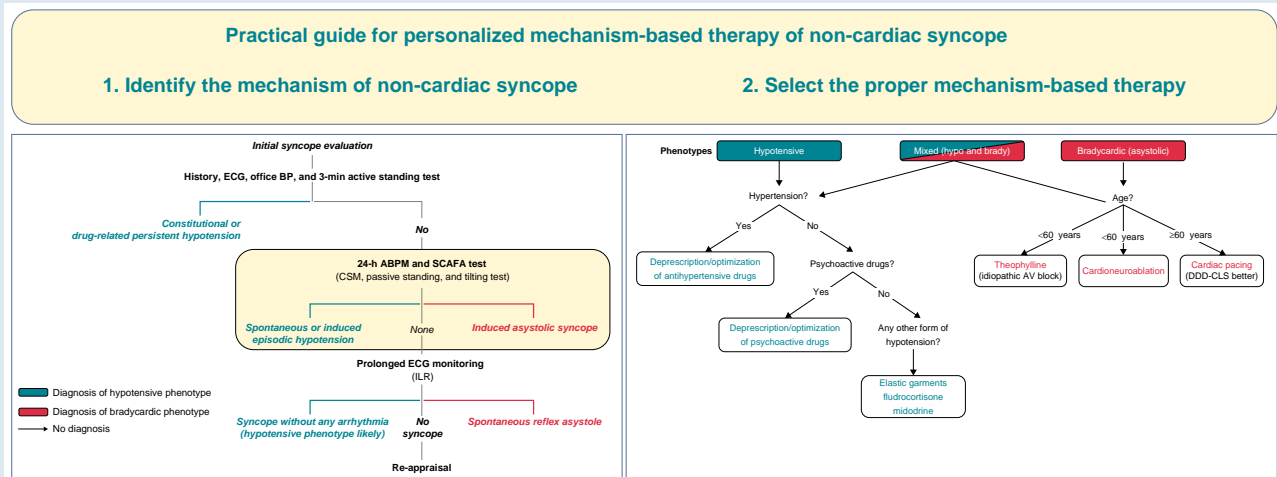The term non-cardiac syncope includes all forms of syncope, in which primary intrinsic cardiac mechanism and non-syncopal transient loss of consciousness can be ruled out. Reflex syncope and orthostatic hypotension are the most frequent aetiologies of non-cardiac syncope. As no specific therapy is effective 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.

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## 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**

*Initial syncope evaluation*

History, ECG, office BP, and 3-min active standing test

*Constitutional or drug-related persistent hypotension*

**No**

**24-h ABPM and SCAFA test**
(CSM, passive standing, and tilting test)

*Spontaneous or induced episodic hypotension* — None — *Induced asystolic syncope*

**Prolonged ECG monitoring**
(ILR)

*Syncope without any arrhythmia (hypotensive phenotype likely)* — **No syncope** — *Spontaneous reflex asystole*

**Re-appraisal**

- Diagnosis of hypotensive phenotype
- Diagnosis of bradycardic phenotype
- → No diagnosis

Phenotypes: Hypotensive | Mixed (hypo and brady) | Bradycardic (asystolic)

Hypertension?
- Yes → Deprescription/optimization of antihypertensive drugs
- No → Psychoactive drugs?
  - Yes → Deprescription/optimization of psychoactive drugs
  - No → Any other form of hypotension? → Elastic garments fludrocortisone midodrine

Age?
- <60 years → Theophylline (idiopathic AV block)
- <60 years → Cardioneuroablation
- ≥60 years → Cardiac pacing (DDD-CLS better)

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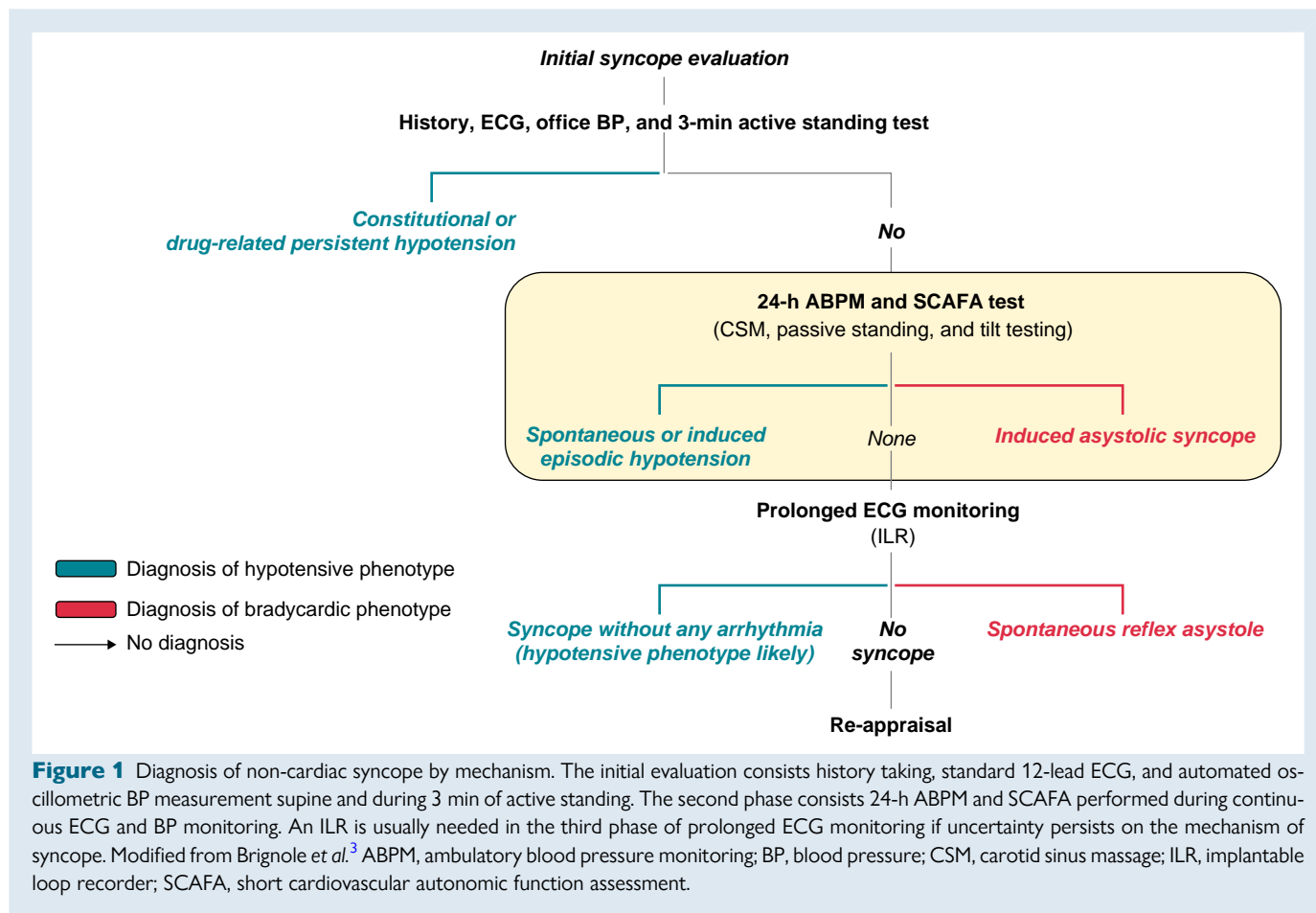
## Diagnostic work-up for the investigation of the mechanism of non-cardiac syncope

The term non-cardiac syncope includes forms of syncope, in which cardiac mechanism, such as primary intrinsic cardiac arrhythmias or structural flow obstruction, and non-syncopal forms of transient loss of consciousness, such as epileptic seizure or psychogenic pseudosyncope, can be ruled out.[1,2] 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.[2]

A brief autonomic diagnostic pathway[3] 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.[1] Other autonomic tests (e.g. Valsalva manoeuvre or deep breathing test) may be helpful in identifying cardiovascular autonomic dysfunction[4] 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[1] 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

**Figure 1** Diagnosis of non-cardiac syncope by mechanism. The initial evaluation consists history taking, standard 12-lead ECG, and automated oscillometric BP measurement supine and during 3 min of active standing. The second phase consists 24-h ABPM and SCAFA performed during continuous ECG and BP monitoring. An ILR is usually needed in the third phase of prolonged ECG monitoring if uncertainty persists on the mechanism of syncope. Modified from Brignole et al.[3] ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CSM, carotid sinus massage; ILR, implantable loop recorder; SCAFA, short cardiovascular autonomic function assessment.

test to investigate the possible presence of OH as many OH patients are asymptomatic in normal conditions.[8] 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.[9,10] Moreover, ABPM might also reveal hypotensive episodes, i.e. isolated daytime systolic BP (SBP) drops <90 mmHg or SBP drops <100 mmHg.[11] 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.[12]

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.[1] 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.[13] 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 arrhythmia 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.[14] 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

**Table 1** Hypotensive phenotype: diagnostic criteria (modified from Brignole *et al.*[3])

| Diagnosis | Definition | Test | Blood pressure cut-offs |
|---|---|---|---|
| Constitutional hypotension | Persistently low BP in the absence of hypotensive medications, independent of triggering events | Office BP<br>24-h ABPM | Persistent SBP <110 mmHg (males) or <100 mmHg (females)<br>*Males*<br>24 h SBP <105 mmHg<br>Daytime SBP <115 mmHg<br>Nighttime SBP <97 mmHg<br>*Females*<br>24 h SBP <98 mmHg<br>Daytime SBP <105 mmHg<br>Nighttime SBP <92 mmHg |
| Drug-related persistent hypotension | SBP values persistently below the recommended target in patients receiving hypotensive medications | Office BP<br><br>24-h ABPM | Age <65: persistent SBP <120 mmHg<br>Age ≥65: persistent SBP <130 mmHg<br>24 h SBP <120 mmHg |
| Hypotensive (intermittent) episodes | Orthostatic hypotension | Office BP and tilt testing | Symptomatic SBP fall ≥20 mmHg or standing SBP <90 mmHg within 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)[a] |
| | Post-prandial hypotension | 24-h ABPM | Symptomatic SBP fall >20 mmHg within 75 min of eating meals, compared to the mean of the last three BP measurements before the meal |
| | Hypotensive drops | 24-h ABPM | ≥1 episode of daytime SBP <90 mmHg<br>≥2 episodes of daytime SBP <100 mmHg |
| Hypotensive reflex syncope | (1) Induction of syncope during tilt testing | Tilt testing | Typical haemodynamic pattern of mixed or vasodepressor vasovagal syncope with hypotension and bradycardia but without asystolic pauses >3 s |
| | (2) Reproduction of (pre)syncope during carotid sinus massage (method of symptoms) | Carotid sinus massage | Reproduction of spontaneous (pre)syncope, recognized by the patient itself, with fall in SBP >50 mmHg or below 85 mmHg[b] and the absence of asystolic pause/s > 3 s |

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]See Fedorowski *et al.*[5] and Torabi *et al.*[6]
[b]See Solari *et al.*[7]

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 (hypo-brady) 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 prodromal 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 2** Bradycardic phenotype: diagnostic criteria according to 2018 ESC guidelines[1]

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

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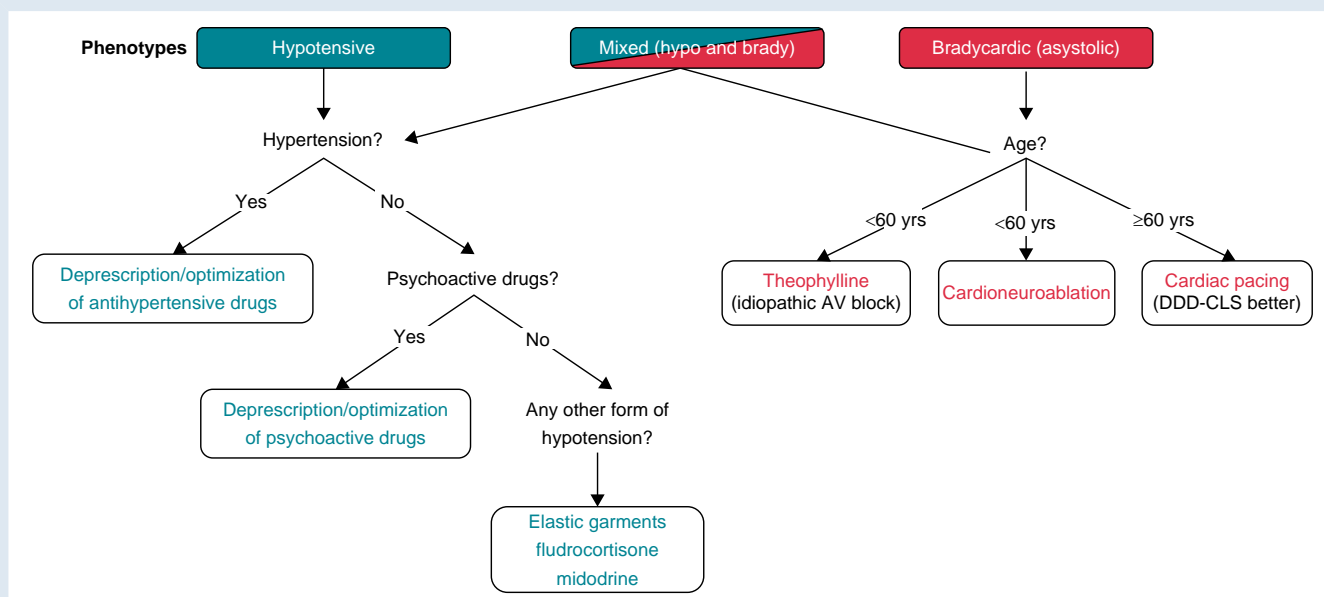


**Figure 2** Mechanism-based first-choice therapy of patients with severe, recurrent, or unpredictable non-cardiac syncope. AV, atrioventricular; DDD-CLS, dual-chamber pacemaker with close-loop stimulation mode.

# Hypotensive phenotype
## Deprescribing of antihypertensive drugs

In the randomized stop-VD study,[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,[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 SynABPM2 proof-of-concept study,[17] the increase in average 24-h SBP on ABPM up to 13 mmHg, regardless of applied interventional strategy, was almost linearly correlated with the reduction of daytime SBP drops <90 and <100 mmHg. In an exploratory analysis of SynABPM2,[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.[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.[19–21] Drug withdrawal, rather than simply dose reduction, is mostly required to achieve the above targets.[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

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**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 hypotension, 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.

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**Box 2 Therapy of bradycardic phenotype**

*Goal*: To prevent asystolic episodes

    *Interventions and target*:

- Dual-chamber cardiac pacing with adaptative pacing rate response (CLS probably most optimal) in patients with spontaneous or induced asystolic syncope aged >60 years.
- Cardioneuroablation 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).

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**Box 3 Therapy of mixed (hypo-brady) phenotype**

*Goal*: To increase average 24-h SBP and prevent SBP drops on ABPM and to prevent asystolic episodes

    *Interventions and target*: The most appropriate intervention(s) among the above should be combined in a dual therapy (see *Boxes 1* and *2*).

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risk of OH, such as ACE inhibitors or angiotensin receptor antagonists,[2,22,23] 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.[23–26] However, the current state of knowledge claims for more evidence on the long-term benefits and safety of deprescribing.

**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 dopamine receptors, leading to cutaneous, mesenteric, and renal vasodilation.[27] 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.[28,29]

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 vasodilation mediated by α-adrenergic receptor blockade.[30,31] Serotonin-selective reuptake inhibitors (SSRIs) are reported to have lower hypotensive effects, although impaired orthostatic BP response has been described.[31,32]

Benzodiazepines have a significant hypotensive effect when administered intravenously in intensive care settings. In a recent study,[33] users of oral benzodiazepine had lower SBP values than controls and a significantly greater BP drop at 10 s after standing. The mechanism is unclear.

Trazodone is a multifunctional drug that also determines inhibition of α-adrenergic receptors.[34] Orthostatic hypotension is reported in 1–7% of patients, thus representing the most common cardiovascular adverse effect. Trazodone-related hypotension more likely occurs in patients with advanced age or cardiac diseases. Hypotensive effects are dose related and lower when using slow-release formulations.

Opioids, including morphine, hydrocodone, hydromorphone, and meperidine, can induce histamine release, resulting in a significant decrease of vascular resistance and BP, particularly in patients with reduced cardiac function or taking hypotensive medications.[35]

In summary, psychoactive medications may have relevant hypotensive effects that are often overlooked in clinical practice. Discontinuation or optimization of these drugs should be carefully considered in patients with hypotensive phenotype, with the same goals and targets of antihypertensive drugs (see section above).

## 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[36–39] 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.[38]

*Fludrocortisone*

The mineralocorticoid fludrocortisone expands intravascular volume by increasing renal water and sodium reabsorption, with possible long-term effects on vascular resistance.[22] The double-blind randomized controlled Prevention of Syncope Trial (POST 2)[40] 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.[41] In an exploratory analysis of the SynABPM2 study,[42] fludrocortisone at a dose of 0.1–0.3 mg/day

**Table 3** Personalized mechanism-based treatment strategies for patients affected by non-cardiac syncope. For definitions, refer to *Tables 1 and 2*

| WHO? | HOW? | TREATMENT TARGET? |
| --- | --- | --- |
| *Hypertension and drug-related hypotension* <br> Any of the following forms: <br> - Persistent hypotension <br> - Hypotensive episodes <br> - Hypotensive reflex syncope | *Deprescribing of antihypertensive drugs.* <br> Preference given to deprescribing of α-blockers, nitrates, diuretics, β-blockers and calcium antagonists. <br> Drugs withdrawal, rather than dose reduction, is usually required. | Absolute SBP ≥134 mmHg and/or an increase ≥12 mmHg on 24-hour ABPM. <br> SBP should not exceed 140 mmHg (<160 mmHg may be acceptable in frail older and very symptomatic patients). |
| *Hypotension caused by psychoactive drugs.* <br> Any of the following forms: <br> - Persistent hypotension <br> - Hypotensive episodes <br> - Hypotensive reflex syncope | *Discontinuation or dose reduction of antipsychotics, antidepressants, benzodiazepines, trazodone, opioids.* <br> Consult the appropriate specialist, if needed. | Absolute SBP ≥134 mmHg and/or an increase ≥12 mmHg on 24-hour ABPM. <br> SBP should not exceed 140 mmHg (<160 mmHg may be acceptable in frail older and very symptomatic patients). |
| *Drug-unrelated hypotension and constitutional hypotension.* <br> Any of the following forms: <br> - Persistent hypotension <br> - Hypotensive episodes <br> - Hypotensive reflex syncope | *Elastic garments:* <br> Abdominal binders 20-40 mmHg; leg stocking 40-60 mmHg (ankles) and 30-40 mmHg (hip) <br> *Fludrocortisone:* <br> Starting dose 0.2 mg per day (range 0.1 – 0.3 mg per day) <br> *Midodrine:* Starting dose 5 mg t.i.d 4 hours apart, with the intent to adjust the dose within a range of 2.5 mg b.i.d and 10 mg t.i.d. | Absolute SBP ≥116 mmHg and/or increase ≥9 mmHg on 24-hour ABPM |
| *Idiopathic paroxysmal AV block* <br> (low adenosine syncope) | *Theophylline:* <br> Starting dose 300 mg b.i.d. to be tailored in the range 100 mg b.i.d to 300 mg t.i.d. | Maximum tolerated dose |
| *Cardioinhibitory reflex syncope, age <60 years:* <br> Any of the following forms: <br> - Induced by tilt testing <br> - Induced by carotid sinus massage <br> - Spontaneous asystolic pauses during ECG monitoring | *Cardioneuroablation:* <br> Catheter ablation of superior and inferior paraseptal ganglionated vagal plexi | Procedural success defined as increase in heart rate, lengthening of AH interval and shortening of Wenckebach cycle length and significant long-term increase in heart rate with a decrease in heart rate variability |
| *Cardioinhibitory reflex syncope, age >60 years:* <br> Any of the following forms: <br> - Induced by tilt-induced <br> - Induced by carotid sinus massage <br> - Spontaneous asystolic pauses during ECG monitoring (ILR) | *Dual chamber adaptive pacemaker, CLS mode preferable* | Starting CLS programming: basic rate of 50 bpm, maximum CLS rate at 120 bpm, CLS rate-adaptive response 'Medium', and resting rate control OFF <br> Personalized programming guided by tilt testing in case of syncopal recurrences |

ABPM, ambulatory blood pressure monitoring; AV, atrioventricular; CLS, closed-loop stimulation; ILR, implantable loop recorder; SBP, systolic blood pressure.

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,[43] 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[44] 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] 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.

## Bradycardic phenotype
### Idiopathic paroxysmal atrioventricular block (low adenosine syncope)

Syncope due to idiopathic atrioventricular (AV) block is a distinct clinical form of syncope characterized by the following: (i) no/very short prodrome; (ii) ECG documentation of paroxysmal complete AV block (one or multiple consecutive pauses), occurring without P-P cycle lengthening or PR interval prolongation and not triggered by atrial or ventricular premature beats nor by rate variations; and (iii) the absence of cardiac and ECG abnormalities. Contrary to vasovagal syncope, these patients usually show low values of plasma adenosine, which acts on the AV node and is supposed to be involved in the occurrence of paroxysmal AV blocks.[45] However, the typical clinical and ECG features of the syndrome allow to start therapy even in the absence of an adenosine value. Theophylline, a non-selective adenosine receptor antagonist, was shown to be effective in abolishing paroxysmal AV block during long-term ECG monitoring in syncope patients with no prodrome and no cardiac disease.[46,47] In a propensity score–matched multicentre trial,[48] theophylline at maximum tolerated dose was effective in reducing asystolic AV block events during ILR monitoring from 12 to 3% (relative risk reduction of 83%). Beneficial effects were less in low adenosine patients with sinus arrest (absolute risk reduction from 17 to 14%, relative risk reduction of 56%). Based on this evidence, theophylline can represent a valuable treatment option in patients with syncope without prodrome, with normal heart and normal ECG, with particular reference to those with ECG evidence of paroxysmal AV block. Effectiveness might be limited by side effects, which are usually not severe, but may lead to treatment discontinuation in a considerable proportion of patients.

### Cardioneuroablation

Catheter ablation of the vagal plexi that are close to the sinuatrial and AV nodes, i.e. the superior and inferior paraseptal ganglionated plexus, respectively, has been shown to decrease the vagal outflow responsible for cardioinhibition and to prevent the recurrence of syncope during the first 2 years of follow-up in patients with spontaneous or induced asystolic syncope aged <60 years.[49] A meta-analysis of 14 observational studies[50] reported an average freedom of syncopal recurrence in 92% of patients. A randomized controlled trial[51] reported a decrease of syncopal recurrences from 54 to 8% (relative risk reduction of 85%). Successful ganglia ablation results in a periprocedural modification of electrophysiological parameters (increase in heart rate, shortening of AH interval, and shortening of Wenckebach cycle length) and a significant long-term increase in heart rate with a decrease in heart rate variability.[52] Current evidence, however, does not support cardioneuroablation in older patients (age >60 years).

### Cardiac pacing

Eight randomized controlled trials consistently showed the superiority of active dual-chamber pacing compared with not paced controls.[2] The 3-year recurrence rate after pacing was similar in patients with cardioinhibitory carotid sinus syndrome (16%), asystolic tilt response (23%), and spontaneous asystole documented by ILR (24%), thus suggesting similar indications and benefits for the three forms of reflex syncope.[53] In the most recent multicentre, randomized, placebo-controlled BIOSync trial,[54] dual-chamber pacemaker with closed-loop stimulation (CLS)

features highly significantly 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 TT-induced vasovagal reflex study,[55] CLS determined an average increase of CLS rate up to $105 \pm 14$ 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 antibradycardic 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,[56] tilt training,[57] atomoxetine,[58] and droxidopa.[59]
- 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.

## Funding

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

## References
1. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A *et al.* ESC guidelines for the diagnosis and management of syncope. *Eur Heart J* 2018;**39**:1883–948.
2. Brignole M, Rivasi G. New insights in diagnostics and therapies in syncope: a novel approach to non-cardiac syncope. *Heart* 2021;**107**:864–73.
3. Brignole M, Rivasi G, Fedorowski A, Ståhlberg M, Groppelli A, Ungar A. Tests for the identification of reflex syncope mechanism. *Expert Rev Med Devices* 2023;**20**:109–19.
4. Fedorowski A, Fanciulli A, Raj SR, Sheldon R, Shibao CA, Sutton R. Cardiovascular autonomic dysfunction in post-COVID-19 syndrome: a major health-care burden. *Nat Rev Cardiol* 2024. https://doi.org/10.1038/s41569-023-00962-3

5. Fedorowski A, Hamrefors V, Sutton R, van Dijk JG, Freeman R, Lenders JW et al. Do we need to evaluate diastolic blood pressure in patients with suspected orthostatic hypotension? Clin Auton Res 2017;27:167–73.

6. Torabi P, Ricci F, Hamrefors V, Sutton R, Fedorowski A. Classical and delayed orthostatic hypotension in patients with unexplained syncope and severe orthostatic intolerance. Front Cardiovasc Med 2020;7:21.

7. Solari D, Maggi R, Oddone D, Solano A, Croci F, Donateo P et al. Assessment of the vasodepressor reflex in carotid sinus syndrome. Circ Arrhythm Electrophysiol 2014;7:505–10.

8. Fedorowski A, Ricci F, Hamrefors V, Sandau KE, Hwan Chung T, Muldowney JAS et al. Orthostatic hypotension: management of a complex, but common, medical problem. Circ Arrhythm Electrophysiol 2022;15:e010573.

9. Divison-Garrote JA, Ruilope LM, de la Cruz JJ, de la Sierra A, de la Cruz JJ, Vinyoles E. Magnitude of hypotension based on office and ambulatory blood pressure monitoring: results from a cohort of 5066 treated hypertensive patients aged 80 years and older. J Am Med Dir Assoc 2017;18:452.e1–e6.

10. Rivasi G, Mossello E, Turrin G, D'Andria MF, Tortù V, Ceolin L. Hypotensive episodes revealed by ambulatory blood pressure monitoring in nursing home residents. J Am Geriatr Soc 2022;70:902–5.

11. Rivasi G, Groppelli A, Brignole M, Soranna D, Zambon A, Bilo G. Association between hypotension during 24 h ambulatory blood pressure monitoring and reflex syncope: the SynABPM 1 study. Eur Heart J 2022;43:3765–76.

12. Russo V, Tomaino M, Parente E, Comune A, Sabatini A, Laezza N et al. Short duration head-up tilt test potentiated with potentiated with sublingual nitroglycerin in suspected vasovagal syncope: the fast Italian protocol. Eur Heart J 2023;44:2473–9.

13. Brignole M, Deharo JC, Menozzi C, Moya A, Sutton R, Tomaino M. The benefit of pacemaker therapy in patients with neurally mediated syncope and documented asystole: a meta-analysis of implantable loop recorder studies. Europace 2018;20:1362–6.

14. Saal DP, Thijs RD, van Zwet EW, Bootsma M, Brignole M, Benditt DG et al. Temporal relationship of asystole to onset of transient loss of consciousness in tilt-induced reflex syncope. JACC Clin Electrophysiol 2017 Dec 26;3:1592–8.

15. Solari D, Tesi F, Unterhuber M, Gaggioli G, Ungar A, Tomaino M. Stop vasodepressor drugs in reflex syncope: a randomised controlled trial. Heart 2017;103:449–55.

16. Moonen JEF, Foster-Dingley JC, de Ruijter W, van der Grond J, de Craen AJ, van der Mast RC. Effect of discontinuation of antihypertensive medication on orthostatic hypotension in older persons with mild cognitive impairment: the DANTE study Leiden. Age Ageing 2016;45:249–55.

17. Groppelli A, Rivasi G, Fedorowski A, de Lange F, Russo V, Maggi R, et al. Interventions aimed to increase average 24-hour systolic blood pressure reduce blood pressure drops in patients with reflex syncope and orthostatic intolerance. Europace 2024;26:euae026.

18. Groppelli A, Rivasi G, Fedorowski A, de Lange F, Russo V, Maggi R, et al. Targets for deprescribing in patients with hypertension and reflex syncope. https://doi.org/10.5281/zenodo.10874903 2024.

19. Rivasi G, Brignole M, Rafanelli M, Bilo G, Pengo MF, Ungar A et al. Blood pressure management in hypertensive patients with syncope: how to balance hypotensive and cardiovascular risk. J Hypertens 2020;38:2356–62.

20. Rivasi G, Tortù V, D'Andria MF. Hypertension management in frail older adults: a gap in evidence. J Hypertension 2021;39:400–7.

21. Rivasi G, Fedorowski A. Harm vs. benefit of antihypertensive treatment in very old and frail people—do not miss the forest for the trees. J Hypertens 2023;41:1551–3.

22. Rivasi G, Rafanelli M, Mossello E, Brignole M, Ungar A. Drug-related orthostatic hypotension: beyond anti-hypertensive medications. Drugs Aging 2020;37:725–38.

23. Iyer S, Naganathan V, McLachlan AJ, Le Couteur DG. Medication withdrawal trials in people aged 65 years and older: a systematic review. Drugs Aging 2008;25:1021–31.

24. Reeve E, Jordan V, Thompson W, Sawan M, Todd A, Gammie TM et al. Withdrawal of antihypertensive drugs in older people. Cochrane Database Syst Rev 2020;6:CD012572.

25. Nelson MR, Reid CM, Krum H, Ryan P, Wing LM, McNeil JJ. Management Committee, Second Australian National Blood Pressure Study. Short-term predictors of maintenance of normotension after withdrawal of antihypertensive drugs in the second Australian National Blood Pressure Study (ANBP2). Am J Hypertens 2003;16:39–45.

26. van der Wardt V, Harrison JK, Welsh T, Conroy S, Gladman J. Withdrawal of antihypertensive medication: a systematic review. J Hypertens 2023;35:1742–1749.

27. Wood LD. Clinical review and treatment of select adverse effects of dopamine receptor agonists in Parkinson's disease. Drugs Aging 2010;27:295–310.

28. Mackin P. Cardiac side effects of psychiatric drugs. Hum Psychopharmacol 2008;23:3–14.

29. Gugger JJ. Antipsychotic pharmacotherapy and orthostatic hypotension: identification and management. CNS Drugs 2011;25:659–71.

30. Darowski A, Chambers SA, Chambers DJ. Antidepressants and falls in the elderly. Drugs Aging 2009;26:381–94.

31. Press Y, Punchik B, Freud T. Orthostatic hypotension and drug therapy in patients at an outpatient comprehensive geriatric assessment unit. J Hypertens 2016;34:351–8.

32. Briggs R, Carey D, McNicholas T, Claffey P, Nolan H, Kennelly SP et al. The association between antidepressant use and orthostatic hypotension in older people: a matched cohort study. J Am Soc Hypertens 2018;12:597–604.e1.

33. Rivasi G, Kenny RA, Ungar A, Romero-Ortuno R. Effects of benzodiazepines on orthostatic blood pressure in older people. Eur J Intern Med 2020;72:73–8.

34. Haria M, Fitton A, McTavish D. Trazodone: a review of its pharmacology, therapeutic use in depression and therapeutic potential in other disorders. Drugs Aging 1994;4:331–55.

35. Chen A, Ashburn MA. Cardiac effects of opioid therapy. Pain Med 2015;16:S27–31.

36. Denq JC, Opfer-Gehrking TL, Giuliani M, Felten J, Convertino VA, Low PA. Efficacy of compression of different capacitance beds in the amelioration of orthostatic hypotension. Clin Auton Res 1997;7:321–6.

37. Smit AA, Wieling W, Fujimura J, Denq JC, Opfer-Gehrking TL, Akarriou M et al. Use of lower abdominal compression to combat orthostatic hypotension in patients with autonomic dysfunction. Clin Auton Res 2004;14:167–75.

38. Podoleanu C, Maggi R, Brignole M, Croci F, Incze A, Solano A et al. Lower limb and abdominal compression bandages prevent progressive orthostatic hypotension in elderly persons: a randomized single-blind controlled study. J Am Coll Cardiol 2006;48:1425–32.

39. Fanciulli A, Goebel G, Metzler B, Sprenger F, Poewe W, Wenning GK et al. Elastic abdominal binders attenuate orthostatic hypotension in Parkinson's disease. Mov Dis Clin Practice 2015;3:156–60.

40. Sheldon R, Raj SR, Rose MS, Morillo CA, Krahn AD, Medina E et al. Fludrocortisone for the prevention of vasovagal syncope: a randomized, placebo-controlled trial. J Am Coll Cardiol 2016;68:1–9.

41. Veazie S, Peterson K, Ansari Y, Chung KA, Gibbons CH, Raj SR et al. Fludrocortisone for orthostatic hypotension. Cochrane Database of Syst Revs 2021;5:CD012868.

42. De Lange F, Rivasi G, Groppelli A, Russo V, Maggi R, Capacci M, et al. Effect of BP rising drug therapy in patients with symptoms due to hypotension. https://doi.org/10.5281/zenodo.10875142 2024

43. Sheldon R, Faris P, Tang A, Ayala-Paredes F, Guzman J, Marquez M et al. Midodrine for the prevention of vasovagal syncope: a randomized clinical trial. Ann Intern Med 2021;174:1349–56.

44. Lei LY, Raj SR, Sheldon RS. Midodrine for the prevention of vasovagal syncope: a systematic review and meta-analysis. Europace 2022;24:1171–8.

45. Brignole M, Deharo JC, De Roy L, Menozzi C, Blommaert D, Dabiri L et al. Syncope due to idiopathic paroxysmal atrioventricular block. Long term follow-up of a distinct form of atrioventricular block. J Am Coll Cardiol 2011;58:167–73.

46. Brignole M, Solari D, Iori M, Bottoni N, Guieu R, Deharo JC. Efficacy of theophylline in patients affected by low adenosine syncope. Heart Rhythm 2016;13:1151–4.

47. Brignole M, Iori M, Solari D, Bottoni N, Rivasi G, Ungar A et al. Efficacy of theophylline in patients with syncope without prodromes with normal heart and normal ECG. Int J Cardiol 2019;289:70–3.

48. Brignole M, Iori M, Strano S, Tomaino M, Rivasi G, Ungar A et al. Theophylline in patients with syncope without prodrome, normal heart, and normal electrocardiogram: a propensity-score matched study verified by implantable cardiac monitor. Europace 2022;24:1164–70.

49. Brignole M, Aksu T, Calò L, Debruyne P, Deharo JC, Fanciulli A et al. Clinical controversy: methodology and indications of cardioneuroablation for reflex syncope. Europace 2023;25:euad033.

50. Vandenberk B, Lei LY, Ballantyne B, Vickers D, Liang Z, Sheldon RS et al. Cardioneuroablation for vasovagal syncope: a systematic review and meta-analysis. Heart Rhythm 2022;19:1804–12.

51. Piotrowski R, Baran J, Sikorska A, Krynski T, Kulakowski P. Cardioneuroablation for reflex syncope: efficacy and effects on autonomic cardiac regulation—a prospective randomized trial. JACC Clin Electrophysiol 2023;9:85–95.

52. Aksu T, Brignole M, Calò L, Debruyne P, Di Biase L, Deahro JC et al. Cardioneuroablation for the treatment of reflex syncope and functional bradyarrhythmias. A scientific statement of the European Heart Rhythm Association (EHRA) of the ESC, the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS) and the Latin American Heart Rhythm Society (LAHRS). Europace 2024. in press.

53. Brignole M, Arabia F, Ammirati F, Tomaino M, Quartieri F, Rafanelli M et al. Standardized algorithm for cardiac pacing in older patients affected by severe unpredictable reflex syncope: 3-year insights from the Syncope Unit Project 2 (SUP 2) study. Europace 2016;18:1427–33.

54. Brignole M, Russo V, Arabia F, Oliveira M, Pedrote A, Aerts A et al. Cardiac pacing in severe recurrent reflex syncope and tilt-induced asystole. Eur Heart J 2021;42:508–16.

55. Russo V, Tomaino M, Parente E, Comune A, Giacopelli D, Napoli P, et al. Temporal relationship between hemodynamic changes and activation of closed loop stimulation during tilt-induced vasovagal syncope. Europace 2024;26:euae045.

56. van der Stam AH, Shmuely S, de Vries NM, Bloem BR, Thijs RD. The impact of head-up tilt sleeping on orthostatic tolerance: a scoping review. Biology (Basel) 2023;12:1108.

57. Vyas A, Swaminathan PD, Zimmerman MB, Olshansky B. Are treatments for vasovagal syncope effective? A meta-analysis. Int J Cardiol 2013;167:1906–11.

58. Sheldon RS, Lei L, Guzman JC, Kus T, Ayala-Paredes FA, Angihan J et al. A proof of principle study of atomoxetine for the prevention of vasovagal syncope: the Prevention of Syncope Trial VI. Europace 2019;21:1733–41.

59. Elgebaly A, Abdelazeim B, Mattar O, Gadelkarim M, Salah R, Negida A. Metaanalysis of the safety and efficacy of droxidopa for neurogenic orthostatic hypotension. Clin Auton Res 2016;26:171–80.