2015 Heart Rhythm Society Expert Consensus Statement on the Diagnosis and Treatment of Postural Tachycardia Syndrome, Inappropriate Sinus Tachycardia, and Vasovagal Syncope

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Introduction

This international consensus statement was written by experts in the field who were chosen by the Heart Rhythm

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Society, in collaboration with representatives from the American Autonomic Society (AAS), the American College of Cardiology (ACC), the American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), the European Heart Rhythm Association (EHRA), the Pediatric and Congenital Electrophysiology Society (PACES), and the *Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia* (SOLAECE)-Latin American Society of Cardiac Pacing and Electrophysiology.

This document is intended to help front-line cardiologists, arrhythmia specialists, and other health care professionals interested in the care of patients who present with presumed postural tachycardia syndrome (POTS), inappropriate sinus tachycardia (IST), and vasovagal syncope (VVS). It is not intended to be a comprehensive narrative review, as excellent reviews, chapters, and entire volumes have appeared recently.[1–3] This document has 3 objectives: (1) establish working criteria for the diagnosis of POTS, IST, and VVS; (2) provide guidance and recommendations on their assessment and management; and (3) identify key areas in which knowledge is lacking, to highlight opportunities for future collaborative research efforts.

To maintain this pragmatic focus, we excluded several related topics, including a detailed approach to syncope and other syndromes of transient loss of consciousness, the impact of syncope on other disorders, most orthostatic hypotension syndromes, the effects of the autonomic system on arrhythmias, the use of syncope scores or syncope units, and recommendations on training programs and staffing criteria. A number of sections contain very brief reviews, given that the material has recently been covered elsewhere. We refer readers to the excellent European Society of Cardiology guidelines[2] and related recent reviews.[1,4]

The writing group aimed to provide a succinct, evidence-based document at a uniform level, rather than a comprehensive narrative review. As much as possible, we made recommendations based on published evidence. There was a wide range in terms of the level of evidence available, and we included the highest-level evidence for each section. Inevitably, this led to heterogeneity in the level of evidence included. Each section, indeed the entire document, is a compromise among clinical need, succinctness, clarity, and level of evidence. The specific wording of definitions, recommendations, and the choice of references were the result of prolonged debate, consensus-seeking, and repeated votes.

Each section was drafted by compact writing groups with 3–5 members who completed the first versions and developed preliminary recommendations. The group assignments were based on individual interests and expertise. The recommendations and text underwent iterative revisions to resolve differences, increase clarity, and align the document format with that recommended by the American College of Cardiology.[5] All members of the writing group and peer reviewers provided disclosure statements of all relationships that might present real or perceived conflicts of interest, as shown in the Appendices.

The recommendations and definitions in this document are based on the consensus of the full writing group following the Heart Rhythm Society's process for establishing consensus-based guidance for clinical care. To identify consensus, we conducted surveys of the entire writing group, using a predefined threshold for agreement as a vote of $>75\%$ on each recommendation. An initial failure to reach consensus was resolved by subsequent discussion and re-voting. The final minimum consensus was 76% and the mean was 94%.

The consensus recommendations in this document use the commonly used class I, IIa, IIb, and III classifications and the corresponding language according to the most recent statement of the American College of Cardiology.[6] Class I is a strong recommendation, denoting benefit greatly exceeding risk. Class IIa is a somewhat weaker recommendation, denoting benefit probably exceeding risk, and class IIb denotes benefit equivalent or possibly exceeding risk. Class III is a recommendation against a specific treatment, because either there is no net benefit or there is net harm. Level A denotes the highest level of evidence, usually from multiple clinical trials with or without registries. Level B evidence is of a moderate level, either from randomized trials (B-R) or well-executed nonrandomized trials (B-NR). Level C evidence is from weaker studies with significant limitations, and level E is simply a consensus opinion in the absence of credible published evidence.

When considering the guidance provided in this document, it is important to remember that there are no absolutes with regard to many clinical situations. The writing group was struck by the large number of issues lacking high-level evidence. To this end, the document provides evidence-informed recommendations, striking a balance between the need for recommendations and the availability of evidence. Health care providers and patients need to jointly make the final decision regarding care in light of their individual circumstances.

Section 1: Postural Tachycardia Syndrome

Definition

POTS is a clinical syndrome usually characterized by (1) frequent symptoms that occur with standing, such as lightheadedness, palpitations, tremor, generalized weakness, blurred vision, exercise intolerance, and fatigue; (2) an increase in heart rate of ≥ 30 beats per minute (bpm) when moving from a recumbent to a standing position (or ≥ 40 bpm in individuals 12 to 19 years of age); and (3) the absence of orthostatic hypotension (>20 mm Hg drop in systolic blood pressure). The symptoms associated with POTS are those that occur with standing, such as lightheadedness and palpitations; not associated with particular postures, such as bloating, nausea, diarrhea, and abdominal pain; and systemic, such as fatigue, sleep disturbance, and migraine headaches.[7] The standing (or orthostatic) heart rate of individuals with POTS is often ≥ 120 bpm,[8–13] and undergoes greater increases in the morning than in the evening. The increases in orthostatic heart rate gradually decrease with age and not abruptly at age 20. POTS is a systemic illness, with postural tachycardia one of several criteria. Many patients with POTS faint occasionally, although presyncope is much more common. It is important to note that the diagnoses of POTS and vasovagal syncope are not mutually exclusive.

Definition: Postural Tachycardia Syndrome

Postural tachycardia syndrome (POTS) is defined as a clinical syndrome that is usually characterized by (1) frequent symptoms that occur with standing such as lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue; (2) an increase in heart rate of ≥30 bpm when moving from a recumbent to a standing position held for more than 30 seconds (or ≥40 bpm in individuals 12 to 19 years of age); and (3) the absence of orthostatic hypotension (>20 mm Hg drop in systolic blood pressure).

Epidemiology and Natural History

The prevalence of POTS is approximately 0.2%, with little variance among 4 published reports.[9,12,14,15] Most patients present with POTS between the ages of 15 and 25 years,[7] and more than 75% are female.[7–9,11–14,16] POTS is also common in patients with chronic fatigue syndrome.[17] The chronic and usually systemic symptoms and the frustration caused by the difficulty in obtaining medical help can significantly lower the quality of life. Little has been reported on long-term outcomes, although there have been a few reported cases of patients over 50 years of age and no reported mortality. The perception is that POTS is a chronic condition with no known mortality, and with eventual improvement. Its course probably varies substantially from patient to patient.

Physiology

A number of mechanisms have been described in patients with POTS,[18] including autonomic denervation, hypovolemia, hyperadrenergic stimulation, deconditioning, and hypervigilance, which is a careful and at times unusual focus on bodily sensations. These mechanisms often appear to co-exist in patients with POTS.

Peripheral autonomic denervation

Reports from tertiary care centers have indicated that up to 50% of patients with POTS have a restricted autonomic neuropathy of small and distal postganglionic sudomotor fibers,[19,20] predominantly of the feet and toes.[21–23] It is believed that impaired sympathetic tone (as measured by norepinephrine spillover) reduces venoconstriction, leading to venous pooling in the lower limbs and splanchnic beds.[24] This neuropathic manifestation of POTS requires a high cardiac output to compensate for reduced splanchnic and peripheral resistance and venous pooling.[25–28] Abnormal connective tissue in the dependent blood vessels of patients with Ehlers-Danlos syndrome can cause veins to distend excessively in response to ordinary hydrostatic pressures and thus predispose patients to orthostatic intolerance.[29] The autonomic denervation might be due to an autoimmune disease in some patients.[30,31]

Hypovolemia

Blood volume is reduced in up to 70% of patients with POTS. Paradoxically, some of these patients have low plasma renin activity and aldosterone levels compared with healthy subjects.[32] This is a low-flow subtype with inappropriately high angiotensin II levels.

Hyperadrenergic POTS

This manifestation, which occurs in up to 50% of patients, is associated with systolic blood pressure increases of ≥10 mm Hg while standing upright for 10 minutes and plasma norepinephrine levels ≥600 pg/mL while standing. There is considerable heterogeneity among reporting sites, which could reflect differences among patient populations. These patients have heart rate increases similar to those of other patients with POTS but tend to have prominent sympathetic activation symptoms, such as palpitations, anxiety, tachycardia, and tremor.[12] These patients are hypersensitive to isoproterenol and have marked tachycardic responses to dosages that do not induce hemodynamic changes in healthy individuals.[33]

Deconditioning

Patients with POTS often have poor exercise tolerance and deconditioning.[34] Deconditioned patients with POTS have reduced left ventricular mass, stroke volume, and blood volume,[35] which improve with exercise training. Stroke volume decreases in POTS, with impaired cardiac filling when standing.[36] This situation suggests that orthostatic symptoms induced by an initial illness can, in some patients, lead to overinterpretation of the symptoms due to hypervigilance, which in turn leads to reduced physical activity and deconditioning. However, it is unclear whether deconditioning is the primary cause or a secondary phenomenon.

Anxiety and hypervigilance

Anxiety and somatic vigilance are significantly higher in patients with POTS, which raises the issue of the role of somatic hypervigilance in the source of the symptoms.[36,37] Masuki et al[36] attempted to dissect the psychological and physiologic contributions to tachycardia. Detailed physiologic and psychometric studies showed that although anxiety is commonly present in POTS, the heart rate response to orthostatic stress is not caused by anxiety but is instead a response to an underlying physiologic abnormality.

Recommendations—Investigation of POTS

	Class	Level
A complete history and physical exam with orthostatic vital signs and 12-lead ECG should be performed on patients being assessed for POTS.	I	E
Complete blood count and thyroid function studies can be useful for selected patients being assessed for POTS.	IIa	E
A 24-hour Holter monitor may be considered for selected patients being assessed for POTS, although its clinical efficacy is uncertain.	IIb	E
Detailed autonomic testing, transthoracic echocardiogram, tilt-table testing, and exercise stress testing may be considered for selected patients being assessed for POTS.	IIb	E

Diagnosis

The evaluation of a patient suspected of having POTS should include a complete history and physical examination, orthostatic vital signs, and a 12-lead electrocardiogram (ECG). Selected patients might benefit from a thyroid function test and hematocrit, 24-hour Holter, transthoracic echocardiogram, and exercise stress testing. The clinical history should focus on defining the chronicity of the condition, possible causes of orthostatic tachycardia, modifying factors, impact on daily activities, potential triggers, and family history. Particular attention should be focused on the patient's diet and exercise history. The symptoms of POTS are commonly exacerbated by dehydration, heat, alcohol, and exercise. A full autonomic system review should assess symptoms of autonomic neuropathy. If orthostatic vital signs are normal and the clinical suspicion of POTS is high, a tilt-table test might be helpful because it can provide vital signs over more prolonged periods than a simple stand test. A hematocrit, ECG, Holter, and echocardiogram are sufficient to screen for a potential cardiovascular or systemic etiology. For most patients, this minimal approach is sufficient to establish a diagnosis and initiate treatment. However, if the patient's symptoms do not resolve or markedly improve, a more extensive evaluation at a center experienced with the autonomic testing of patients with POTS should be considered.

An expanded approach to the evaluation could include a thermoregulatory sweat test to detect autonomic neuropathy (which manifests as abnormal patterns of body sweating), supine and upright plasma epinephrine and norepinephrine level tests, a 24-hour urine sample to assess sodium intake, and a psychological assessment.[14] These tests should not be performed routinely as there is no evidence that they improve the care or the process of care in the majority of patients.

Recommendations—Treatment for POTS

	Class	Level
A regular, structured, and progressive exercise program for patients with POTS can be effective.	IIa	B-R
It is reasonable to treat patients with POTS who have short-term clinical decompensations with an acute intravenous infusion of up to 2 L of saline.	IIa	C
Patients with POTS might be best managed with a multidisciplinary approach.	IIb	E
The consumption of up to 2–3 L of water and 10–12 g of NaCl daily by patients with POTS may be considered.	IIb	E
It seems reasonable to treat patients with POTS with fludrocortisone or pyridostigmine.	IIb	C
Treatment of patients with POTS with midodrine or low-dose propranolol may be considered.	IIb	B-R
It seems reasonable to treat patients with POTS who have prominent hyperadrenergic features with clonidine or alpha-methyldopa.	IIb	E
Drugs that block the norepinephrine reuptake transporter can worsen symptoms in patients with POTS and should not be administered.	III	B-R
Regular intravenous infusions of saline in patients with POTS are not recommended in the absence of evidence, and chronic or repeated intravenous cannulation is potentially harmful.	III	E
Radiofrequency sinus node modification, surgical correction of a Chiari malformation type I, and balloon dilation or stenting of the jugular vein are not recommended for routine use in patients with POTS and are potentially harmful.	III	B-NR

Treatment

The treatment of POTS is difficult; there are no therapies that are uniformly successful, and combinations of approaches are often needed. Few treatments have been tested with the usual rigor of randomized clinical trials, and there is no consensus as to whether specific treatments should be targeted to subsets of POTS or whether a uniform approach should be used. This section provides recommendations on general approaches and highlights treatments with more than minimal evidence. Other approaches (either novel or still under investigation) should be discussed with centers specializing in the treatment of POTS.

Several centers have reported that treatment might be provided more comprehensively with a collaborative, multidisciplinary approach that includes physicians, psychologists, nurses, physical therapists, occupational therapists, and recreational therapists.

Nonpharmacologic treatments should be attempted first with all patients. These include withdrawing medications that might worsen POTS, such as norepinephrine transport inhibitors, increasing blood volume with enhanced salt and fluid intake, reducing venous pooling with compression garments, and limiting deconditioning. Patients should engage in a regular, structured, graduated, and supervised exercise program featuring aerobic reconditioning with some resistance training for the thighs.[35,38] Initially, exercise should be restricted to non-upright exercises including the use of rowing machines, recumbent cycles, and swimming to minimize orthostatic stress on the heart.

Pharmacologic treatment

If nonpharmacologic approaches are not completely effective, pharmacologic therapies may be targeted at specific problems. Patients who are known to or are strongly suspected of having hypovolemia[32] should drink at least 2–3 L of water per day, and dietary salt intake should be increased to approximately 10–12 g/day, if tolerated, using salt tablets, if necessary. Fludrocortisone might be useful for boosting sodium retention and expanding the plasma volume, although these pharmacodynamic effects might last only 1–2 days, and its effectiveness has not been tested in randomized clinical trials.[39] Midodrine is metabolized to a peripheral alpha-1 agonist that constricts veins and arteries and might be useful for increasing venous return. Midodrine significantly reduces orthostatic tachycardia but to a lesser degree than intravenous saline.[40] Midodrine has a rapid onset with only brief effects and should be administered 3 times daily. The drug should only be administered during daytime hours as it can cause supine hypertension.

A related strategy is to augment blood volume with intravenous saline. Expert centers report anecdotally that 1 L of normal saline infused over 1 hour decreases orthostatic tachycardia and improves symptoms for several hours to 2 days.[40,41] Although it has not yet been assessed in a clinical trial, this approach is recommended as rescue therapy for patients who are clinically decompensated and whose symptoms have worsened significantly. This approach could also prevent hospitalizations. Long-term infusions of intravenous saline are not recommended for routine care, because they usually require the insertion of a chronic central venous catheter, with its attendant complications.

To reduce unpleasant sinus tachycardia and palpitations, low-dose propranolol (10–20 mg PO) acutely lowers standing heart rate and improves symptoms in patients with POTS, while higher doses of propranolol are less well tolerated.[42] Long-acting propranolol does not improve the quality of life of patients with POTS,[43] and other beta-blockers have not been studied. Ivabradine slows sinus rates without impacting blood pressure. Approximately 60% of patients with POTS treated with ivabradine in an open-label study had symptom improvement.[44] However, ivabradine is not currently available in the United States. Pyridostigmine is a peripheral acetylcholinesterase inhibitor that increases synaptic acetylcholine in the autonomic ganglia and at peripheral muscarinic receptors. The drug blunts orthostatic tachycardia and can improve chronic symptoms but is limited by adverse effects such as diarrhea, abdominal pain and cramps, nausea, and increased urinary urgency and frequency.[45,46]

Central sympatholytic agents can be useful in patients with the central hyperadrenergic form of POTS but might not be as well tolerated in neuropathic POTS. Clonidine is an alpha-2 agonist that can stabilize hemodynamics in patients with high sympathetic nervous system involvement.[47] Methyldopa is sometimes better tolerated.[48] Unfortunately, both drugs can cause drowsiness and fatigue and can worsen mental clouding, a condition that troubles many patients. Modafinil may be considered for the fatigue and cognitive dysfunction ("brain fog") seen in patients with POTS.[49] Modafinil, however, can worsen the symptoms of tachycardia.[49]

Invasive interventions

Radiofrequency sinus node modification for the sinus tachycardia of POTS is not recommended, because it often worsens symptoms and occasionally results in the patient requiring a pacemaker.[50] Although a number of patients with POTS have been found to have herniation of their cerebellar tonsils (Chiari I), there is no association between cerebellar tonsil herniation and POTS.[51] Nonetheless, a number of neurosurgical centers decompress the cerebellar tonsils in an effort to "cure" POTS.[52] This approach should not be offered until prospective controlled data have demonstrated its efficacy.

Section 2: Inappropriate Sinus Tachycardia

Definition

The syndrome of IST is defined as a sinus heart rate >100 bpm at rest (with a mean 24-hour heart rate >90 bpm not due to primary causes) and is associated with distressing symptoms of palpitations.

Definition: Inappropriate Sinus Tachycardia

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Epidemiology and Natural History

The prevalence of IST was estimated in a middle-aged population of men and women with and without hypertension.[53] Using a definition of a resting heart rate >100 bpm and an average heart rate of >90 bpm on 24-hour Holter monitoring, the IST prevalence was 1.2% (7 of 604 patients), including both symptomatic and asymptomatic patients. Little has been reported on long-term outcomes, although there is no known mortality. IST is believed to be a chronic condition, but whether and how quickly patients improve are unknown.

Physiology

The mechanisms leading to IST are not completely understood,[3] but there are several underlying diseases that can result in this syndrome, including increased sinus node automaticity, beta-adrenergic hypersensitivity, decreased parasympathetic activity, and impaired neurohumoral modulation.[54] β-Adrenergic receptor antibodies can sensitize β-adrenergic receptors in some patients, while other patients might have increased sympathetic activity and sensitivity, with or without inherent impaired sinus node automaticity.

Recommendations—Investigation of IST

	Class	Level
A complete history, physical exam, and 12-lead ECG are recommended.	I	E
Complete blood counts and thyroid function studies might be useful.	IIa	E
A 24-hour Holter monitoring might be useful.	IIb	E
Urine/serum drug screening might be useful.	IIb	E
It might be worth considering autonomic testing.	IIb	E
It might be worth considering treadmill exercise testing.	IIb	E

Diagnosis

A thorough medical history review and physical examination should be performed, focusing on the possible causes of sinus tachycardia, such as thyroid disease, medications, and drugs. Patients should be examined for hypovolemia; a review of the other primary causes of sinus tachycardia is beyond the scope of this document. A 12-lead ECG is useful for documenting tachycardia and determining sinus rhythm, which helps differentiate IST from other atrial tachyarrhythmias. A 24-hour Holter monitor can be useful for confirming the diagnosis. Patients with POTS and patients with IST can present similar symptoms, but IST is induced by both physiologic and emotional stresses, while POTS is generally induced only by orthostatic stress. Other causes, such as drug effects, physiologic and psychological triggers, occult substance abuse, panic attacks, and, of course, POTS, should be ruled out, given that control of the sinus rate can exacerbate its symptoms. IST is rarely associated with tachycardia-mediated cardiomyopathy.[55,56]

There are multiple measures of cardiovascular autonomic reflexes, including heart rate responses to deep breathing, standing, Valsalva,[57,58] cold face test (diving test),[59] heart rate variability,[59,60] and baroreflex sensitivity.[61] These tests should not be used routinely given their unproven clinical usefulness. Treadmill exercise testing might be useful to document an exaggerated tachycardic response to exertion,[59] although this assertion has not been validated.

Recommendations—Treatment for IST

	Class	Level
Reversible causes of sinus tachycardia should be sought and treated.	I	E
Ivabradine can be useful for treating patients with IST.	IIa	B-R
Sinus node modification, surgical ablation, and sympathetic denervation are not recommended as a part of routine care for patients with IST.	III	E

Treatment

IST is frequently associated with a significant loss of quality of life. There are no long-term, prospective, placebo-controlled clinical trials of any therapeutic intervention that have demonstrated a substantial improvement in outcomes, and symptoms can continue despite heart rate control.

Patients with IST require significant care and attention due to the nearly ubiquitous psychosocial distress and the complexity of their problems. Close attention and effective communication can improve outcomes.[62] Lifestyle changes should be discussed early on with all patients. There are very few treatments with solid evidence for patients with IST. β-Adrenergic blockers are not usually effective and can cause adverse effects. Other treatments have been suggested, including fludrocortisone, volume expansion, pressure stockings, phenobarbital, clonidine, psychiatric evaluation, exercise training, and erythropoietin.[3]

Ivabradine holds considerable promise for the treatment of IST. The drug blocks the I_f current and has a dramatic and generally well-tolerated effect on heart rate. At doses of 5–7.5 mg twice daily, the drug slows the heart rate by 25–40 bpm. Several small case series have reported that ivabradine reduced heart rate and improved quality of life. Furthermore, the data suggested that combinations of metoprolol and ivabradine might be safe and effective. The strongest evidence to date comes from a small, randomized crossover study in which 21 patients with IST were randomized to placebo or ivabradine 5 mg twice daily for a total of 12 weeks.[63] Ivabradine eliminated symptoms in 70% of patients and increased exercise performance. Furthermore, ivabradine can provide benefits when added to beta-blocker therapy.[64] Ivabradine is not yet available in all countries, although it might appear in the next 2–3 years.

Several groups have described modification or ablation of the sinus node in IST. In general, primary success rates are reasonably good, but there is a high rate of symptom recurrence, and the complication rates are significant. These complications include requirements for permanent pacing, transient or permanent phrenic nerve paralysis, and transient superior vena cava syndrome. In addition, sinus node modification or ablation might not relieve all IST-associated symptoms. There is also no agreement on the optimal approach, including modification or ablation, open chest versus conventional intravascular access, and mapping methods. Finally, there is no evidence of symptomatic improvement over several years. Patients and referring physicians need to be aware that despite the potentially substantial symptoms and the patients' high motivation, the consequences of aggressive therapy might seriously outweigh any potential benefit. Given the young age of the patients and the highly invasive nature of ablations, we do not recommend that they be part of routine care. However, ablations may be offered in highly select circumstances or as part of research protocols.

Section 3: Vasovagal Syncope

Definition

Syncope is defined as a transient loss of consciousness, associated with an inability to maintain postural tone, rapid and spontaneous recovery, and the absence of clinical features specific to another form of transient loss of consciousness such as epileptic seizure. "Clinical features" indicates all the information obtained from the history, physical signs, and feasible, reasonable, limited investigations such as an ECG.

Definition: Syncope

Syncope is defined as a transient loss of consciousness, associated with an inability to maintain postural tone, rapid and spontaneous recovery, and the absence of clinical features specific for another form of transient loss of consciousness such as epileptic seizure.

Vasovagal syncope is a syncope syndrome that usually (1) occurs with an upright posture held for more than 30 seconds or with exposure to emotional stress, pain, or medical settings; (2) features diaphoresis, warmth, nausea, and pallor; (3) is associated with hypotension and relative bradycardia, when known; and (4) is followed by fatigue.

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Epidemiology and Natural History

The incidence and prevalence of vasovagal syncope are not precisely known. Most studies have examined specific clinical populations or have not differentiated among the various causes of syncope. Furthermore, the term "prevalence" is problematic for a syndrome that includes individuals who might faint only once or twice in their lives. It is for this reason that the term "cumulative incidence" is preferred. Taking this approach and by using actuarial methodology, several groups have reported consistent findings. Vasovagal syncope is very common; by age 60, 42% of women and 32% of men will have had at least 1 vasovagal syncope, which is their cumulative incidence.[65,66] Vasovagal syncope is manifested in approximately 1%–3% of toddlers as pallid syncope, and the incidence begins to increase markedly around age 11. The median age of the first syncope is approximately 14 years, and most people with vasovagal syncope will have had their first syncope before age 40.[67]

In specialty clinics, late first presentations of vasovagal syncope occur with some regularity.

The proportion of all syncopes represented by vasovagal syncope depends on the setting. In studies of healthy young and middle-aged participants living in the community, almost all individuals who faint have vasovagal syncope. Emergency department studies generally feature older patients with mean ages around 60–65 years. The estimate for emergency departments is obscured by the fact that approximately 35% of patients with syncope remain undiagnosed. Approximately 30%–50% of patients with syncope, however, are diagnosed with an autonomically mediated form of syncope, and most of these are vasovagal. A much smaller proportion of cases are due to carotid sinus syncope.

The outcome for patients with vasovagal syncope is generally benign, given that there is no increased mortality. There is, however, a high rate of recurrence. The overall 1-year recurrence rate in many reports is approximately 25%–35%, and this rate can be predicted by the number of syncopes in the year prior to assessment.[68] Those patients with frequently recurring vasovagal syncope often have a significant loss of quality of life. Most patients stop fainting after assessment and in the absence of specific therapy. The reason for this recovery is not known.[69–72]

Physiology

The physiology of the vasovagal reflex remains a matter of debate. Rising to an upright position increases gravitational forces and leads to the pooling of 500 to 800 mL of blood in the venous system, in the pelvic and splanchnic circulation, and in the lower limbs. This abrupt reduction in venous return decreases cardiac output and blood pressure, which are rapidly sensed by the arterial and cardiopulmonary baroreceptors, thus triggering sympathetic noradrenergic vasoconstriction and venoconstriction accompanied by an increase in heart rate.[73] During a vasovagal syncope episode, an ineffective reflex response causes venous pooling in the periphery and/or splanchnic regions.[73–76] Ultimately, paradoxical vasodilation can occur, leading to further hypotension and loss of consciousness.[77] This syncope is usually associated with a vagally mediated relative or absolute reduction in heart rate, a process known as cardioinhibition. The vasovagal response always includes hypotension and often includes bradycardia with, at times, prolonged asystole in the sinus and AV nodes.

The initial reduction in blood pressure during vasovagal syncope provoked by orthostatic stress is driven by a 50% decline in cardiac output, with coincident vasodilatation in only a subset of patients.[78–80] In many patients, the hypotension due to decreased preload alone can reduce cerebral perfusion sufficiently to induce presyncope or syncope. In some patients, however, decreased preload does not play a dominant role in causing symptoms; instead, peripheral vasodilation plays an important role. Fu and Levine[81] reported a moderate decline in cardiac output with coincident vasodilation in the majority of participants with presyncope and no changes in total peripheral resistance during presyncope in a minority of participants. Sympathetic vasoconstriction and baroreflex sensitivity prior to the onset of presyncope were well preserved, and muscle sympathetic nerve activity (MSNA) withdrawal occurred late after the onset of hypotension. The age differences among these reports suggest that a failure of venous return could be the main factor in older patients, while younger patients might also have active vasodilation.

For many years, vasovagal syncope was thought to be the result of loss of peripheral sympathetic activity, and the proposed pathophysiologic mechanism leading to vasovagal syncope was the blunting or cessation of MSNA.[82–84] However, 2 groups have recently reported persistence of MSNA during vasovagal syncope, bringing into question the role of sympathetic activity withdrawal as the final physiologic event that precipitates loss of consciousness.[85,86] These studies challenge the hypothesis that abrupt sympathetic nerve activity withdrawal causes the vasovagal syncope response.

Patients with recurrent postural vasovagal syncope might have sympathetic nervous system phenotypes.[87] This study assessed the sympathetic nervous system by measuring MSNA, norepinephrine (NE) spillover to plasma, and sympathetic protein expression. Patients were divided into a low-pressure phenotype (systolic blood pressure <100 mm Hg) and a normal-pressure phenotype (systolic blood pressure >100 mm Hg). NE spillover was below normal during tilt in both phenotypes. NE spillover in the low-pressure phenotype was associated with low tyrosine hydroxylase levels, which probably reduced NE synthesis. In contrast, the normal blood pressure phenotype features increased norepinephrine transporter levels consistent with augmented norepinephrine reuptake. MSNA was normal in the normal blood pressure phenotype and increased in the low blood pressure phenotype group. This outcome suggests that vasovagal syncope can have 2 distinct physiologic groups that can be clinically detected based on supine blood pressure. Both phenotypes have reduced NE availability, which ultimately impairs the neurocirculatory response to orthostatic stress.[87]

Recommendations—Investigation of Vasovagal Syncope

	Class	Level
Tilt-table testing can be useful for assessing patients with suspected vasovagal syncope who lack a confident diagnosis after the initial assessment.	IIa	B-NR
Tilt-table testing is a reasonable option for differentiating between convulsive syncope and epilepsy, for establishing a diagnosis of pseudosyncope, and for testing patients with suspected vasovagal syncope but without clear diagnostic features.	IIa	B-NR
Implantable loop recorders (ILRs) can be useful for assessing older patients with recurrent and troublesome syncope who lack a clear diagnosis and are at low risk of a fatal outcome.	IIa	B-R
Tilt testing is not recommended for predicting the response to specific medical treatments for vasovagal syncope.	III	B-R

Diagnosis

The diagnosis of vasovagal syncope is based on the clinical history, and there are abundant observational and quantitative data in this area. There are 4 categories of key diagnostic features: predisposing situations, prodromal symptoms, physical signs, and recovery time and symptoms. Fainting usually occurs after prolonged standing or sitting but can be triggered even in the supine position by exposure to medical or dental situations, pain, and scenes of injury. "Prolonged" can mean as little as 2–3 minutes, and the time period is a key feature distinguishing vasovagal syncope from initial orthostatic hypotension. Prodromal features include progressive presyncope, diaphoresis, a sense of warmth, flushing, nausea, abdominal discomfort, visual blurring, and vision loss. While unconscious, the patient is usually motionless. However, fine and coarse myoclonic movements have been observed in approximately 10% of cases (even by untrained individuals), which can result in the condition being erroneously diagnosed as epilepsy.[88] Videometric analysis and home videos can prove helpful in difficult cases. Unconsciousness usually lasts less than 1–2 minutes, but full recovery can be sluggish. Patients often feel very tired for minutes to hours after the episode. A careful and focused medical history review will often determine the diagnosis, with no further investigation needed.[89]

Diagnostic scores have been developed based on patients with rigorously defined diagnoses.[90–93] Generally, attempts at validation have not been conducted with patients as rigorously defined as in the derivation studies.[94,95] Although these scores report overall high degrees of accuracy, they likely require revision and validation in larger populations. Nonetheless, the scores serve as useful reminders of important diagnostic points, and they form reproducible criteria for entry into observational, genetic, and randomized, controlled interventional trials.[91,96,97]

Tilt-table testing

The usefulness of investigation strategies depends on the patient mix and the purpose of the investigation. In most cardiology settings, it is important to determine whether the patients' syncope is caused by arrhythmia. Ruling out cardiac syncope is of less importance, however, for clinics specializing in providing assessment and care of patients with autonomic disorders. There are 2 general approaches: determine whether the patient has the substrate for particular types of syncope and determine whether the patient has syncope associated with specific heart rhythm abnormalities or characteristics.

Tilt-table tests feature prolonged passive postural stress to determine whether patients have the autonomic substrate for vasovagal syncope. The vasovagal reflex is often triggered by adjunctive agents such as isoproterenol, nitrates, and clomipramine. However, with increasingly aggressive protocols comes the likelihood of decreased specificity. A positive response is defined as clinically reminiscent presyncope or syncope associated with hypotension and usually bradycardia. Depending on the method, most patients with probable vasovagal syncope develop presyncope or syncope, while most control patients do not. When patient populations with strong presumptive evidence (ie, a high pretest probability) for vasovagal syncope are studied, the sensitivity approaches 78%–92%, and the currently recommended protocols have specificities of approximately 90% compared with the response of asymptomatic patients. The use of high doses of isoproterenol during tilts exceeding 10 minutes at 80° head-up tilt is accompanied by reduced specificity.[98] The tilt test can prove useful for elderly patients due to the difficulties in obtaining an informative history in some older patients and due to its usefulness in identifying the cause of unexplained falls.[99,100]

The tilt test has not been prospectively validated with populations with rigorously defined vasovagal syncope. In addition, there is no "ideal" protocol, given that there is an inexorable trade-off between sensitivity and specificity. Furthermore, the supplemental role of tilt testing when added to medical histories reviews by experts, with or without quantitative diagnostic scores, has not been assessed, and its indications are a matter of expert consensus.[101]

Tilt testing, when positive, suggests a tendency or predisposition to vasovagal syncope and does not establish it as the cause of the patient's syncope. Although the importance of tilt testing in the investigation of patients with

syncope of cardiogenic etiology is diminishing, the test continues to be helpful in clinics devoted to the care of patients with cardiovascular autonomic disorders such as autonomic neuropathy, neurogenic orthostatic hypotension, neurally mediated syncope, and POTS.

Tilt-table testing can be helpful in the following specific circumstances:

- differentiating convulsive syncope from true seizure activity
- situations in which, despite careful questioning, the cause of syncope remains unclear
- establishing a diagnosis of pseudosyncope.

Pseudosyncope is a poorly reported syndrome of apparent syncopal episodes in the absence of cerebral hypoperfusion or hemodynamic changes that might cause cerebral hypoperfusion.

Prolonged electrocardiographic monitoring

The current gold standard for diagnosing syncope due to cardiac arrhythmias is recording an ECG during an episode of clinical syncope. A syncopal episode with suppression of both AV and sinus node activity is very likely the result of vasovagal syncope. However, a syncopal episode associated with a normal sinus rhythm can be due to several disorders such as orthostatic hypotension, vasovagal and carotid sinus reflexes, and even pseudosyncope. The yield depends on the duration of monitoring and is significantly greater with implanted monitors. External monitors have a loop memory that continuously records and deletes the ECGs, storing them when activated. Diagnostic accuracy is approximately 10%–25% after 1 month of monitoring. ILRs store ECG evidence when activated by the patient after a syncope episode and after automatic detection based on rate or rhythm criteria. The devices are implanted subcutaneously under local anesthesia and last up to 3 years.

Numerous observational studies have shown that ILRs can deliver diagnoses for approximately 35% of patients during the devices' lifetime. It is important to note that there have been randomized controlled trials of the devices' clinical effectiveness, and the results consistently show that for older patients with unexplained syncope, recorders should be used earlier in the investigation rather than later.[102–104] The study populations of these trials were predominantly composed of patients in their 70s and 80s. Compared with conventional approaches, external ECG monitors provide more and earlier diagnoses and are cost effective. However, the devices have been shown to improve care in only the subset of patients who are older, have asystole documented on the ILR, and whose tilt test results were negative, probably because many of the diagnoses are of vasovagal syncope. These patients appear to benefit from permanent pacing.[105–112]

Conservative and Medical Treatment

Vasovagal syncope is generally benign, with a natural history that can include clusters of syncopes interspersed with long quiescent periods without recurrences. Younger and older individuals differ markedly, with the latter group more likely to have complicating comorbidities and medical therapies than the former group. Despite the apparently benign profile of vasovagal syncope, patients with frequent episodes occasionally need treatment. When considering therapy for vasovagal syncope, it is important to weigh the natural history, the potential for harm, and the marked reduction in syncope (seen in all control arms of randomized trials on vasovagal syncope) against symptom severity and the overall likelihood of treatment efficacy. The likelihood of a patient fainting after specialist assessment can be predicted from the number of syncopes in the preceding year. In the Prevention of Syncope Trial (POST) study,[91] patients with no syncope in the previous year had a 7% likelihood of fainting in the next year, while those with at least 1 syncope had a 40% likelihood of fainting.[68]

Reducing the number of medications that cause hypotension can be helpful, provided that it does not worsen conditions such as hypertension and heart failure. Several narrative and systematic reviews have evaluated the benefits of lifestyle and medical therapies.[113–117] While results have generally been positive in uncontrolled trials and short-term controlled trials, those of long-term, placebo-controlled prospective trials have been less encouraging. Furthermore, only the most motivated patients will commit to medical therapy to prevent a handful of yearly syncopal episodes.

Physical counterpressure maneuver

Two clinical studies have reported that isometric exercise of the large muscles induces a significant blood pressure increase during the phase of impending reflex syncope on tilt tests, enabling the patient to avoid or delay losing consciousness.[118,119] In a randomized, prospective parallel clinical trial, a physical counterpressure maneuver was superior to controls, with a relative risk reduction of 39%.[120] However, syncope recurred in a substantial minority of patients, and the study was open label. The maneuvers do not work for patients with a minimal or absent prodrome. Nonetheless, these maneuvers are risk-free and should constitute a core management strategy for patients with vasovagal syncope of all severities.[120]

Tilt-training

Tilt training has 2 forms. In the first, patients start training using repetitive tilt tests under monitored conditions. In the second, patients simply practice standing quietly at home for prolonged periods of time. While the former might be beneficial, the latter is not.[114] Most of the studies on tilt-training were poorly controlled. This treatment is hampered by poor patient compliance when conducting the program for an extended period of time and by an as yet undetermined biologic mechanism. In the absence of consistently positive evidence and the presence of reports of poor long-term compliance, the writing group could not make a recommendation on this intervention.

Beta-blocker therapy

Adequately designed and controlled randomized studies have found that beta-blockers are not effective for treating vasovagal syncope. The largest prospective, placebo-controlled, randomized critical trial of beta-blocker therapy was the POST I trial, which analyzed the use of metoprolol for patients with tilt-positive presumed vasovagal syncope.[91] Atenolol was no more effective than placebo in preventing recurrent syncope in another double-blind randomized clinical trial.[121] However, in a meta analysis of a prespecified, prestratified substudy of POST 1 and a large earlier observational study, there was evidence of benefit in patients older than 40 years.[122] A prospective, multicenter, randomized clinical trial is now testing this effect (POST 5). In the absence of compelling evidence, it seems reasonable to attempt therapy with metoprolol in older patients and avoid using the drug in younger patients.

Fludrocortisone

The POST 2 trial compared fludrocortisone to placebo in patients with recurrent, apparent, vasovagal syncope and showed only a strong trend to treatment benefit. The trial has not undergone peer review and has not been published. A small pediatric trial showed that children who took placebo had a better long-term outcome with respect to presyncope and syncope than those who took fludrocortisone.[123] In the absence of compelling evidence, it seems reasonable to attempt therapy with fludrocortisone in patients whose symptom severity merits it.

Midodrine

Four randomized trials on midodrine have shown a consistent risk reduction of approximately 70%. However, due to selection or design issues, none of the trials provided high-level evidence for adults. The trials studied children, used tilt test outcomes as the main measure, studied extraordinarily symptomatic patients, or were open label. A small and underpowered crossover study reported the efficacy of low-dose midodrine in participants who had previously been trained in physical counterpressure maneuevres.[124] In this 23-patient trial, there was only an insignificant trend to benefit from midodrine in the exposure arms limited to 3 months. None of the studies were conventional, placebo-controlled, randomized clinical trials of moderately to severely symptomatic patients.[125–128] Such a study (POST 4) is now ongoing but the results will not be known for several years.[129] The major limitations of midodrine are the need for frequent dosing, its effects on supine hypertension, and a lack of knowledge of its teratogenic effects. Caution is advised when administering the drug to older men due to the potential for urinary retention. In the absence of compelling evidence, it seems reasonable to attempt therapy with midodrine for patients whose symptom severity merits it.

Serotonin transporter inhibitors

There is ample evidence for the involvement of serotonin in the midbrain regulation of heart rate and blood pressure. Based on this evidence, there have been several observational studies and 3 small, randomized trials on serotonin transport inhibitors for the prevention of vasovagal syncope.[130–132] There remains considerable uncertainty about the efficacy of serotonin transport inhibitors in preventing syncope.

Recommendations—Lifestyle and Medical Treatment for Vasovagal Syncope

	Class	Level
Education, reassurance, and promoting salt and fluid intake are indicated for patients with vasovagal syncope, unless contraindicated.	I	E
Reducing or withdrawing medications that can cause hypotension can be beneficial for patients with vasovagal syncope.	IIa	E
Physical counterpressure maneuvers can be useful for patients with vasovagal syncope who have a sufficiently long prodromal period.	IIa	B-R
The use of fludrocortisone seems reasonable for patients with frequent vasovagal syncope who lack contraindications for its use.	IIb	E
Beta-blockers may be considered for patients older than 40 years with frequent vasovagal syncope.	IIb	B-R
The use of midodrine seems reasonable for patients with frequent vasovagal syncope and no hypertension or urinary retention.	IIb	B-R

Treatment strategy

We therefore recommend the following approach to pharmacologic and conservative treatment for established vasovagal syncope. For patients with only an occasional syncope: Reassure patients, stress fluid and salt intake, and teach counterpressure maneuvers. Do not treat patients who have not fainted in the past year.

For patients with recurrent episodes: Begin conservatively as described above. Examine the patient's history for drugs that might cause hypotension and reduce or withdraw

them if possible. For patients with recurrent episodes of vasovagal syncope and who are unlikely to respond adequately to conservative treatment: It is reasonable to consider fludrocortisone, midodrine, or beta blockers (if the patient is older than 40 years) prior to pacing, while recognizing that there is no high-level evidence for their use.

Pacemaker Treatment

In general, cardiac pacing has a very limited role in patients with typical vasovagal syncope. Although earlier observational, open-label, and single-blind studies have been uniformly positive, the results of 2 subsequent double-blind studies in adults were negative.[133–138] There are currently no positive placebo-controlled studies on pacemakers with patients younger than 40 years with vasovagal syncope; for these patients, cardiac pacing should be the last choice. Pacing should be considered only in highly selected patients, such as those significantly older than 40 years and patients who experience frequent recurrences associated with repeated injury, limited prodromes, and documented asystole. The fact that pacing can be effective in some patients with syncope does not mean that it is necessary. Establishing a relationship between symptoms and severe bradycardia is essential before considering permanent pacing. Prolonged ECG monitoring, usually by an ILR, is usually necessary.

Suspected or known vasovagal syncope and ECG-documented asystole

Typically, the vasovagal reflex is both hypotensive and cardioinhibitory, and there is emerging evidence that tilt-table testing identifies patients with predominant reflex hypotension.[112] Accordingly, tilt-table testing can be performed to assess hypotensive susceptibility and identify patients who might not respond to permanent cardiac pacing. Although the documentation of a prolonged asystolic reflex during tilt-table testing predicts a similar response during spontaneous syncope, the benefit of pacing for patients with tilt-positive cardioinhibitory syncope remains unproven.[111]

In the Third International Study on Syncope of Uncertain Etiology (ISSUE-3; a randomized, double-blind trial), 511 patients aged 40 years and older with recurrent reflex syncope were given an ILR.[111] Only 17% of the patients had syncope with documented asystole, or $\geq$6 seconds of asystole without syncope. Most of these patients were randomly assigned to dual-chamber pacing with rate-drop response or to sensing only. During follow-up, the 2-year estimated syncope recurrence rate was 57% with the pacemaker off and 25% with the pacemaker on, with a relative risk reduction of 57%.

A recent subanalysis of ISSUE-3 showed that the syncope recurrence rate for patients with asystole, with or without syncope, was 5% for patients with negative tilt test results and 55% for those with positive tilt test results, which is similar to the results observed in controls without pacing.[112] Patients with an asystolic response during tilt testing fared no better than those with nonasystolic responses. By showing that patients with prolonged pauses during syncope but negative tilt test results benefit most from cardiac pacing, ISSUE-3 suggested that a positive tilt test result could be used to select patients who should not undergo permanent cardiac pacing.

Unexplained syncope, no prodromes, and normal heart

A syncope syndrome with low plasma adenosine levels has been described in patients with unexplained syncope, sudden onset and no prodrome, and a normal heart and normal ECG. This syncope is not thought to be due to the vasovagal reflex but is included because the population with this type of syncope shares clinical features with those who have vasovagal syncope. Patients with unexplained syncope have low plasma adenosine levels, and exogenous injections with adenosine triphosphate or adenosine can cause transient complete heart block in these patients more often than in control patients. This outcome occurs without sinus node slowing or progressive atrioventricular conduction delay. During clinical syncope, paroxysmal AV block occurs with 1 or multiple consecutive pauses but with no preceding or accompanying changes in sinus or AV node function. Cardiac pacing effectively prevents syncopal recurrences.[112,139,140] In a small multicenter trial performed on 80 selected elderly patients with unexplained syncope, dual-chamber cardiac pacing significantly reduced 2-year syncopal recurrence from 69% in the control group to 23% in the active group.[141]

Pediatric patients

A small, single-blind randomized trial reported that permanent cardiac pacing greatly reduced syncope burden in young children, with frequent syncope associated with documented asystole.[142] These patients were refractory to multiple medications and appeared to benefit from cardiac pacing. However, this apparently beneficial response is also seen ubiquitously in single-blind adult trials, a response that is not reproduced in properly conducted double-blind trials.

Pacing mode

Dual-chamber pacing was used in almost all the above-mentioned trials, with a rate-drop response feature in the pacemaker that instituted rapid dual-chamber pacing if the device detected a rapid decrease in heart rate. However, no comparisons between conventional single-chamber and dual-chamber pacing have been conducted.

Recommendations—Pacemakers for Syncope

	Class	Level
Dual-chamber pacing can be effective for patients 40 years of age or older with recurrent and unpredictable syncope who have a documented pause ≥3 seconds during clinical syncope or an asymptomatic pause ≥6 seconds.	IIa	B-R
Tilt-table testing may be considered to identify patients with a hypotensive response who would be less likely to respond to permanent cardiac pacing.	IIb	B-NR
Pacing may be considered for pediatric patients with recurrent syncope with documented symptomatic asystole who are refractory to medical therapy.	IIb	B-R
Dual-chamber pacing may be considered in adenosine-susceptible older patients who have unexplained syncope without a prodrome, a normal ECG, and no structural heart disease.	IIb	C

Section 4: Postural Tachycardia Syndrome and Vasovagal Syncope in the Young

The relatively limited pediatric literature on this topic has meant that most insights and treatments for POTS and vasovagal syncope have come from the adult medical literature. This section provides a high-level view of the features shared by adults and children and comments on the evidence, research, and treatments specific to children and adolescents.

Diagnosis of POTS and Vasovagal Syncope

Although the cornerstone for the diagnosis of pediatric POTS is the medical history, an orthostatic test is required to confirm the diagnosis. The diagnostic standard for tilt-table testing for POTS in young people requires symptoms of orthostatic intolerance and an orthostatic increase in heart rate of at least 40 bpm, which is greater than in adults.[11] The 10-minute standing tests for POTS provided reasonable accuracy in a small study on adults, but these tests have not been validated for pediatric populations.[143] A 24-hour Holter monitor can be performed to distinguish POTS from IST.

Symptoms resulting from vasovagal syncope are usually more clearly articulated in young patients than in much older adults, and establishing the diagnosis is usually straightforward. Syncope during exercise usually raises concern about a rare cardiac electrical or structural cause, but the most common cause of exercise-related syncope in pediatric populations is still vasovagal syncope.[144] Nonetheless, patients with exercise-induced syncope should be assessed for cardiomyopathy and arrhythmia as the cause of the syncope. Pseudosyncope should be suspected when patients present with very frequent (at least daily) or prolonged syncope, with similar symptoms to vasovagal syncope. Many of these patients also have an earlier history of *bona fide* vasovagal syncope, and untangling the medical history requires particular care.

Given that the medical history usually provides a clear diagnosis and that tilt testing has imperfect sensitivity and specificity in pediatric patients, such testing is usually not indicated. An ECG is a simple and well-tolerated test to screen for relatively uncommon but dangerous causes of syncope, including myocarditis, inheritable cardiomyopathies, long QT, and other inherited or acquired causes of arrhythmia. Prolonged ambulatory cardiac rhythm monitoring (external loop event monitor or an ILR) is reasonable if the clinical history suggests an inheritable arrhythmia or cardiomyopathy or severe bradycardia or if the patient is refractory to medical therapy.

Treatment of Children with Vasovagal Syncope or POTS

There are no quantitative data on the outcome of pediatric patients with vasovagal syncope or POTS. The number of syncopal episodes varies widely, and many young patients appear to stop fainting in late adolescence. This fact dulls enthusiasm for specific medical treatment of young people, particularly the use of pacemakers. There is little evidence that any treatment helps children with vasovagal syncope or POTS, and physicians rely on insights from adult medical literature. In general, it is reasonable to reassure patients and their families, promote salt and fluid intake, and teach physical counterpressure techniques. Two randomized clinical trials reported that midodrine improved either hemodynamic changes to orthostasis or clinical symptoms in patients with POTS.[145,146] A small randomized trial reported that midodrine was effective in preventing recurrent syncope.[128] Two randomized studies of children with syncope found placebo more effective than fludrocortisone and salt in preventing syncope[123] and placebo more effective than metoprolol in preventing syncope.[147] Finally, a small, double-blind study reported that pacing improved symptoms in very young patients with frequent vasovagal syncope.[142]

Recommendations—POTS and Vasovagal Syncope in the Young

	Class	Level
Pediatric patients presenting with suspected vasovagal syncope or POTS should undergo a detailed medical history review and physical examination and undergo a 12-lead ECG.	I	E
Pediatric patients with suspected POTS should undergo orthostatic testing.	I	E
Tilt-table testing is reasonable for highly selected pediatric patients with suspected vasovagal syncope.	IIa	C
It seems reasonable to treat selected pediatric patients with vasovagal syncope with midodrine.	IIb	B-R
It seems reasonable to treat pediatric patients with vasovagal syncope or POTS with interventions that are recommended for adults with these disorders.	IIb	E

Section 5: Future Opportunities

The writing group identified numerous opportunities for better understanding the causes, diagnosis, risk stratification, and treatment of these disorders. The first and formative step is to agree on uniform definitions for the syndromes, which the Heart Rhythm Society provides in this document. Once validated, these definitions will provide uniform criteria for inclusion of patients in clinical studies. Many subsequent studies will require multiple centers, and the formation of standing networks to address these problems is warranted. Indeed, there are semipermanent networks already in place in Europe (eg, the ISSUE group) and North America (eg, the POST group). Agreeing on priorities, common terms, and data fields is an important first step, and an international registry with common terms seems highly desirable.

There is relatively little known about the natural history of these 3 syndromes, although it is widely suspected that they are chronic disorders with waxing and waning severity. This knowledge could be acquired at relatively low cost if the studies were integrated into daily clinical practice. Similarly and despite professional guidelines, there is little evidence on the optimum strategy for assessing patients who might have these disorders. Given the disparate natures of health care systems, these studies might best be performed internationally with networks of investigators, accruing locally relevant information leading to solidly grounded, evidence-based guidelines.

None of the syndromes have investigative approaches that make much use of recent advances in information technology in medical care. We lack portable, beat-to-beat blood pressure monitors, and these could easily be integrated into current and cutting-edge technologies.

There is still a large gap in our understanding of the causes of the physiologic disturbances underlying these syndromes. These questions include fundamental issues such as whether POTS is a syndrome with varied manifestations or a collection of related syndromes. Similarly, is vasovagal syncope a single syndrome with a range of molecular, physiologic, and clinical manifestations or a collection of related syndromes? Are there genetic causes for these syndromes or are they secondary to life events? Should therapy be targeted to specific subgroups, or is a single approach sufficient?

To date, there are no effective therapies that have passed the scrutiny of even moderately sized, randomized clinical trials for any of these syndromes. Given the apparent heterogeneity of presentations among reporting sites, it will be important for external validity and clinical implementation that studies be conducted across a number of representative sites. However, this approach quickly leads to a critical and perhaps insurmountable problem: the wide range of regulatory regimens among provinces, states, and countries. It will take imagination and persistence to develop solutions to this fractious impediment to clinical research, which is conducted to improve the care of our patients.

Appendix 1

See pages e58–e63 page for Tables A and B.

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Table A Writing Group Author Disclosure Table

Writing Group	Employment	Consultant/Advisory Board/Honoraria	Speakers' Bureau	Research Grant	Fellowship Support	Equity Interests/ Stock Options	Others
Robert S. Sheldon, MD, PhD, FHRS	Libin Cardiovascular Institute of Alberta, Alberta, Canada	None	None	None	None	None	None
Blair P. Grubb II, MD	University of Toledo, Toledo, Ohio	1; Biotronik; Medtronic, Inc.	None	1; Medtronic, Inc.	None	None	None
Richard Sutton, DSc, FHRS	National Heart and Lung Institute, Imperial College, London, United Kingdom	3; Medtronic, Inc.	1; St. Jude Medical	3; Medtronic	None	3; Boston Scientific Corp. 5; Advanced Circulatory Systems, Inc.	None
Julian M. Stewart, MD, PhD	New York Medical College, Valhalla, New York	None	None	5; National Institutes of Health	None	None	None
Satish R. Raj, MD, MS, MSCI, FHRS	Libin Cardiovascular Institute of Alberta, Alberta, Canada Vanderbilt University School of Medicine, Nashville, Tennessee	1; Medtronic, Inc.; GE Healthcare; Lundberk	None	1; Dysautonomia International 5; National Institutes of Health	None	None	Officers/Trustees: 0; Association of Clinical and Translational Sciences; American Autonomic Society; Dysautonomia International Medical Advisory Board; Dysautonomia Information Network; Red Lily Foundation; POTS UK
Hugh Calkins, MD, FHRS, CCDS	Johns Hopkins University, Baltimore, Maryland	None	None	3; Medtronic, Inc.; St. Jude Medical	None	None	None
Carlos A. Morillo, MD, FHRS	McMaster University Population Health Research Institute, Hamilton, Canada	1; Sanofi Aventis; Biotronik 2; Boehringer Ingelheim; Merck Pharmaceuticals	1; Boehringer Ingelheim; Sanofi Aventis 2; Merck Pharmaceuticals	3; St. Jude Medical 4; Medtronic, Inc.; Boston Scientific Corp.	None	None	None

Table A (*continued*)

Writing Group	Employment	Consultant/Advisory Board/Honoraria	Speakers' Bureau	Research Grant	Fellowship Support	Equity Interests/ Stock Options	Others
Brian Olshansky, MD, FHRS, CCDS	The University of Iowa Hospitals, Iowa City, Iowa	1; Boston Scientific Corp; Boehringer Ingelheim; Medtronic, Inc.; BioControl Medical Ltd; Sanofi Aventis; Amarin; Daiichi Sankyo; Biotronik; On-X; Lundbeck	None	None	None	None	None
Mitchell I. Cohen, MD, FHRS, CCDS	Phoenix Children's Hospital, University of Arizona School of Medicine–Phoenix, Arizona Pediatric Cardiology Consultants/ Mednax, Phoenix, Arizona	None	None	None	None	None	None
Win-Kuang Shen, MD, FHRS	Mayo Clinic, Phoenix, Arizona	None	None	None	None	None	None
Andrew D. Krahn, MD, FHRS	University of British Columbia, Vancouver, Canada	1; Medtronic, Inc.; Bayer Healthcare, LLC; Boehringer Ingelheim	None	1; Boston Scientific Corp. 2; St. Jude Medical	None	None	None
Roopinder K. Sandhu, MD, FHRS	University of Alberta, Alberta, Canada	None	None	None	None	None	None
Kenneth A. Mayuga, MD	Cleveland Clinic Foundation, Cleveland, Ohio	None	None	None	None	None	None
M. Khalil Kanjwal, MD	John Hopkins University, Baltimore, Maryland	None	None	None	None	None	None

Table A (*continued*)

Writing Group	Employment	Consultant/Advisory Board/Honoraria	Speakers' Bureau	Research Grant	Fellowship Support	Equity Interests/ Stock Options	Others
Karen J. Friday, MD	Stanford University School of Medicine, Stanford, California	None	None	None	None	None	Arbor Pharmaceuticals (Stepson)
Denise Tessariol Hachul, MD, PhD	Heart Institute–University of Sao Paulo Medical School, Sao Paulo, Brazil	None	None	None	None	None	None
Paola Sandroni, MD, PhD	Mayo Clinic, Rochester, Minnesota	1; Lundbeck	None	None	None	None	None
Michele Brignole, MD	Ospedali del Tigullio, Lavagna, Italy	None	None	None	None	None	None
Jeffrey P. Moak, MD	Children's National Medical Center, Washington, District of Columbia	None	None	None	None	None	None
Dennis H. Lau, MBBS, PhD	Centre for Heart Rhythm Disorders, University of Adelaide; Department of Cardiology, Royal Adelaide Hospital; and South Australian Health and Medical Research Institute, Adelaide, Australia	None	None	None	4; National Health and Medical Research Council of Australia	None	None

Number Value: 0 = $0; 1 = <$10,000; 2 = >$10,000 to <$25,000; 3 = >$25,000 to <$50,000; 4 = >$50,000 to <$100,000; 5 = >$100,000

Table B Peer Reviewer Disclosure Table

Peer Reviewers	Employment	Consultant/Advisory Board/Honoraria	Speakers' Bureau	Research Grant	Fellowship Support	Equity Interests/Stock Options	Others
C. Chris Anderson, MD, CEPS	Providence Center for Congenital Heart Disease, Spokane, Washington	None	None	None	None	None	None
Heather L. Bloom, MD	Atlanta VA Medical Center, Decatur, Georgia	1; Biotronik; Motive Medical; Medical Legal Consulting	None	None	None	None	None
David J. Bradley, MD	University of Michigan–C.S. Mott Children's Hospital, Ann Arbor, Michigan	None	None	None	None	2; Medtronic	None
David J. Callans, MD	Hospital of the University of Pennsylvania, Merion Station, Pennsylvania	1; Biosense Webster, Inc.; Biotronik; Medtronic, Inc.; St. Jude Medical; Hansen Medical; Impulse Dynamics USA 2; Boston Scientific Corp.	None	None	1; Boston Scientific Corp.; St. Jude Medical, Medtronic, Inc.	None	None
Gisela Chelimsky, MD	Medical College of Wisconsin, Milwaukee, Wisconsin	1; Grand Rounds NY	None	None	None	None	Spouse-Advisory Board: 1; Lundbeck; Ironwood Pharmaceuticals
Mina K. Chung, MD, FHRS	Cleveland Clinic, Cleveland, Ohio	0; Zoll Medical Corp.; Amarin; Biotronik 1; National Institutes of Health; Japanese Society of Electrocardiography	1; American College of Cardiology Foundation	5; National Institutes of Health			Royalty Income: 1; Up to Date; Jones & Bartlett Publishers
James P. Daubert, MD, FHRS	Duke University Medical Center, Durham, North Carolina	1; Medtronic, Inc.; St. Jude Medical; Boston Scientific Corp.; Sorin Group; Cardio Focus, Inc.; Gilead Sciences, Inc.; Biosense Webster, Inc.; Biotronik; Sanofi Aventis	None	5; Boston Scientific Corp.; Biosense Webster, Inc.; Medtronic, Inc.; Gilead Sciences, Inc.	3; Medtronic, Inc.; Boston Scientific Corp.; Biotronik, St. Jude Medical; Biosense Webster, Inc.; Bard Electrophysiology	None	None

Table B (*continued*)

Peer Reviewers	Employment	Consultant/Advisory Board/Honoraria	Speakers' Bureau	Research Grant	Fellowship Support	Equity Interests/Stock Options	Others
Susan P. Etheridge, MD, FHRS, CEPS	University of Utah, Department Pediatric Cardiology, Salt Lake City, Utah	None	None	None	None	None	Officers/Trustees: 0; American College of Cardiology EP Committee; SADS Foundation; Pediatric and Congenital Electrophysiology Society Executive Committee
Wayne H. Franklin, MD, MPH	University of Illinois Chicago, Chicago, Illinois	None	None	None	None	None	Ownership/ partnership/ principal: 1; SafeCG
Roy Freeman, MD							
Zachary D. Goldberger, MD, FHRS, FACC	Harborview Medical Center, Seattle, Washington	None	None	None	None	None	None
Bulent Gorenek, MD, FACC, FESC	Eskisehir Osmangazi University, Eskisehir-Turkey	None	None	None	None	None	None
Huon H. Gray, MD, FACC	University Hospital of Southampton, Southampton, United Kingdom	None	None	None	None	None	None
Julia H. Indik, MD, PhD, FHRS	University of Arizona, Sarver Heart Center, Tucson, Arizona	None	None	None	None	None	None
Jose A. Joglar, MD, FACC	UT Southwestern Medical Center, Dallas, Texas	None	None	None	None	None	None
Robert Macfadyen, MD	University of Melbourne, Ballarat Clinical School, Melbourne, Australia	None	None	None	None	None	None
Srinivas Murali, MBBS, FACC	Temple University School of Medicine and Allegheny Health Network, Pittsburgh, Pennsylvania	1; Actelion, Inc.	1 ; Actelion, Inc.; Bayer, Inc.	3; Cariokinetics, Actelion, Inc.; Sunshine Heart	None	None	Officers/Trustees: 0; American College of Cardiology; American Heart Association
Luigi Padeletti, MD, PhD	Carregi Hospital, Florence, Italy	1; Biotronik; St. Jude Medical 2; Boston Scientific Corp.; Medtronic, Inc. 3; Sorin Group	None	None	None	None	None

Table B (*continued*)

Peer Reviewers	Employment	Consultant/Advisory Board/Honoraria	Speakers' Bureau	Research Grant	Fellowship Support	Equity Interests/Stock Options	Others
Swee Chye Quek, MBBS, FACC	National University of Singapore, Singapore	None	None	None	None	None	None
David Robertson, MD	Vanderbilt University, Nashville, Tennessee	None	None	None	None	None	Spouse Salary Support: American Heart Association
Aurora Ruiz, MD	Juan A Fernandez Hospital, cardiology and in Instituto Fleni, Buenos Aires, Argentina	None	None	None	None	None	None
Martin K. Stiles, MBCHB, PhD	Waikato Hospital, Cardiology, New Zealand	1; Boston Scientific Corp.; Medtronic, Inc.	None	None	2; St. Jude Medical; Medtronic, Inc.; Johnson and Johnson	None	None
Hung-Fat Tse, MD, PhD	University of Hong Kong, Hong Kong, China	1; Boston Scientific Corp.; Medtronic, Inc.; Bayer; BMS; Pfizer; MSD; Takeda; Otsuka 3; St. Jude Medical; AstraZaneca; Sanofi	1, Boston Scientific Corp.; Medtronic, Inc.; Bayer; BMS; Pfizer; MSD; Takeda 3; St. Jude Medical; AstraZaneca; Sanofi	None	1; Boston Scientific Corp.; Medtronic, Inc.; Biotronik; BMS; Pfizer 3; St. Jude Medical; AstraZaneca; Sanofi	None	None
Alejandro Villamil, MD	Hospital Santojanni, Buenos Aires, Argentina	None	None	None	None	None	None
Paul J. Wang, MD, FHRS, CCDS	Stanford University School of Medicine, Stanford, California	1; Medtronic, Inc.; Atricure, Inc.	None	2; Medtronic, Inc.	2; Medtronic, Inc.; Boston Scientific Corp.; Biosense Webster, Inc.; St. Jude Medical	1; Vytronus	None
Frank J. Zimmerman, MD, CEPS	The Heart Institute or Children, Oak Lawn, Illinois	None	None	None	None	None	None

Number Value: 0 = $0; 1 = <$10,000; 2 = >$10,000 to <$25,000; 3 = >$25,000 to <$50,000; 4 = >$50,000 to <$100,000; 5 = >$100,000