Internal and Emergency Medicine (2023) 18:23–30
https://doi.org/10.1007/s11739-022-03102-w

IM - REVIEW

Current approach to the treatment of vasovagal syncope in adults

Tarek Hatoum[1] · Satish Raj[1] · Robert Stanley Sheldon[1]

Received: 10 August 2022 / Accepted: 5 September 2022 / Published online: 18 September 2022

Abstract
Vasovagal syncope (VVS) is the most common cause of transient loss of consciousness. Although not associated with mortality, it causes injuries, reduces quality of life, and is associated with anxiety and depression. The European and North American cardiac societies recently published syncope clinical practice guidelines. Most patients with VVS do well after specialist evaluation, reassurance and education. Adequate hydration, increased salt intake when not contraindicated, and careful withdrawal of diuretics and specific hypotension-inducing drugs are a reasonable initial strategy. Physical counterpressure maneuvers might be helpful but can be of limited efficacy in older patients and those with short or no prodromes. Orthostatic training lacks long term efficacy and is troubled by non-compliance. Yoga might be helpful, although the biomedical mechanism is unknown. Almost a third of VVS patients continue to faint despite these conservative measures. Metoprolol was not helpful in a pivotal randomized clinical trial. Fludrocortisone and midodrine significantly reduce syncope recurrences with tolerable side effects, when titrated to target doses. Pacing therapy with specialized sensors appears promising in carefully selected population who have not responded conservative measures. Cardioneuroablation may be helpful but has not been studied in a formal clinical trial.

Keywords Vasovagal syncope · Quality of life · Injuries · Fludrocortisone · Midodrine · CLS pacemaker

Introduction

Vasovagal syncope (VVS) is the most common cause of syncope in all decades of life. The lifetime cumulative incidence of VVS up to age 60 years is estimated to be about 42% [1, 2], with additional cases presenting first in older subjects. VVS usually begins in adolescence and young adulthood [3], has a lifelong predilection, and is more common in females than males [4].

Although VVS is not associated with an increased risk of mortality, it can be alarming and worrisome [5], and it remains a significant cause of emergency department visits, cost, morbidities, and reduced quality of life [5]. Depending on the country, the admission rate through emergency departments to inpatient hospital beds ranges from 10% to 80%, despite the lack of evidence that hospital admissions reduce mortality [6, 7]. In fact, two propensity analyses have reported that hospital admission is associated with increased mortality [6, 7], when accounting for baseline factors. Even the use of syncope risk scores does not seem to reduce admissions significantly.

The likelihood of syncope recurrence is best estimated from numerous observational and randomized studies of patients with moderately frequent syncope [8]. In a large multicenter prospective study, Toarta et al. [9] followed about 5000 patients for 1 month after emergency room discharge. The discharge diagnosis was presumed to be VVS in 53.3% of patients and cardiac syncope in 5.4%. No deaths were reported in the VVS group. In observational and randomized studies of VVS [8] the median number of historical syncope spells is in the range of 10–20 faints, and the likelihood of fainting again in the next 1–2 years is 30–60%. The strongest predictor of syncope recurrence is the number of faints in the year before specialist assessment [10]. The high number of lifetime spells and high likelihood of recurrence is not generally appreciated, and they are associated with injury, poor quality of life, anxiety, and depression.

✉ Robert Stanley Sheldon
sheldon@ucalgary.ca

[1] Libin Cardiovascular Institute, University of Calgary, 3280 Hospital Drive NW, Calgary, AB T2N 4N1, Canada

Table 1 Impact of vasovagal syncope on patients

Impacts of vasovagal syncope on patients
Worsened anxiety
Worsened quality of life
Negative impacts on education and employment
Driving restrictions
Injuries in 15% of faints
Injuries in 30% of patients
Recurring health care visits

Quality of life and injuries in vasovagal syncope

Syncope and injuries

Although VVS is usually considered a benign disorder, the potential for injury is worrisome (Table 1). A recent systematic review of 23 studies and 3593 VVS patients reported the proportion of patients injured due to syncope [11]. At least 82% had had at least 3 syncopal spells. The mean proportion of injured patients was high, at 34%. The likelihood of injury was higher in older subjects and had no relationship with sex, positive tilt test, or hypertension. The proportions of patients ever injured with syncope were 26% in younger patients (mean age < 50 years) and 43% in older patients ($p = 0.002$). Major injuries occurred in 14% of patients. This systematic review based on retrospective studies concluded that injuries due to syncope are frequent, and the risk of major injuries is substantial [11].

This review of retrospective studies was complemented by an analysis of injury data prospectively collected in 3 Prevention of Syncope Trials (POST) [12]. POST 2 and 4 were randomized trials of fludrocortisone and midodrine in younger adults, and POST 3 was a pragmatic trial of two interventions in much older syncope patients with bifascicular heart block. Injury was defined as minor (bruising, abrasions), moderate (lacerations), and severe (fractures, burns, joint pain), and recorded up to 1 year after enrolment. In a total of 459 patients (median age 39 years) 186 fainted, sustaining a total of 710 faints. Fully 30% of patients with syncope were injured (12% of the overall group). Injuries occurred with 14% of faints, and of these injuries 19% were deemed to be moderate or severe. Neither patient age, sex, nor the presence of prodromal symptoms were associated with injury-free survival. In VVS patients, pharmacological therapy significantly reduced the likelihood of an injury due to a syncopal spell (relative risk 0.64, 95% CI 0.43–0.96, $p = 0.015$).

Both retrospective [11] and prospective studies [12] consistently report that about 30% of syncope patients are injured at some time due to a faint, about 15% of faints are associated with physical trauma, and about 20% of injuries are moderate to severe. Counterintuitively we failed to confirm that a syncope-related injury negatively impacts HRQoL [13].

Syncope and quality of life

The poor quality of life in syncope patients (Table 1) has been documented repeatedly since first noted by Linzer et al. [14]. Several factors including associated presyncopal episodes, recurrent faints, new onset syncope, and comorbidities were associated with significantly worse social and emotional functioning, general health and vitality compared to a Dutch general population [15]. Similar findings were reported in a VVS population [5]. VVS patients had significantly poorer physical functioning and general health perception, greater role limitations, poorer emotional well-being and social functioning compared to a healthy matched control population [5]. Health-related quality of life measures were found to improve in as little as 6 months, with sustained improvement at one year. These improvements occurred regardless of allocation to placebo or active therapy or type of therapy. It is worth noting that recurrent faints during follow up were associated with less improvement in quality of life.

Conservative treatment for vasovagal syncope

The mainstay of management remains conservative non-pharmacologic interventions with its three pillars (Table 2) being (1) reassurance of the benign nature of the disease, (2) education on triggers and strategies to avoid them and (3) lifestyle interventions [16].

Table 2 Conservative treatment approach

Conservative treatments
Describe the diagnosis and explain the mechanism
Reassure about the good prognosis
Explain that it may happen again at some point
Avoid identifiable triggers
Increase salt and fluid intake if not contraindicated
Teach physical manouevres: supine leg raising, squatting, leg crossing and lower body isometric tension
Yoga, but not hot yoga

Natural history and placebo

There are large decreases in recurrences following specialist evaluation even without specific medical therapy. A recent meta-analysis evaluated prospective cohorts and placebo arms of randomized controlled trials (RCTs) [8]. The analysis included 1912 subjects from 11 RCTs and 6 observational cohorts with a median pre-enrolment observation period of 1 year and a median follow-up of 2 years. The patients reported improvement with no specific intervention aside from being evaluated and enrolled in trials. Compared to the pre-enrollment year during which 97% of the patients fainted with an average 2.6 faints, in the follow up period only 36% of those patients fainted, with a risk ratio of 0.44. These improvements occurred regardless of the type of intervention in the active comparator arm of RCTs. This might be due to the placebo effect, due to education about acting on prodromal symptoms, or due to regression to the mean. In addition, syncope events tend to cluster before the index event, which is usually around the time of evaluation [17]. Placebo intervention has great potential but studies of placebo effect are difficult [18]. This very large risk reduction in control arms does emphasize the need for strictly controlled studies.

Education

A small nonrandomized study with up to 30 month follow-up reported that education significantly reduced recurrences by 70% in VVS patients with a positive head-up tilt (HUT) test [19]. Aydin et al. followed VVS patients for 2 years after a standardized educational approach [20] including instructions on upper and lower extremities counter pressure maneuvers using their Hamburg syncope prevention protocol (adapted in Table 2). Recurrence rates were comparable to the preceding study with 72.5% of patients being free from recurrence at 2 years regardless of the tilt test result. The frequency of traumatic injuries was also reduced by 40%.

Salt and fluid

Increased fluid and salt intake may improve orthostatic tolerance [21], but hydration alone is not sufficient to prevent symptoms [22]. In the absence of contraindications patients should be encouraged to increase their hydration with close monitoring of blood pressure in patients at risk of hypertension. In addition, reducing anti-hypertensive polypharmacy may help. In a small cohort of elderly hypertensive patients with confirmed VVS, withdrawing or reducing hypotensive therapy resulted in significant reduction in presyncope and syncope [23]. These patients were tightly controlled and adjusting therapy meant having to allow the systolic blood pressure to rise up to 140–150 mmHg. Finally, an easy lifestyle modification that might increase orthostatic tolerance and increase the prodromal time allowing for further action is head-up sleeping with the head of the bed elevated to 10° [24].

Physical manouevres

Physical counterpressure maneuvers are valuable techniques to abort VVS in patients with prodromes. The first open-label, randomized controlled trial of these maneuvers showed a 36% relative risk reduction in recurrence with counterpressure maneuvers [25]. However, there was no sham intervention in the control arm. Somewhat later the effectiveness of counterpressure maneuvers was questioned in elderly patients and patients with no or minimal prodromes [26]. In a recent meta-analysis of 688 patients enrolled in 11 studies out of which 2 were randomized trials, Dockx et al. [27] concluded that counterpressure maneuvers might be effective for prevention of VVS, but with a low level of evidence. There is no evidence for effectiveness in patients above age 40 years. The most effective maneuver, and the most appropriate ages, remain to be determined.

Orthostatic training

Tilt training consists of maintaining upright posture either through repeated tilt testing or home training against a wall with feet 15–30 cm away from the wall for up to 30 min [28]. Tilt training and less well-monitored stand training appeared to have benefits in open-label observational studies, but not in properly randomized, controlled studies [29, 30]. Perhaps this is due to true inefficacy, or perhaps it is because it is difficult to persuade people to stand quietly doing nothing else for 30–60 min every day. Long term compliance is poor. More aggressive tilt training up to 6 times a week was associated with a higher non-compliance rate and no effectiveness in other randomized trials [29–32]. Thus, overall home orthostatic training is of little value in managing VVS.

Physical exercise

Takahagi et al. [33] reported a randomized, open-label study that supervised physical exercise reduced syncope outcomes compared to a control group without any supervised exercise [33]. More recently Aghajani et al [34] reported a prospective, parallel arm, open label randomized clinical trial of closely monitored and encouraged exercise and stand training in patients with recurrent, moderate risk VVS. The results highly favored the intervention arm. The intervention arm subjects received the same instructions, *and* supervised, periodic, ongoing personal training in tilt training, *and* personal, supervised, periodic, ongoing moderate-intensity physical exercise under the supervision of a physical

medicine and rehabilitation specialist at a Cardiac Rehabilitation Center. Therefore, the intervention arm patients received four interventions in total: personalized instruction, ongoing tilt test training advice and encouragement, ongoing, moderate-intensity physical therapy, and personalized training in an expert environment. At least two of these—those involving personalized interactions—are powerful factors in placebo [18] and other incremental interventions are lesser but still significant placebo factors.

Yoga

Two recent randomized open-label studies hint that yoga programmes may be effective in preventing VVS [35, 36]. Both yoga studies were longitudinal, both included several poses, and one of them featured meditation, focused breathing, and Shavasana, the corpse pose. These suggest a powerful effect above the level of the brainstem, possibly as ways to trigger a beneficial placebo effect.

Pharmacological therapies

Up to 30% of VVS patients continue to suffer recurrent symptoms despite education, lifestyle modifications, and counterpressure maneuvers [8], particularly those with shorter prodromes. Several drugs targeting different aspects of the vasovagal reflex cascade show promising results in randomized studies (Table 3). There are no data regarding the effectiveness or safety of pharmacologic therapies in pregnant women [37]. The physiologic cascade leading to syncope is usually failure of venoconstriction and reduced preload, hypotension, and terminal bradycardia and, in some patients, arteriolar vasodilation. VVS is due to inappropriate sympathetic withdrawal causing vasodepression, reflex cardioinhibitory bradycardia, or a combination of both, leading to marked hypotension.

Fludrocortisone

The rationale for the use of the mineralocorticoid fludrocortisone was that it would cause fluid retention and maintain cardiac preload. The Prevention of Syncope Trial II (POST2) [38] was a randomized, placebo-controlled, double-blind trial that assessed the effects of fludrocortisone in VVS over a 1-year treatment period. It enrolled 210 patients with VVS who otherwise had normal blood pressure and randomized them to 0.1–0.2 mg of fludrocortisone. In a multivariable model, fludrocortisone significantly reduced the likelihood of syncope (Hazard Ratio 0.63; 95% CI 0.42–0.94; $p = 0.024$). When the analysis was restricted to outcomes after 2 weeks of dose stabilization, there was a significant benefit due to fludrocortisone (Hazard Ratio 0.62; 95% CI 0.40–0.95; $p = 0.019$). In patients who received the target dose of 0.2 mg daily there was a highly significant 49% relative risk reduction. Therefore, fludrocortisone 0.2 mg daily is a reasonable first line medical therapy, and should be avoided in patients with hypertension, heart failure, or fluid overload.

Midodrine

The rationale for the use of midodrine is that it is a prodrug whose active metabolite is a peripherally acting alpha agonist. This should reduce venous pooling and peripheral vasodilation, with the intent of maintaining preload and blood pressure. The Prevention of Syncope Trial IV [39] was a randomized, placebo-controlled, double-blind trial that assessed the effects of midodrine in VVS over a 1-year treatment period. It enrolled 133 patients who had had a median of 6 syncope episodes in the prior year (median age, 32 years; 73% female). They were randomized to placebo or midodrine 5 mg orally every 4 h, three times daily, with forced dose-adjustment in the first 2 weeks. Midodrine was associated with a significantly reduced relative risk of 0.69

Table 3 Medical treatments for troublesome vasovagal syncope

Treatment	Specific comments
Fludrocortisone	Best known dose 0.2 mg daily
	Contraindicated with hypertension or heart failure
Midodrine	Start with 5 mg orally every 4 h, three times daily
	Avoid doses before sleep hours
	Contraindicated with hypertension or heart failure
Beta blockers	Not indicated
Serotonin-specific reuptake inhibitors	Small studies
	There may be an initial lag awaiting neuroremodelling
Closed loop stimulation pacemaker	For highly symptomatic older patients with documented neurogenic asystole
Cardioneuroablation	Not for use outside research studies

Best practice is to try to discontinue drug treatments after 1 year

(95% CI 0.49–0.97; $p=0.035$). The number needed to prevent a person fainting over 1 year was 5.3. After allowing for dose adjustment in the first 2 weeks, the hazard ratio for syncope recurrence in the midodrine arm fell to 0.60 (95% CI 0.41–0.90; $p=0.013$). A subsequent meta-analysis found a reduced relative risk with midodrine of 0.71 (95% CI 0.53–0.95), $p=0.02$ [40]. The effect sizes were much larger in unblinded randomized studies and in studies with tilt test outcomes, emphasizing the importance of rigorous trial design and conduct.

Therefore, midodrine 2.5–10 mg three times daily is a reasonable first line medical therapy, and should be avoided in patients with hypertension, heart failure, or liver disease.

Beta blockers

Nonrandomized trials of beta blockers showed conflicting data for efficacy; several randomized controlled trials later confirmed lack of benefit [41–43]. A small study on atenolol showed positive results [44]. Beta blockers have a limited role, if any, in the prevention of VVS.

Serotonin-specific reuptake inhibitors

The rationale for the study of serotonin-specific reuptake inhibitors is the known role of at least 2 serotonin receptors in regulating blood pressure, considerable early, small, uncontrolled acute studies that were positive. The potential effects of serotonin are confounded by the ability of the SSRI clomipramine to acutely induce VVS [45], and possible remodeling over time of the neurophysiologic pathways. Nonetheless 3 small randomized controlled studies were positive [46–48], and SSRI agents could be considered. The difficulty clinicians face is the high numbers of seemingly depressed patients who are taking these medications, and not knowing if they are pro-syncopal or anti-syncopal.

Norepinephrine transport inhibitors

Norepinephrine transporter (NET) inhibition shows promise as a treatment option. Norepinephrine that is released at synapses is either cleared by diffusion or reuptake through active transport into terminals by the presynaptic NET, which recaptures as much as 90% of released norepinephrine [49]. This decreases intrasynaptic norepinephrine, effectively decreasing sympathetic nervous system tone. VVS patients might benefit from pharmacological NET inhibitors, which would restore sympathetic tone. Both reboxetine, a clinical antidepressant in Europe, and sibutramine, an anorexigenic, are highly specific NET inhibitors, and both prevent syncope induced by tilt table testing [50]. Sibutramine appeared to suppress VVS in an open-label case series of severely symptomatic patients [51].

We reported a randomized, placebo-controlled trial of the efficacy of atomoxetine in preventing VVS on tilt tests [52]. Significantly fewer VVS patients fainted with atomoxetine than with placebo. Atomoxetine, a selective NET inhibitor available in North America, was found to inhibit tilt test-induced syncope, terminal bradycardia, and hypotension in VVS patients [52]. A recent meta-analysis of NET inhibitors for syncope showed a consistent and highly significant decrease in syncope with NET inhibition during tilt tests [50].

There is currently no strong evidence that NET inhibition prevents clinical VVS in the community. However, NET inhibition is promising, in particular because it seems to be safe in patients with hypertension, which occurs in many older patients with VVS.

Invasive therapies

Permanent pacemakers

This has been an active field of investigation for 25 years, generally featuring industry-funded studies. Early observational and open label randomized studies were uniformly positive, but the negative results of the more tightly controlled and conducted VPS II [53] and SYNPACE [54] trials cast doubt on the treatment. Most of the early positive results appeared to be due to a placebo effect [55].

More recently the ISSUE-3 trial [56] was the first double blind RCT to show a significant 57% relative risk reduction in syncope recurrence with pacing for VVS. The understanding of this study has been complicated by an ISSUE-3 substudy that found that found that preimplant positive tilt tests, including those with asystole, predicted a complete lack of benefit from pacing [57]. These results were replicated by the Syncope Unit Project 2 investigators registry [58]. After 3 year follow up, patients receiving PPM and a negative tilt test had a 5% recurrence versus 23% recurrence in patients with a positive tilt test response.

Two recent clinical trials of closed loop stimulation (CLS) have produced fascinating results (Table 3). CLS is a pacing algorithm utilizing a contractility sensor aiming to deliver early pacing therapy in the reflex cascade, ahead of vasodilation and cardio inhibition. Both the double-blind SPAIN trial [59] and the double-blind BIOSYNC [60] trial reported highly significant benefit from CLS pacing. In the SPAIN study CLS pacing significantly reduced the syncope burden by more than 50% with 8.7% of patients fainting while in CLS pacing mode compared to 46% while in sham pacing [59]. The BIOSYNC trial [60] was terminated early due to superiority of CLS pacing over no pacing with a hazard ratio of 0.23 (95% CI 0.11–0.47), $p=0.00005$, and a number needed to treat of 2.2. A meta-analysis of CLS trials

[61] (excluding the recent BIOSYNC trial) confirmed the benefit of this pacing mode in patients with positive tilt test. In patients with confirmed cardioinhibitory response on tilt testing, a DDD–CLS device appears useful (Table 3).

Cardioneuroablation

The rationale for the study of endocardial ablation to cure VVS is involvement of epicardial autonomic ganglia in the vasovagal reflex. In the past decade, catheter-based modulation of the intrinsic cardiac autonomic nervous system, or cardioneuroablation (CNA), has emerged as an innovative therapy for VVS [62]. Most of the autonomic neurons involved with the cardiac autonomic nervous system are in epicardial ganglionated plexi. CNA is an invasive procedure during which the locations of these ganglionated plexi are mapped and subsequently ablated with radiofrequency ablation or cryoablation [62]. Well-designed randomized clinical trials are lacking. Previous studies have used varied methodologies, anatomic targets, acute procedural success criteria, and clinical outcomes [62]. Although all studies report high success rates, none has been adequately controlled or blinded (Table 3).

It is very important when considering both these invasive treatments to remember that VVS is not associated with mortality, is associated with moderate to severe injuries in only 4% of faints and about 1% of patients, and that VVS usually enters remission. The enthusiasm for cardioneuroablation generally arises in cardiologists who perform atrial fibrillation ablations [63], and not in physicians with experience, expertise, and engagement in providing care to patients with syncope. Physicians might use these therapies in many patients, but should they?

Future directions for VVS management

The phenotypic variability of VVS dictates careful evaluation and in the era of precision medicine-warrants targeted management. It seems likely that VVS has a strong genetic predisposition. Humans are the only animals known to faint [64]. Furthermore, gender and age susceptibility, reproducibility of triggering factors, reproducibility of both inducibility and non-inducibility all point to genetic origin to VVS. This is further supported by pedigree analysis showing strong evidence to familial clustering of VVS [2]. In a kindred candidate gene analysis catecholamine methyltransferase, the serotonin transporter, and a serotonin receptor gene 5HT1A were significantly associated with the vasovagal phenotype [65]. Genome-wide association studies have reported several other linkage variants of uncertain physiologic mechanisms [66–68]. Perhaps further genetic studies will provide more precise therapeutic targets.

Final words

Most patients with VVS have a reasonably normal disease-related quality of life with education, reassurance, and minor lifestyle interventions. Medical and drug history should include comorbidities requiring vasoactive drug therapy; reasonably adjusting such medications may reduce the burden of VVS. Counter pressure maneuvers in physically capable patients are a valuable tool in delaying and preventing spells.

For the few patients who require more than this, fludrocortisone and midodrine have good evidence for effectiveness, but should be avoided in patients with hypertension or heart failure. SSRIs might have a limited role in these patients, and NET inhibitors are under investigation. Pacing therapy should be reserved for patients older than 40 years with documentation of > 3 s pauses either on tilt tests or implantable loop recorders, preferably with a CLS-capable pacemaker. Ablation should be avoided except in clinical studies.

Funding This research received no external funding.

Institutional Review Board Statement Not applicable.

Declarations

Conflict of Interest The authors declare no conflict of interest.

Informed Consent Statement Not applicable.

References

1. Ganzeboom KS, Mairuhu G, Reitsma JB, Linzer M, Wieling W, van Dijk N (2006) Lifetime cumulative incidence of syncope in the general population: a study of 549 Dutch subjects aged 35–60 years. J Cardiovasc Electrophysiol 17:1172–1176
2. Serletis A, Rose S, Sheldon AG, Sheldon RS (2006) Vasovagal syncope in medical students and their first-degree relatives. Eur Heart J 27:1965–1970
3. Sheldon RS, Sheldon AG, Connolly SJ, Morillo CA, Klingenheben T, Krahn AD et al (2006) Age of first faint in patients with vasovagal syncope. J Cardiovasc Electrophysiol 17:49–54
4. Deveau AP, Sheldon R, Maxey C, Ritchie D, Doucette S, Parkash R (2020) Sex differences in vasovagal syncope: a post hoc analysis of the prevention of syncope trials (POST) I and II. Can J Cardiol 36:79–83
5. Ng J, Sheldon RS, Ritchie D, Raj V, Raj SR (2019) Reduced quality of life and greater psychological distress in vasovagal syncope patients compared to healthy individuals. Pacing Clin Electrophysiol 42:180–188
6. Kaul P, Tran DT, Sandhu RK, Solbiati M, Costantino G, Sheldon RS (2020) Lack of benefit from hospitalization in patients with syncope: a propensity analysis. J Am Coll Emerg Phys Open. https://doi.org/10.1002/emp2.12229

7. Probst MA, Su E, Weiss RE, Yagapen AN, Malveau SE, Adler DH et al (2019) Clinical benefit of hospitalization for older adults with unexplained syncope: a propensity-matched analysis. Ann Emerg Med 74:260–269
8. Pournazari P, Sahota I, Sheldon R (2017) High remission rates in vasovagal syncope. JACC: Clin Electrophysiol 3:384–392
9. Toarta C, Mukarram M, Arcot K, Kim SM, Gaudet S, Sivilotti MLA et al (2018) Syncope prognosis based on emergency department diagnosis: a prospective cohort study. Acad Emerg Med 25:388–396
10. Sumner GL, Rose MS, Koshman ML, Ritchie D, Sheldon RS (2010) Recent history of vasovagal syncope in a young, referral-based population is a stronger predictor of recurrent syncope than lifetime syncope burden. J Cardiovasc Electrophysiol 21:1375–1380
11. Jorge JG, Raj SR, Teixeira PS, Teixeira JAC, Sheldon RS (2021) Likelihood of injury due to vasovagal syncope: a systematic review and meta-analysis. Europace 23:1092–1099
12. Jorge JG, Pournazari P, Raj SR, Maxey C, Sheldon RS (2020) Frequency of injuries associated with syncope in the prevention of syncope trials. Europace 22:1896–1903
13. Jorge J, Raj S, Liang Z, Sheldon R (2022) Quality of life and injury due to vasovagal syncope [letter]. Clin Auton Res 32(2):147–149
14. Linzer M, Gold DT, Pontinen M, Divine GW, Felder A, Brooks WB (1994) Recurrent syncope as a chronic disease: preliminary validation of a disease-specific measure of functional impairment. J Gen Intern Med 9:181–186
15. van Dijk N, Sprangers MA, Colman N, Boer KR, Wieling W, Linzer M (2006) Clinical factors associated with quality of life in patients with transient loss of consciousness. J Cardiovasc Electrophysiol 17:998–1003
16. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A et al (2018) 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J 39:1883–1948
17. Sahota IS, Maxey C, Pournazari P, Sheldon RS (2017) Clusters, gaps, and randomness: vasovagal syncope recurrence patterns. JACC Clin Electrophysiol 3:1046–1053
18. Sheldon R, Opie-Moran M (2017) The placebo effect in cardiology: understanding and using it. Can J Cardiol 33:1535–1542
19. Baron-Esquivias G, Errazquin F, Pedrote A, Cayuela A, Gomez S, Aguilera A et al (2004) Long-term outcome of patients with vasovagal syncope. Am Heart J 147:883–889
20. Aydin MA, Mortensen K, Salukhe TV, Wilke I, Ortak M, Drewitz I et al (2012) A standardized education protocol significantly reduces traumatic injuries and syncope recurrence: an observational study in 316 patients with vasovagal syncope. Europace 14:410–415
21. Cooper VL, Hainsworth R (2002) Effects of dietary salt on orthostatic tolerance, blood pressure and baroreceptor sensitivity in patients with syncope. Clin Auton Res 12:236–241
22. Bellard EFJO, Custaud MA, Victor J, Greenleaf J, Lefthériotis G (2007) Increased hydration alone does not improve orthostatic tolerance in patients with neurocardiogenic syncope. Clin Auton Res 17:99–105
23. Solari D, Tesi F, Unterhuber M, Gaggioli G, Ungar A, Tomaino M et al (2017) Stop vasodepressor drugs in reflex syncope: a randomised controlled trial. Heart 103:449–455
24. Cooper VL, Hainsworth R (2008) Head-up sleeping improves orthostatic tolerance in patients with syncope. Clin Auton Res 18:318–324
25. van Dijk N, Quartieri F, Blanc JJ, Garcia-Civera R, Brignole M, Moya A et al (2006) Effectiveness of physical counterpressure maneuvers in preventing vasovagal syncope: the Physical Counterpressure Manoeuvres Trial (PC-Trial). J Am Coll Cardiol 48:1652–1657
26. Tomaino M, Romeo C, Vitale E, Kus T, Moya A, van Dijk N et al (2014) Physical counter-pressure manoeuvres in preventing syncopal recurrence in patients older than 40 years with recurrent neurally mediated syncope: a controlled study from the Third International Study on Syncope of Uncertain Etiology (ISSUE-3)†. Europace 16:1515–1520
27. Dockx K, Avau B, De Buck E, Vranckx P, Vandekerckhove P (2019) Physical manoeuvers as a preventive intervention to manage vasovagal syncope: a systematic review. PLoS ONE 14:e0212012
28. Reybrouck T, Heidbuchel H, Van De Werf F, Ector H (2002) Long-term follow-up results of tilt training therapy in patients with recurrent neurocardiogenic syncope. Pacing Clin Electrophysiol 25:1441–1446
29. On YK, Park J, Huh J, Kim JS (2007) Is home orthostatic self-training effective in preventing neurally mediated syncope? Pacing Clin Electrophysiol 30:638–643
30. Podd S, Hunt J, Sulke N (2015) Home orthostatic training in elderly patients with vasovagal syncope—a prospective randomised controlled trial. Eur Cardiol 10:123–127
31. Duygu H, Zoghi M, Turk U, Akyuz S, Ozerkan F, Akilli A et al (2008) The role of tilt training in preventing recurrent syncope in patients with vasovagal syncope: a prospective and randomized study. Pacing Clin Electrophysiol 31:592–596
32. Foglia-Manzillo G, Giada F, Gaggioli G, Bartoletti A, Lolli G, Dinelli M et al (2004) Efficacy of tilt training in the treatment of neurally mediated syncope. A randomized study. Europace 6:199–204
33. Takahagi VC, Costa DC, Crescêncio JC, Gallo JL (2014) Physical training as non-pharmacological treatment of neurocardiogenic syncope. Arq Bras Cardiol 102:288–294
34. Aghajani F, Tavolinejad H, Sadeghian S, Bozorgi A, Jalali A, Vasheghani-Farahani A et al (2022) Implementation of supervised physical training to reduce vasovagal syncope recurrence: a randomized controlled trial. J Cardiovasc Electrophysiol. https://doi.org/10.1111/jce.15578
35. Sharma G, Ramakumar V, Sharique M, Bhatia R, Naik N, Mohanty S et al (2022) Effect of yoga on clinical outcomes and quality of life in patients with vasovagal syncope (LIVE-yoga). JACC Clin Electrophysiol 8:141–149
36. Shenthar J, Gangwar RS, Banavalikar B, Benditt DG, Lakkireddy D, Padmanabhan D (2021) A randomized study of yoga therapy for the prevention of recurrent reflex vasovagal syncope. Europace 23:1479–1486
37. Chatur S, Islam S, Moore LE, Sandhu RK, Sheldon RS, Kaul P (2019) Incidence of syncope during pregnancy: temporal trends and outcomes. J Am Heart Assoc 8:e011608
38. Sheldon R, Raj SR, Rose MS, Morillo CA, Krahn AD, Medina E et al (2016) Fludrocortisone for the prevention of vasovagal syncope: a randomized, placebo-controlled trial. J Am Coll Cardiol 68:1–9
39. Sheldon R, Faris P, Tang A, Ayala-Paredes F, Guzman J, Marquez M et al (2021) Midodrine for the prevention of vasovagal syncope : a randomized clinical trial. Ann Intern Med 174:1349–1356
40. Lei LY, Raj SR, Sheldon RS (2022) Midodrine for the prevention of vasovagal syncope: a systematic review and meta-analysis. Europace 24:euab323
41. Sheldon R, Connolly S, Rose S, Klingenheben T, Krahn A, Morillo C et al (2006) Prevention of Syncope Trial (POST): a randomized, placebo-controlled study of metoprolol in the prevention of vasovagal syncope. Circulation 113:1164–1170
42. Madrid AH, Ortega J, Rebollo JG, Manzano JG, Segovia JG, Sanchez A et al (2001) Lack of efficacy of atenolol for the prevention of neurally mediated syncope in a highly symptomatic population: a prospective, double-blind, randomized and placebo-controlled study. J Am Coll Cardiol 37:554–559

43. Flevari P, Livanis EG, Theodorakis GN, Zarvalis E, Mesiskli T, Kremastinos DT (2002) Vasovagal syncope: a prospective, randomized, crossover evaluation of the effect of propranolol, nadolol and placebo on syncope recurrence and patients' well-being. J Am Coll Cardiol 40:499–504
44. Mahanonda N, Bhuripanyo K, Kangkagate C, Wansanit K, Kulchot B, Nademanee K et al (1995) Randomized double-blind, placebo-controlled trial of oral atenolol in patients with unexplained syncope and positive upright tilt table test results. Am Heart J 130:1250–1253
45. Flevari P, Leftheriotis D, Komborozos C, Fountoulaki K, Dagres N, Theodorakis G et al (2009) Recurrent vasovagal syncope: comparison between clomipramine and nitroglycerin as drug challenges during head-up tilt testing. Eur Heart J 30:2249–2253
46. Theodorakis GN, Leftheriotis D, Livanis EG, Flevari P, Karabela G, Aggelopoulou N et al (2006) Fluoxetine vs. propranolol in the treatment of vasovagal syncope: a prospective, randomized, placebo-controlled study. Europace 8:193–198
47. Flevari P, Leftheriotis D, Repasos E, Katsaras D, Katsimardos A, Lekakis J (2017) Fluoxetine vs. placebo for the treatment of recurrent vasovagal syncope with anxiety sensitivity. Europace 19:127–131
48. Di Girolamo E, Di Iorio C, Sabatini P, Leonzio L, Barbone C, Barsotti A (1999) Effects of paroxetine hydrochloride, a selective serotonin reuptake inhibitor, on refractory vasovagal syncope: a randomized, double-blind, placebo-controlled study. J Am Coll Cardiol 33:1227–1230
49. Schomig E, Fischer P, Schonfeld CL, Trendelenburg U (1989) The extent of neuronal re-uptake of 3H-noradrenaline in isolated vasa deferentia and atria of the rat. Naunyn Schmiedebergs Arch Pharmacol 340:502–508
50. Lei LY, Raj SR, Sheldon RS (2020) Pharmacological norepinephrine transporter inhibition for the prevention of vasovagal syncope in young and adult subjects: a systematic review and meta-analysis. Heart Rhythm 17:1151–1158
51. Sheldon RS, Ritchie D, McRae M, Raj S (2013) Norepinephrine transport inhibition for treatment of vasovagal syncope. J Cardiovasc Electrophysiol 24:799–803
52. Sheldon RS, Lei L, Guzman JC, Kus T, Ayala-Paredes FA, Angihan J et al (2019) A proof of principle study of atomoxetine for the prevention of vasovagal syncope: the Prevention of Syncope Trial VI. Europace 21:1733–1741
53. Connolly SJ, Sheldon R, Thorpe KE, Roberts RS, Ellenbogen KA, Wilkoff BL et al (2003) Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: Second Vasovagal Pacemaker Study (VPS II): a randomized trial. J Am Med Assoc 289:2224–2229
54. Raviele A, Giada F, Menozzi C, Speca G, Orazi S, Gasparini G et al (2004) A randomized, double-blind, placebo-controlled study of permanent cardiac pacing for the treatment of recurrent tilt-induced vasovagal syncope. The vasovagal syncope and pacing trial (SYNPACE). Eur Heart J 25:1741–1748
55. Sud S, Massel D, Klein GJ, Leong-Sit P, Yee R, Skanes AC et al (2007) The expectation effect and cardiac pacing for refractory vasovagal syncope. Am J Med 120:54–62
56. Brignole M, Donateo P, Tomaino M, Massa R, Iori M, Beiras X et al (2014) Benefit of pacemaker therapy in patients with presumed neurally mediated syncope and documented asystole is greater when tilt test is negative: an analysis from the third International Study on Syncope of Uncertain Etiology (ISSUE-3). Circ Arrhythm Electrophysiol 7:10–16
57. Brignole M, Deharo JC, Menozzi C, Moya A, Sutton R, Tomaino M et al (2018) The benefit of pacemaker therapy in patients with neurally mediated syncope and documented asystole: a meta-analysis of implantable loop recorder studies. Europace 20:1362–1366
58. Brignole M, Ammirati F, Arabia F, Quartieri F, Tomaino M, Ungar A et al (2015) Assessment of a standardized algorithm for cardiac pacing in older patients affected by severe unpredictable reflex syncopes. Eur Heart J 36:1529–1535
59. Baron-Esquivias G, Morillo CA, Moya-Mitjans A, Martinez-Alday J, Ruiz-Granell R, Lacunza-Ruiz J et al (2017) Dual-chamber pacing with closed loop stimulation in recurrent reflex vasovagal syncope: the SPAIN study. J Am Coll Cardiol 70:1720–1728
60. Brignole M, Russo V, Arabia F, Oliveira M, Pedrote A, Aerts A et al (2021) Cardiac pacing in severe recurrent reflex syncope and tilt-induced asystole. Eur Heart J 42:508–516
61. Ruzieh M, Ghahramani M, Nudy M, Naccarelli GV, Mandrola J, Grubb BP et al (2019) The benefit of closed loop stimulation in patients with cardioinhibitory vasovagal syncope confirmed by head-up tilt table testing: a systematic review and meta-analysis. J Interv Card Electrophysiol 55:105–113
62. Vandenberk B, Lei LY, Ballantyne B, Vickers D, Liang Z, Sheldon RS et al (2022) Cardioneuroablation for vasovagal syncope: a systematic review and meta-analysis. Heart Rhythm. https://doi.org/10.1016/j.hrthm.2022.06.017
63. Vandenberk B, Morillo CA, Sheldon RS, Chew DS, Aksu T, Raj SR (2021) Clinician needs and perceptions about cardioneuroablation for recurrent vasovagal syncope: an international clinician survey. Heart Rhythm 18:2160–2166
64. Sheldon RS, Sandhu RK (2019) The search for the genes of vasovagal syncope. Front Cardiovasc Med. https://doi.org/10.3389/fcvm.2019.00175
65. Sheldon R, Rose MS, Ritchie D, Martens K, Maxey C, Jagers J et al (2019) Genetic association study in multigenerational kindreds with vasovagal syncope. Circ Arrhythm Electrophysiol 12:e006884
66. Hadji-Turdeghal K, Andreasen L, Hagen CM, Ahlberg G, Ghouse J, Bækvad-Hansen M et al (2020) Genome-wide association study identifies locus at chromosome 2q32.1 associated with syncope and collapse. Cardiovasc Res 116:138–148
67. Demir E, Hasdemir C, Ak H, Atay S, Aydin HH (2016) Genome-wide association study of copy number variations in patients with familial neurocardiogenic syncope. Biochem Genet 54:487–494
68. Klein KM, Bromhead CJ, Smith KR, O'Callaghan CJ, Corcoran SJ, Heron SE et al (2013) Autosomal dominant vasovagal syncope: clinical features and linkage to chromosome 15q26. Neurology 80:1485–1493