Published in final edited form as:

Auton Neurosci. 2014 September ; 184: 77–82. doi:10.1016/j.autneu.2014.05.009.

Ongoing Clinical Trials for Vasovagal Syncope: Where are we in 2014?

Samuel T Coffin, MD^{1,2} and Satish R Raj, MD, MSCI^{1,2,3}

¹Autonomic Dysfunction Center, Vanderbilt University School of Medicine

²Department of Medicine, Vanderbilt University School of Medicine

³Department of Pharmacology, Vanderbilt University School of Medicine

Abstract

Vasovagal Syncope (VVS) can lead to a markedly diminished quality of life for some patients. While there are many treatments for this condition including physical, mechanical, pharmacologic, and device-based control of heart rate, there are few that have been shown to be effective in randomized clinical trials. In our local experience, we have achieved significant improvement in symptom frequency and quality of life using algorithms based on the data available and on clinical acumen for the majority of patients with VVS. Despite this, there are still many patients who suffer from treatment refractory VVS. Fortunately, there are a number of ongoing clinical trials that are likely to add to our knowledge. Ongoing clinical trials are reviewed to examine new treatment methods for VVS that were listed on public trial registries as of April 15, 2014. Data from these trials should inform future strategies in the care of patients with VVS.

Keywords

syncope; vasovagal; treatment; medications; pharmacological; device

INTRODUCTION

Vasovagal syncope (VVS) can result in significant injury in 5% of cases, and can lead to impaired quality of life.(Bartoletti et al., 2008; van Dijk et al., 2007) This reflex occurs due to bradycardia and hypotension brought on by multiple different types of stimuli including prolonged sitting or standing, pain and anxiety, large muscle use, and exercise.(Sheldon, Morillo, & Krahn, 2004)

© 2014 Elsevier B.V. All rights reserved.

Corresponding Author & Address for Reprints: Satish R. Raj MD MSCI, Autonomic Dysfunction Center, Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University School of Medicine, AA3228 Medical Center North, 1161 21st Avenue South, Nashville, TN, 37232-2195, USA, Tel. 615-343-3649 Fax 615-343-8649, satish.raj@vanderbilt.edu.

Conflicts of Interest – None

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Many approaches have been proposed for the treatment of vasovagal syncope.(Raj & Coffin, 2013) These include physical countermeasures, pharmacological approaches, and device-based modulation of heart rate. Our local treatment plans include early education, avoiding environmental triggers, and lifestyle changes. These strategies are often quite effective. If these are not effective, then the next step is pharmacologic or invasive electrophysiological treatments, although very few of these therapies have been shown to be effective in randomized clinical trials. Unfortunately, a small but significant minority of patients do not achieve adequate symptom control using usual treatments.

There are many challenges in the study and treatment of VVS.(Raj & Freeman, 2012) Patients have variable symptoms and may or may not have a prodromal period prior to syncope events. Symptoms may be inextricably tied to psychological states or unavoidable environmental triggers. The treatments are often time-sensitive and require significant “buy-in” for the patients in order to be effective. Compliance may be low due to a necessarily strict treatment regimen, and this may negatively affect outcomes.

There are a number of ongoing clinical trials that seek to provide further data about optimal treatments for VVS. The large, randomized, double-blinded, placebo-controlled studies will likely have significant influence over future treatments for VVS. However, all trials (randomized and observational) can be limited by enrollment and patient compliance with treatments.

Ongoing trials for VVS that are registered in publically accessible registries as of April 15, 2014 are listed below. These trials are important in building evidenced-based knowledge that can expand our arsenal of treatments. Clinicians who treat patients with VVS are encouraged to refer eligible patients into suitable clinical trials.

METHODS

Publically available clinical trial registries were searched for ongoing trials on the clinical treatment of VVS. These included the National Institutes of Health funded ClinicalTrials.Gov (NCT) at <http://www.clinicaltrials.gov>, the European Union Clinical Trials Register <http://www.clinicaltrialsregister.eu>, the International Standard Randomised Controlled Trial Number Register (ISRCTN) at <http://www.controlled-trials.com> and the World Health Organization’s International Clinical Trials Registry Platform (ICTRP) at <http://www.who.int/ictcp/en/>.

Different combinations of the search terms “syncope”, “vasovagal”, and “neurocardiogenic” were used to search for trials on these websites. The returned trials were then screened for clinical relevance and to determine if the trial was still ongoing or had already been completed. A PubMed search was then performed to ensure that there were no publications already reporting results related to these ongoing studies.

Once accepted for inclusion, the trial data were evaluated for planned enrollment, study design, methods, primary and secondary outcomes, and inclusion and exclusion criteria. A brief list of trials is enumerated in Table 1, and more detailed trial data are included in the text.

RESULTS

RANDOMIZED CONTROLLED TRIALS

Assessment of Midodrine in the Prevention of Vasovagal Syncope: The Prevention of Syncope Trial IV (POST 4). (Raj, Faris, McRae, & Sheldon, 2012; Sheldon, 2014)—Identifier NCT01456481 (<http://clinicaltrials.gov/show/NCT01456481>)

Principal Investigator: Robert S. Sheldon MD PhD, University of Calgary (Canada)

Sponsor: Canadian Institutes of Health Research

Trial Design: Phase 4, randomized, double-blinded, placebo-controlled, parallel assessment

Comparators: Midodrine 10 mg TID vs. Placebo

Placebo-Control: Yes

Primary Outcome: Syncope recurrence in 1 year of follow-up.

Key Secondary Outcomes

- The time between the 1st and 2nd syncope recurrences in 1 year
- the frequency of syncope spells in 1 year
- the health-related quality of life assessed by the EuroQol [EQ-5D], (EuroQOL Group, 1990) and Impact of Syncope on Quality of Life [ISQL] (Rose, Koshman, Ritchie, & Sheldon, 2009) surveys over 1 year.

Key Inclusion Criteria

- Two or more syncope spells in the 1 year prior to enrollment, and
- -2 points on the Calgary Syncope Symptoms Score for structurally normal hearts, (Sheldon et al., 2006b) and
- Age ≥ 18 years.

Key Exclusion Criteria

- Other causes of syncope, or
- inability to give informed consent, or
- heart or rhythm abnormalities, or
- hypertrophic cardiomyopathy, or
- permanent pacemaker, or
- seizure disorder, or
- urinary retention, or
- blood pressure >140/90 mmHg, or

- significant liver disease, or
- glaucoma, or
- orthostatic tachycardia on a 5 minute stand test or
- orthostatic hypotension on a 5 minute stand test.

Start of Enrollment: November 2011

End of Enrollment: November 2015

Commentary: The vasodepressor response that can be seen in vasovagal syncope might be due to a failure of venoconstriction, vasoconstriction or both. Alpha-1 adrenergic agonists could address both mechanisms. Midodrine showed promise in 4 prospective controlled studies in vasovagal syncope, although none were adequately designed. One study (Kaufmann, Saadia, & Voustianiouk, 2002) used tilt test outcomes as the endpoint. This endpoint is known not to predict clinical outcomes. Another study (Ward, Gray, Gilroy, & Kenny, 1998) included only extremely symptomatic patients and assessed them for only one month. A third study (Qingyou, Junbao, & Chaoshu, 2006) studied only children and was contaminated with fludrocortisone therapy. Finally, a fourth study (Perez-Lugones et al., 2001) was open label. Overall, these reports suggest an absolute risk reduction in these highly symptomatic populations of about 60%. Recently, Romme et al. (Romme, van, Go-Schon, Reitsma, & Wieling, 2011) reported a more modest (and less significant) relative risk reduction of 26% in a placebo controlled crossover study of midodrine 5mg BID for 3 months per phase in patients in whom physical counter-maneuvers did not prevent syncope. The POST4 study is larger than any of the individual aforementioned studies, has an appropriate clinical endpoint of syncope recurrence and is placebo-controlled and double-blind. These design strengths should allow the POST4 study to provide some clarity to the question of the efficacy of midodrine in vasovagal syncope.

Fifth Prevention of Syncope Trial (POST5) - Metoprolol in Vasovagal Syncope Patients >40 years—Identifier NCT02123056 (<http://www.clinicaltrials.gov/ct2/show/NCT02123056>)

Principal Investigator: Robert S. Sheldon MD PhD, University of Calgary (Canada)

Sponsor: Canadian Institutes of Health Research

Trial Design: Randomized, double-blinded, placebo-controlled

Comparators: Metoprolol 50 mg BID vs. Placebo

Placebo-Control: Yes

Primary Outcome: Time to 1st syncope recurrence.

Key Secondary Outcomes

- Presyncope frequency, duration, and intensity, and

- quality of life.

Key Inclusion Criteria

- Age ≥ 40 years, and
- ≥ 1 syncopal spell in the year preceding enrollment, and
- ≥ -2 points on the Calgary Syncope Symptom Score for Structurally Normal Hearts. (Sheldon et al., 2006b)

Key Exclusion Criteria

- Other causes of syncope (sick sinus syndrome, ventricular tachycardia, heart block, postural hypotension, hypersensitive carotid sinus syndrome), or
- the inability to give informed consent, or
- important valvular, coronary, myocardial, or conduction abnormalities, or
- hypertrophic cardiomyopathy or
- known genetic arrhythmia, or
- a contraindication to beta blockers, or
- another clinical need for beta blockers that cannot be substituted for another drug, or
- a seizure disorder, or
- a major chronic non-cardiovascular disease, or
- an implanted defibrillator.

Start of Enrollment: April 2014

End of Enrollment: Not listed

Commentary: In the original Prevention of Syncope Trial (POST), (Sheldon et al., 2006a) metoprolol was found to be no more effective than placebo at preventing recurrence of vasovagal syncope. A pre-specified subgroup analysis showed a dimorphic response to age. Patients <42 years did much worse with metoprolol than placebo. However, the patients that were ≥ 42 years did seem to benefit from the metoprolol. The POST study was not powered for this subgroup analysis, and this difference did not quite achieve statistical significance. These data were included in a recent meta-analysis that again suggested a benefit of metoprolol in patients aged ≥ 42 years when compared to younger patients. (Sheldon et al., 2012) While the reasons for this age-based response to metoprolol are not entirely clear, it may have been related to higher sympathoneural tone in older patients (that could be blocked by metoprolol), compared with a more vigorous sympathoadrenal response in younger patients (Benditt et al., 2012) and greater vasodilation that cannot be blocked by metoprolol (Fu, Verheyden, Wieling, & Levine, 2012).

The POST5 study is powered to assess for benefit of metoprolol in preventing vasovagal syncope in older patients (age >40 years).

Closed Loop Stimulation for Neuromediated Syncope (SPAIN study). (Baron-Esquivas, 2014)—Identifier NCT01621464 (<http://clinicaltrials.gov/show/NCT01621464>)

Principal Investigator: Gonzalo Baron-Esquivas MD PhD, Spanish Society of Cardiology

Sponsor: Biotronik SE & Co. KG (Spain)

Trial Design: Phase 4, randomized, double-blinded

Comparators: All patients receive dual chamber permanent pacemakers. One group will have pacing capabilities activated while the other will have the devices remain in DDI setting.

Placebo-Control: No placebo, but pacing mode will be blinded

Primary Outcome: Reduction in the number of syncope events at 1 year post-procedure.

Key Secondary Outcomes

- time to first syncope event,
- number of syncope recurrences at 1 year,
- quality of life at 1 year.

Key Inclusion Criteria

- 5 previous neurally mediated syncope events, and
- a positive tilt test, and
- a witnessed cardioinhibitory response with tilt test, or
- heart rate <40 bpm for at least 10 seconds or a pause of greater than 3 seconds recorded on telemetry without a tilt test, and
- age ≥ 40 years, and
- geographic stability with ability to come to the clinic, and
- informed consent.

Key Exclusion Criteria

- Beta blocker therapy, or
- chronic polyneuropathy, or
- cardiomyopathy, or
- contraindications to dual chamber pacing, or

- syncope due to carotid sinus hypersensitivity, or
- other causes of syncope, or
- current enrollment in other clinical trials, or
- pregnancy, or
- lack of adequate contraception if patient has child-bearing potential.

Start of Enrollment: May 2006

End of Enrollment: April 2014 study ongoing, but closed to enrollment)

Commentary: Most pacemaker algorithms for vasovagal syncope are triggered based on a sudden drop in intrinsic heart rate that can be seen at the time of a faint. The Closed-Loop Stimulation (CLS) algorithm is different. It uses bioelectrical impedance recordings from the RV pacemaker lead tip to the pulse generator to create a pattern seen with a normal contraction. It then uses changes from that normal pattern to ascertain periods of increased sympathetic tone and increased myocardial contractility, as one would expect before the vasovagal response according to the Sharpey-Shafer model (SHARPEY-SCHAFER, 1956). In theory, the pacemaker could then fire earlier and more reliably during a vasovagal reaction.

This study apparently compares default DDI pacing with the CLS-driven pacing. If positive, this study would be the first vasovagal syncope pacing algorithm to be better than regular pacing. If positive, it would be very interesting to see a comparative effectiveness study of CLS-driven pacing compared to proprietary vasovagal syncope algorithms from other companies.

To Study the Clinical Curative Effect of Improved Valsalva on Patients with Vasovagal Syncope. (Lun, 2014)—Identifier ChiCTR-TRC-12002514 (<http://www.who.int/trialsearch/trial.aspx?trialid=ChiCTR-TRC-12002514>)

Principal Investigator: Li Lun MD, Puai Hospital, Huazhong University of Science and Technology (Wuhan, Hubei, China)

Sponsor: Puai Hospital, Huazhong University of Science and Technology

Trial Design: Single-blind, open-label, parallel trial.

Comparators: Valsalva maneuvers once daily for 50–60 minutes compared to control

Placebo-Control: Yes

Primary Outcome: Not fainting during tilt table testing.

Key Secondary Outcomes: None listed.

Key Inclusion Criteria

- Positive tilt test, and
- 3 lifetime syncope spells prior to the tilt test, and
- Age between 18 to 80 years.

Key Exclusion Criteria

- Syncope of non-vasovagal cause, or
- Inability to give informed consent, or
- serious disease or psychopathology, or
- pregnancy, or
- being fertile and planning on pregnancy, or
- breast-feeding.

Start of Enrollment: October 2012

End of Enrollment: December 2014

Commentary: The Valsalva maneuver can provide important insights into the functioning of the cardiovascular system and of cardiovascular autonomic reflexes. This study seems predicated on a long-term and lingering effect of repeated Valsalva maneuvers in reconditioning cardiac reflexes. The basis for this hypothesis is not clear. This study has severe design limitations, including an open-label design with a tilt-test drive outcome. This study is unlikely to generate insights that will alter our future clinical management of vasovagal syncope.

OBSERVATIONAL COHORT STUDIES

Influence of Yoga in Patients with Neurocardiogenic Syncope (SYNC-YOGA). (Lakkireddy, 2013)—Identifier NCT01695525 (<http://clinicaltrials.gov/show/NCT01695525>)

Principal Investigator: Dhanunjaya Lakkireddy MD, University of Kansas

Sponsor: University of Kansas Medical Center Research Institute

Trial Design: Open-label, efficacy trial

Comparators: Yoga exercises for 1 year

Placebo-Control: No

Primary Outcome: Frequency of syncope spells at 3 months and 1 year compared to baseline.

Key Secondary Outcomes: None listed.

Key Inclusion Criteria

- Age between 18 to 60 years, and
- diagnosis of recurrent neurocardiogenic syncope, and
- 1 episode of syncope or pre-syncope in the last 3 months.

Key Exclusion Criteria

- Psychiatric diagnosis, or
- a history of heart disease or carotid sinus hypersensitivity, or
- tachyarrhythmias or bradyarrhythmias except due to cardioinhibitory neurocardiogenic syncope, or
- history of permanent pacemaker or implantable cardiac defibrillator, or
- pregnancy, or
- uncontrolled hypertension, or
- history of pneumothorax, or
- history of spine disease, or
- carotid stenosis, or
- psychosis, or
- substance abuse, or
- epilepsy, or
- glaucoma, or
- a total hip replacement.

Start of Enrollment: June 2012

End of Enrollment: December 2013 but enrollment listed as ongoing

Commentary: There has been increased interest in the use of alternative or “traditional” therapies for chronic disorders, including yoga. These investigators have recently published a report suggesting that yoga can decrease recurrence of paroxysmal atrial fibrillation (Lakkireddy et al., 2013). These investigators propose to assess yoga for the prevention of vasovagal syncope. There are several challenges with a study such as this one. First, yoga is not 1 approach, but rather a family of approaches that can include alterations of breathing pattern, different exercises and meditation. These components probably require isolated study, and these studies would ideally be blinded. There is good data that there can be a significant placebo effect in patients with vasovagal syncope (Olshansky, 2007; Sheldon, Rose, Flanagan, Koshman, & Killam, 1996), so a positive study would need to be followed by a more rigorous study before strong conclusions could be drawn.

Efficacy of Transcatheter Ablation Using anatomic Approach of Ganglionated Plexi Located in the Right Atrium to Prevent Neuromediated Cardioinhibitory Syncope. (Calo, 2013)—Identifier NCT01814228 (<http://clinicaltrials.gov/show/NCT01814228>)

Principal Investigator: Leonardo Calo MD, Policlinico Casilino ASL RMB (Italy)

Sponsor: Policlinico Casilino ASL RMB

Trial Design: Phase 3 cohort study

Comparators: Transcatheter ablation in the right atrium

Placebo-Control: No

Primary Outcome: Recurrent episode of neurally mediated syncope.

Key Secondary Outcomes: None listed.

Key Inclusion Criteria

- Age between 18 to 60 years, and
- 3 neurally mediated cardioinhibitory syncope episodes within the prior 2 years, and
- Marked cardioinhibitory response to tilt-table testing or documented asystolic pauses with an implanted loop recorder (defined as 3 second pause associated with syncope or 6 second pause associated with presyncope.)

Key Exclusion Criteria

- Significant myocardial or cardiac valve problems on echocardiogram, or
- documented tachyarrhythmias that could be causing the symptoms, or
- channelopathies, or
- ventricular pre-excitation, or
- symptomatic orthostatic hypotension by standing blood pressure measurement, or
- pregnancy, or
- permanent pacemaker.

Start of Enrollment: March, 2013

End of Enrollment: July 2015

Cardioneuroablation for Neurocardiogenic Syncope (Ablate-NCS) (Qingyou et al., 2006)—Identifier NCT02009982 (<http://clinicaltrials.gov/show/NCT02009982>)

Principal Investigator: David B. De Lurgio MD, Emory University (Atlanta, Georgia, USA)

Sponsor: Biosense Webster, Inc.

Trial Design: Open label, parallel assignment, efficacy study

Comparators: Cardioneuroablation in the left atrium (ablation of vagal inputs)

Placebo-Control: No

Key Primary Outcomes: Recurrence of syncope in 12 months.

Key Secondary Outcomes: Incidence of serious adverse events related to the study procedure in 12 months.

Key Inclusion Criteria

- Ability to give informed consent, and
- Age ≥ 18 years, and
- availability for the follow-up protocol and procedures, and
- medically documented history of neurocardiogenic syncope, and
- ≥ 3 episodes of syncope or presyncope in the last 12 months, and
- a positive tilt table test with or without nitroglycerin provocation or atropine challenge, and
- a prior trial of ≥ 1 pharmacologic therapy for ≥ 4 weeks.

Key Exclusion Criteria

- Signs and symptoms of active untreated infection, or
- pregnancy or planned pregnancy during follow-up, or
- concurrent enrollment in another study, or
- lack of syncope episodes in the last 6 months on medical therapy, or
- another documented cause of syncope, or
- myocardial infarction in the last 6 months, or
- severe heart failure, or
- prior heart surgery, or
- structural or infiltrative cardiac disease, or
- other contraindications for left atrial ablation.

Start of Enrollment: December 2013

End of Enrollment: December 2015

Commentary: There are now a series of case reports and case series that suggest that left atrial ablation, presumably targeting epicardial cardiac autonomic ganglia, can be effective in decreasing the syncope burden or even in eliminating this altogether. This study is one of a few studies that are trying to assess this novel therapy in a more systematic way. If these ablations are proven to be effective, then this will open up a new therapeutic option for patients with refractory vasovagal syncope. This therapy would be truly revolutionary if it were effective in patients with a vasodepressor response, and not just in those with a cardioinhibitory response with their vasovagal syncope.

Improving Syncope Risk Stratification in Older Adults. (Sun, 2013)—Identifier
NCT01802398 (<http://clinicaltrials.gov/show/NCT01802398>)

Principal Investigator: Benjamin Sun MD MPP, Oregon Health and Science University (Portland, Oregon, USA)

Sponsor: National Institutes of Health (NIH)

Trial Design: Observational, prospective cohort study

Comparators: None

Placebo-Control: No

Key Primary Outcomes: Combined death and serious cardiac events.

Key Secondary Outcomes: None listed.

Key Inclusion Criteria

- Age ≥ 60 years and
- a complaint of syncope or near-syncope.

Key Exclusion Criteria

- Seizure causing loss of consciousness, or
- stroke or transient ischemic attack causing loss of consciousness, or
- head trauma causing loss of consciousness, or
- baseline confusion, or
- intoxication, or
- hypoglycemia, or
- medical or electrical intervention needed to restore consciousness, or
- poor follow-up options, or
- inability to give consent.

Start of Enrollment: April 2013

End of Enrollment: Not listed

Commentary: Syncope is a symptom with multiple possible underlying causes, and the prognosis can vary widely based upon the cause (Soteriades et al., 2002). The challenge for the Emergency physician when someone presents with syncope is determining patients who require hospital admission for a possible intervention to modify their prognosis vs. those patients that can safely be sent home. Risk stratification efforts to date have been limited. This study is designed to build a cohort to optimize the risk stratification of older patients with syncope who present to the Emergency Department.

Guideline-based Pacing Therapy for Reflex Syncope (SUP2). (Brignole, 2012)

—Identifier NCT01509534 (<http://clinicaltrials.gov/show/NCT01509534>)

Principal Investigator: Michele Brignole MD, Ospedali del Tigullio (Lavagna, Italy)

Sponsor: Gruppo Italiano Multidisciplinare per lo Studio della Sincope

Trial Design: Observational, prospective cohort study

Comparators

- If cardio-inhibitory syncope, then permanent pacemaker implantation
- If positive tilt table test, then permanent pacemaker implantation
- If negative tilt table test, then implantable loop recorder.

Placebo-Control: No

Key Primary Outcomes: Time to 1st syncope recurrence

Key Secondary Outcomes: Syncope burden in the year after pacemaker or loop recorder implantation.

Key Inclusion Criteria

- Severe, recurrent proven or suspected reflex syncope, and
- Age ≥ 40 years.

Key Exclusion Criteria

- Reflex syncope due to reversible causes, or
- suspected or certain cardiac syncope, or
- syncope caused by orthostatic hypotension, or
- non-syncopal causes of transient loss of consciousness.

Start of Enrollment: January 2012

End of Enrollment: April 2014

Commentary: This is a registry-based study to assess outcomes based on approaches advocated by the European Society of Cardiology guidelines. If someone has a clinical episode of cardioinhibitory vasovagal syncope, then they will undergo a pacemaker implantation, as per the ISSUE3 study.(Brignole et al., 2012) Despite the concerns about the ability for a positive vs. a negative tilt test to adequately discriminate prognosis in patients with vasovagal syncope, a positive tilt test would drive a permanent pacemaker implantation, while a negative tilt test would lead to extended monitoring with an implanted loop recorder. It will be interesting to see if the tilt test results are an effective tool for this purpose, especially in light of a recent paper suggesting that patients with a clinical cardioinhibitory response and a negative tilt respond better to pacing.(Brignole et al., 2014)

CONCLUSION

There are ongoing randomized controlled trials and observational cohort studies that will better inform us at Vanderbilt and the larger autonomic community about how to best treat patients with VVS. Efforts should be made to encourage patients to enroll in these clinical trials. This strategy will allow for the creation of a robust knowledge base that will ultimately inform, and hopefully improve, patient care. Special attention should be paid to the large, randomized studies listed above, which could significantly change our pharmacologic VVS treatments in the future.

Acknowledgments

Research Funding – Supported in part by NIH grants R01 HL102387, P01 HL56692, and UL1 TR000445 (Clinical and Translational Science Award).

Reference List

- Baron-Esquivas, G. Closed Loop Stimulation for Neuromediated Syncope (SPAIN Study). 2014. [ClinicalTrials.Gov](http://clinicaltrials.gov/show/NCT01621464)[Electronic version]. Available: <http://clinicaltrials.gov/show/NCT01621464>
- Bartoletti A, Fabiani P, Bagnoli L, Cappelletti C, Cappellini M, Nappini G, et al. Physical injuries caused by a transient loss of consciousness: main clinical characteristics of patients and diagnostic contribution of carotid sinus massage. *Eur Heart J*. 2008; 29:618–624. [PubMed: 18086659]
- Benditt DG, Detloff BL, Adkisson WO, Lu F, Sakaguchi S, Schussler S, et al. Age-dependence of relative change in circulating epinephrine and norepinephrine concentrations during tilt-induced vasovagal syncope. *Heart Rhythm*. 2012; 9:1847–1852. [PubMed: 22863884]
- Brignole, M. Guideline-based Pacing Therapy for Reflex Syncope (SUP2). 2012. [ClinicalTrials.Gov](http://clinicaltrials.gov/show/NCT01509534)[Electronic version]. Available: <http://clinicaltrials.gov/show/NCT01509534>
- Brignole M, Donato P, Tomaino M, Massa R, Iori M, Beiras X, et al. 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*. 2014; 7:10–16. [PubMed: 24336948]
- Brignole M, Menozzi C, Moya A, Andresen D, Blanc JJ, Krahm AD, et al. Pacemaker therapy in patients with neurally mediated syncope and documented asystole: Third International Study on Syncope of Uncertain Etiology (ISSUE-3): a randomized trial. *Circulation*. 2012; 125:2566–2571. [PubMed: 22565936]
- Calo, L. Efficacy of Transcatheter Ablation Using anatomic Approach of Ganglionated Plexi Located in the Right Atrium to Prevent Neuromediated Cardioinhibitory Syncope. 2013. [ClinicalTrials.Gov](http://clinicaltrials.gov/show/NCT01814228)[Electronic version]. Available: <http://clinicaltrials.gov/show/NCT01814228>
- EuroQOL Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990; 16:199–208. [PubMed: 10109801]

- Fu Q, Verheyden B, Wieling W, Levine BD. Cardiac output and sympathetic vasoconstrictor responses during upright tilt to presyncope in healthy humans. *J Physiol.* 2012; 590:1839–1848. [PubMed: 22331415]
- Kaufmann H, Saadia D, Voustianiouk A. Midodrine in neurally mediated syncope: a double-blind, randomized, crossover study. *Ann Neurol.* 2002; 52:342–345. [PubMed: 12205647]
- Lakkireddy, D. Influence of Yoga in Patients with Neurocardiogenic Syncope (SYNC-YOGA). 2013. [ClinicalTrials.Gov](http://clinicaltrials.gov/show/NCT01695525)[Electronic version]. Available: <http://clinicaltrials.gov/show/NCT01695525>
- Lakkireddy D, Atkins D, Pillarisetti J, Ryschon K, Bommana S, Drisko J, et al. Effect of yoga on arrhythmia burden, anxiety, depression, and quality of life in paroxysmal atrial fibrillation: the YOGA My Heart Study. *J Am Coll Cardiol.* 2013; 61:1177–1182. [PubMed: 23375926]
- Lun, L. To study the clinical curative effect of improved Valsalva on patients with vasovagal syncope. International Clinical Trials Registry Platform. 2014. [Electronic version]. Available: <http://www.who.int/trialsearch/trial.aspx?trialid=ChiCTR-TRC-12002514>
- Olshansky B. Placebo and nocebo in cardiovascular health: implications for healthcare, research, and the doctor-patient relationship. *J Am Coll Cardiol.* 2007; 49:415–421. [PubMed: 17258086]
- Perez-Lugones A, Schweikert R, Pavia S, Sra J, Akhtar M, Jaeger F, et al. Usefulness of midodrine in patients with severely symptomatic neurocardiogenic syncope: a randomized control study. *J Cardiovasc Electrophysiol.* 2001; 12:935–938. [PubMed: 11513446]
- Qingyou Z, Junbao D, Chaoshu T. The efficacy of midodrine hydrochloride in the treatment of children with vasovagal syncope. *J Pediatr.* 2006; 149:777–780. [PubMed: 17137891]
- Raj SR, Coffin ST. Medical therapy and physical maneuvers in the treatment of the vasovagal syncope and orthostatic hypotension. *Prog Cardiovasc Dis.* 2013; 55:425–433. [PubMed: 23472781]
- Raj SR, Faris PD, McRae M, Sheldon RS. Rationale for the prevention of syncope trial IV: assessment of midodrine. *Clin Auton Res.* 2012; 22:275–280. [PubMed: 22610268]
- Raj SR, Freeman R. Highlights in clinical autonomic neurosciences: vasovagal syncope - insights on diagnosis, pathophysiology and treatment. *Auton Neurosci.* 2012; 168:1–3. [PubMed: 22444321]
- Romme JJ, van DN, Go-Schon IK, Reitsma JB, Wieling W. Effectiveness of midodrine treatment in patients with recurrent vasovagal syncope not responding to non-pharmacological treatment (STAND-trial). *Europace.* 2011; 13:1639–1647. [PubMed: 21752826]
- Rose MS, Koshman ML, Ritchie D, Sheldon R. The development and preliminary validation of a scale measuring the impact of syncope on quality of life. *Europace.* 2009; 11:1369–1374. [PubMed: 19797151]
- SHARPEY-SCHAFER EP. Syncope. *Br Med J.* 1956; 1:506–509. [PubMed: 13293372]
- Sheldon R, Connolly S, Rose S, Klingenhoben T, Krahn A, Morillo C, et al. Prevention of Syncope Trial (POST): a randomized, placebo-controlled study of metoprolol in the prevention of vasovagal syncope. *Circulation.* 2006a; 113:1164–1170. [PubMed: 16505178]
- Sheldon R, Morillo C, Krahn A. Management of vasovagal syncope: 2004. *Expert Rev Cardiovasc Ther.* 2004; 2:915–923. [PubMed: 15500436]
- Sheldon R, Rose S, Connolly S, Ritchie D, Koshman ML, Frenneaux M. Diagnostic criteria for vasovagal syncope based on a quantitative history. *Eur Heart J.* 2006b; 27:344–350. [PubMed: 16223744]
- Sheldon R, Rose S, Flanagan P, Koshman ML, Killam S. Risk factors for syncope recurrence after a positive tilt-table test in patients with syncope. *Circulation.* 1996; 93:973–981. [PubMed: 8598089]
- Sheldon, RS. Assessment of Midodrine in the Prevention of Vasovagal Syncope: The Prevention of Syncope Trial IV. 2014. [ClinicalTrials.Gov](http://clinicaltrials.gov/show/NCT01456481)[Electronic version]. Available: <http://clinicaltrials.gov/show/NCT01456481>
- Sheldon RS, Morillo CA, Klingenhoben T, Krahn AD, Sheldon A, Rose MS. Age-dependent effect of beta-blockers in preventing vasovagal syncope. *Circ Arrhythm Electrophysiol.* 2012; 5:920–926. [PubMed: 22972872]
- Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ, et al. Incidence and prognosis of syncope. *N Engl J Med.* 2002; 347:878–885. [PubMed: 12239256]
- Sun, B. Improving Syncope Risk Stratification in Older Adults. 2013. [ClinicalTrials.Gov](http://clinicaltrials.gov/show/NCT01802398)[Electronic version]. Available: <http://clinicaltrials.gov/show/NCT01802398>

- van Dijk N, Sprangers MA, Boer KR, Colman N, Wieling W, Linzer M. Quality of life within one year following presentation after transient loss of consciousness. *Am J Cardiol.* 2007; 100:672–676. [PubMed: 17697827]
- Ward CR, Gray JC, Gilroy JJ, Kenny RA. Midodrine: a role in the management of neurocardiogenic syncope. *Heart.* 1998; 79:45–49. [PubMed: 9505918]

Highlights

- Ongoing trials for the treatment of vasovagal syncope are listed.
- The strengths and weaknesses of each ongoing trial are enumerated.
- New trials will inform the future treatment of vasovagal syncope.
- Special attention should be paid to ongoing, large, randomized trials.
- Efforts should be made to enroll patients in these trials.

Table 1

Ongoing Publically Registered Vasovagal Syncope Trials

	Study Name	Principal Investigator	Trial Registration Number
Randomized Trials			
1	POST4	Robert Sheldon	NCT01456481
2	POST5	Robert Sheldon	pending
3	Spain Study	Gonzalo Baron-Esquivas	NCT01621464
4	Valsalva	Li Lun	ChiCTR-TRC- 12002514
Observational Studies			
1	SYNC-YOGA	Dhanunjaya Lakkireddy	NCT01695525
2	Transcatheter Ablation Study	Leonardo Calo	NCT01814228
3	Ablate-NCS	David De Lurgio	NCT02009982
4	SRS	Benjamin Sun	NCT01802398
5	SUP2	Michele Brignole	NCT01509534