2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society

WRITING COMMITTEE MEMBERS*

Win-Kuang Shen, MD, ACC, FAHA, FFRS, Chair†
Robert S. Sheldon, MD, PhD, FFRS, Vice Chair
David G. Benditt, MD, ACC, FFRS‡
Mitchell I. Cohen, MD, ACC, FFRS‡
Daniel E. Forman, MD, ACC, FAHA§
Zachary D. Goldberger, MD, MS, ACC, FAHA, FFRS‡
Blair P. Grubb, MD, FACC
Mohamed H. Hamdan, MD, MBA, FACC, FFRS*‡
Andrew D. Krahm, MD, FFRS*§
Mark S. Link, MD, FACC†
Brian Olschansky, MD, FACC, FAHA, FFRS*‡
Satish R. Raj, MD, MSc, ACC, FFRS*§
Rooinder Kaur Sandhu, MD, MPH‡
Dan Soraja, MD‡
Benjamin C. Sun, MD, MPP, FACEP¶
Clyde W. Yancy, MD, MSc, FACC, FAHA‡¶

Key Words: AHA Scientific Statements, syncope, risk assessment, diagnosis, prognosis, cardiac syncope, reflex syncope, vasovagal syncope, orthostatic hypotension, neurogenic syncope, dehydration, pediatrics, adult congenital heart disease, geriatrics, driving, athletes

© 2017 by the American College of Cardiology Foundation, the American Heart Association, Inc., and the Heart Rhythm Society.
TABLE OF CONTENTS

Preamble ................................................. e26
1. Introduction ...................................... e28
  1.1. Methodology and Evidence Review .......... e28
  1.2. Organization of the Writing Committee .... e28
  1.3. Document Review and Approval .......... e28
  1.4. Scope of the Guideline ................ e28
2. General Principles ............................. e30
  2.1. Definitions: Terms and Classification ... e30
  2.2. Epidemiology and Demographics .......... e31
  2.3. Initial Evaluation of Patients with Syncope:
        Recommendations ........................ e31
        2.3.1. History and Physical Examination:
                Recommendation ..................... e31
        2.3.2. Electrocardiography: Recommendation .. e31
        2.3.3. Risk Assessment: Recommendations ... e32
        2.3.4. Disposition After Initial Evaluation:
                Recommendations ..................... e32
3. Additional Evaluation and Diagnosis .......... e33
  3.1. Blood Testing: Recommendations ........ e33
  3.2. Cardiovascular Testing: Recommendations . e33
      3.2.1. Cardiac Imaging: Recommendations ... e33
      3.2.2. Stress Testing: Recommendation .... e33
      3.2.3. Cardiac Monitoring: Recommendations .... e33
      3.2.4. In-Hospital Telemetry: Recommendation ... e33
      3.2.5. Electrophysiological Study:
              Recommendations ...................... e34
      3.2.6. Tilt-Table Testing: Recommendations ... e34
  3.3. Neurological Testing: Recommendations ... e34
      3.3.1. Autonomic Evaluation: Recommendation e34
      3.3.2. Neurological and Imaging Diagnostics:
              Recommendations ...................... e35
4. Management of Cardiovascular Conditions .... e35
  4.1. Arrhythmic Conditions: Recommendations . e35
      4.1.1. Bradycardia: Recommendation .......... e35
      4.1.2. Supraventricular Tachycardia:
              Recommendations ...................... e35
      4.1.3. Ventricular Arrhythmia: Recommendation .. e35
  4.2. Structural Conditions: Recommendations . e36
      4.2.1. Ischemic and Nonischemic Cardiomyopathy:
              Recommendation ..................... e36
      4.2.2. Valvular Heart Disease: Recommendation .. e36
      4.2.3. Hypertrophic Cardiomyopathy:
              Recommendation ..................... e36
      4.2.4. Arrhythmogenic Right Ventricular Cardiomyopathy:
              Recommendations ...................... e36
      4.2.5. Cardiac Sarcoidosis: Recommendations . e36
  4.3. Inheritable Arrhythmic Conditions:
       Recommendations ........................ e37
      4.3.1. Brugada Syndrome: Recommendations .. e37
      4.3.2. Short-QT Syndrome: Recommendation ... e37
      4.3.3. Long-QT Syndrome: Recommendations . e37
      4.3.4. Catecholaminergic Polymorphic Ventricular
              Tachycardia: Recommendations .......... e37
      4.3.5. Early Repolarization Pattern:
              Recommendations ...................... e37
5. Reflex Conditions: Recommendations ........ e37
  5.1. Vasovagal Syncope: Recommendations ...... e37
  5.2. Pacemakers in Vasovagal Syncope:
       Recommendation ........................ e38
5.3. Carotid Sinus Syndrome: Recommendations ... e38
  5.4. Other Reflex Conditions ................ e38
6. Orthostatic Hypotension: Recommendations . e38
  6.1. Neurogenic Orthostatic Hypotension:
       Recommendations ...................... e38
  6.2. Dehydration and Drugs: Recommendations .. e39
7. Orthostatic Intolerance ....................... e39
8. Pseudosyncope: Recommendations ........ e40
9. Uncommon Conditions Associated with Syncope ... e40
10. Age, Lifestyle, and Special Populations:
      Recommendations ........................ e40
      10.1. Pediatric Syncope: Recommendations ... e40
      10.2. Adult Congenital Heart Disease:
              Recommendations ...................... e41
      10.3. Geriatric Patients: Recommendations ... e41
      10.4. Driving and Syncope: Recommendation ... e41
      10.5. Athletes: Recommendations ........ e41
11. Quality of Life and Healthcare Cost of Syncope .. e42
      11.1. Impact of Syncope on Quality of Life ... e42
      11.2. Healthcare Costs Associated with Syncope ... e42
12. Emerging Technology, Evidence Gaps,
      and Future Directions ................ e42
      12.1. Definition, Classification, and Epidemiology .... e42
      12.2. Risk Stratification and Clinical Outcomes .. e43
      12.3. Evaluation and Diagnosis ................ e43
      12.4. Management of Specific Conditions .... e43
      12.5. Special Populations ................ e43
References ............................................ e44
Appendix 1. Author Relationships With Industry
             and Other Entities (Relevant) ........ e53
Appendix 2. Reviewer Relationships With Industry
             and Other Entities (Comprehensive) .... e55
Appendix 3. Abbreviations ....................... e59

PREAMBLE

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines (guidelines) with recommendations to improve cardiovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a cornerstone for quality cardiovascular care. The ACC and AHA sponsor the development and publication of guidelines without commercial support, and members of each organization volunteer their time to the writing and review efforts. Guidelines are official policy of the ACC and AHA.

Intended Use

Practice guidelines provide recommendations applicable to patients with or at risk of developing cardiovascular disease. The focus is on medical practice in the United States, but guidelines developed in collaboration with other organizations may have a global impact. Although guidelines may be used to inform regulatory or payer decisions, their intent is to improve patients’
quality of care and align with patients’ interests. Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances and should not replace clinical judgment.

Clinical Implementation

Guideline-recommended management is effective only when followed by healthcare providers and patients. Adherence to recommendations can be enhanced by shared decision making between healthcare providers and patients, with patient engagement in selecting interventions based on individual values, preferences, and associated conditions and comorbidities.

METHODOLOGY AND MODERNIZATION

The ACC/AHA Task Force on Clinical Practice Guidelines (Task Force) continuously reviews, updates, and modifies guideline methodology on the basis of published standards from organizations including the Institute of Medicine, and on the basis of internal reevaluation. Similarly, the presentation and delivery of guidelines are reevaluated and modified on the basis of evolving technologies and other factors to facilitate optimal dissemination of information at the point of care to healthcare professionals. Given time constraints of busy healthcare providers and the need to limit text, the current guideline format delineates that each recommendation be supported by limited text (ideally, <250 words) and hyperlinks to supportive evidence summary tables. Ongoing efforts to further limit text are underway. Recognizing the importance of cost–value considerations in certain guidelines, when appropriate and feasible, an analysis of the value of a drug, device, or intervention may be performed in accordance with the ACC/AHA methodology.

To ensure that guideline recommendations remain current, new data are reviewed on an ongoing basis, with full guideline revisions commissioned in approximately 6-year cycles. Publication of new, potentially practice-changing study results that are relevant to an existing or new drug, device, or management strategy will prompt evaluation by the Task Force, in consultation with the relevant guideline writing committee, to determine whether a focused update should be commissioned. For additional information and policies regarding guideline development, we encourage readers to consult the ACC/AHA guideline methodology manual and other methodology articles.

Selection of Writing Committee Members

The Task Force strives to avoid bias by selecting experts from a broad array of backgrounds. Writing committee members represent different geographic regions, sexes, ethnicities, races, intellectual perspectives/biases, and scopes of clinical practice. The Task Force may also invite organizations and professional societies with related interests and expertise to participate as partners, collaborators, or endorsers.

Relationships With Industry and Other Entities

The ACC and AHA have rigorous policies and methods to ensure that guidelines are developed without bias or improper influence. The complete relationships with industry and other entities (RWI) policy can be found online. Appendix 1 of the current document lists writing committee members’ relevant RWI. For the purposes of full transparency, writing committee members’ comprehensive disclosure information is available online, as is comprehensive disclosure information for the Task Force.

Evidence Review and Evidence Review Committees

When developing recommendations, the writing committee uses evidence-based methodologies that are based on all available data. Literature searches focus on randomized controlled trials (RCTs) but also include registries, nonrandomized comparative and descriptive studies, case series, cohort studies, systematic reviews, and expert opinion. Only key references are cited.

An independent evidence review committee (ERC) is commissioned when there are 1 or more questions deemed of utmost clinical importance that merit formal systematic review. This systematic review will determine which patients are most likely to benefit from a drug, device, or treatment strategy and to what degree. Criteria for commissioning an ERC include: a) the absence of a current authoritative systematic review; b) the feasibility of defining the benefit and risk in a time frame consistent with the writing of a guideline; c) the relevance to a substantial number of patients; and d) the likelihood that the findings can be translated into actionable recommendations. ERC members may include methodologists, epidemiologists, healthcare providers, and biostatisticians. The recommendations developed by the writing committee on the basis of the systematic review are marked with **SR**.

Guideline-Directed Management and Therapy

The term guideline-directed management and therapy (GDMT) encompasses clinical evaluation, diagnostic testing, and pharmacological and procedural treatments. For these and all recommended drug treatment...
regimens, the reader should confirm the dosage by reviewing product insert material and evaluate the treatment regimen for contraindications and interactions. The recommendations are limited to drugs, devices, and treatments approved for clinical use in the United States.

Class of Recommendation and Level of Evidence

The Class of Recommendation (COR) indicates the strength of the recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence that supports the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 1).

The reader is encouraged to consult the full-text guideline for additional guidance and details with regard to syncope because this executive summary contains limited information.

Glenn N. Levine, MD, FACC, FAHA
Chair, ACC/AHA Task Force on Clinical Practice Guidelines

1. INTRODUCTION

1.1. Methodology and Evidence Review

The recommendations listed in this guideline are, whenever possible, evidence based. An initial extensive evidence review, which included literature derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline, was conducted from July to October 2015. Key search words included but were not limited to the following: athletes, autonomic neuropathy, bradycardia, carotid sinus hypersensitivity, carotid sinus syndrome, children, death, dehydration, diagnosis, driving, electrocardiogram, electrophysiological study, epidemiology, falls, implantable loop recorder, mortality, older populations, orthostatic hypotension, pediatrics, psychogenic pseudosyncope, recurrent syncope, risk stratification, supraventricular tachycardia, syncope unit, syncope, tilt-table test, vasovagal syncope, and ventricular arrhythmia. Additional relevant studies published through October 2016, during the guideline writing process, were also considered by the writing committee, and added to the evidence tables when appropriate. The finalized evidence tables, included in the Online Data Supplement, summarize the evidence used by the writing committee to formulate recommendations. Lastly, the writing committee reviewed documents related to syncope previously published by the ACC and AHA and other organizations and societies. References selected and published in this document are representative and not all inclusive.

An independent ERC was commissioned to perform a systematic review of clinical questions, the results of which were considered by the writing committee for incorporation into this guideline. The systematic review report “Pacing as a Treatment for Reflex-Mediated (Vasovagal, Situational, or Carotid Sinus Hypersensitivity) Syncope” is published in conjunction with this guideline.

1.2. Organization of the Writing Committee

The writing committee was composed of clinicians with expertise in caring for patients with syncope, including cardiologists, electrophysiologists, an emergency physician, and a pediatric cardiologist. The writing committee included representatives from the ACC, AHA, Heart Rhythm Society (HRS), American Academy of Neurology, American College of Emergency Physicians, and Society for Academic Emergency Medicine.

1.3. Document Review and Approval

This document was reviewed by 2 official reviewers each nominated by the ACC, AHA, and HRS; 1 reviewer each from the American Academy of Neurology, American College of Emergency Physicians and Society for Academic Emergency Medicine, and Pediatric and Congenital Electrophysiology Society; a lay/patient representative; and 25 individual content reviewers. Reviewers’ RWI information was distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC, AHA, and HRS and endorsed by the American College of Emergency Physicians, Society for Academic Emergency Medicine, and the Pediatric and Congenital Electrophysiology Society.

1.4. Scope of the Guideline

The purpose of this ACC/AHA/HRS guideline is to provide contemporary, accessible, and succinct guidance on the management of adult and pediatric patients with suspected syncope. This guideline is intended to be a practical document for cardiologists, arrhythmia specialists, neurologists, emergency physicians, general internists, geriatric specialists, sports medicine specialists, and other healthcare professionals involved in the care of this very large and heterogeneous population. It is not a review of
Table 1. ACC/AHA Recommendation System: Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care* (Updated August 2015)

<table>
<thead>
<tr>
<th>CLASS (STRENGTH) OF RECOMMENDATION</th>
<th>LEVEL (QUALITY) OF EVIDENCE‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLASS I (STRONG)</td>
<td>Benefit &gt;&gt; Risk</td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td></td>
</tr>
<tr>
<td>Is recommended</td>
<td>High-quality evidence‡ from more than 1 RCT</td>
</tr>
<tr>
<td>Is indicated/useful/effective/beneficial</td>
<td>Meta-analyses of high-quality RCTs</td>
</tr>
<tr>
<td>Should be performed/administered/other</td>
<td>One or more RCTs corroborated by high-quality registry studies</td>
</tr>
</tbody>
</table>

| CLASS IIa (MODERATE)                | Benefit >> Risk               |
| Suggested phrases for writing recommendations: |
| Is reasonable                        | Moderate-quality evidence‡ from 1 or more RCTs |
| Can be useful/effective/beneficial   | Meta-analyses of moderate-quality RCTs |
| Comparative Effectiveness Phrases‡:  |                                |
| Treatment/strategy A is recommended/indicated in preference to treatment B |                                |
| Treatment A should be chosen over treatment B |

| CLASS IIb (WEAK)                    | Benefit > Risk                |
| Suggested phrases for writing recommendations: |
| May/might be reasonable              |                                |
| May/might be considered               |                                |
| Usefulness/effectiveness is unknown/unclear/uncertain or not well established |                                |

| CLASS III: No Benefit (MODERATE) (Generally LOE A or B use only) | Benefit = Risk                  |
| Suggested phrases for writing recommendations: |
| Is not recommended                     |                                |
| Is not indicated/useful/effective/beneficial |                                |
| Should not be performed/administered/other |                                |

| CLASS III: Harm (STRONG)            | Risk > Benefit                 |
| Suggested phrases for writing recommendations: |
| Potentially harmful                   |                                |
| Causes harm                           |                                |
| Associated with excess morbidity/mortality |                                |
| Should not be performed/administered/other |                                |

COR and LOE are determined independently (any COR may be paired with any LOE). A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).
† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.
‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.
Shen et al

committee agreed to make Class IIa recommendations because of the paucity of outcome data. The definition of older populations has been evolving. Age >75 years is used to define older populations or older adults in this document, unless otherwise specified. If a study has defined older adults by a different age cutoff, the relevant age is noted in those specific cases. Finally, the guideline addresses the management of syncope with the patient as a focus, rather than larger aspects of health services, such as syncope management units. The goals of the present guideline are:

- To define syncope as a symptom, with different causes, in different populations and circumstances.
- To provide guidance and recommendations on the evaluation and management of patients with suspected syncope in the context of different clinical settings, specific causes, or selected circumstances.
- To identify key areas in which knowledge is lacking, to foster future collaborative research opportunities and efforts.

In developing this guideline, the writing committee reviewed the evidence to support recommendations in the relevant ACC/AHA guidelines noted in Table 2 (in the full-text guideline) and affirms the ongoing validity of the related recommendations in the context of syncope, thus obviating the need to repeat existing guideline recommendations in the present guideline when applicable or when appropriate.

2. GENERAL PRINCIPLES

For the purpose of this guideline, definitions of syncope and relevant terms are provided in Table 2. See Table 3 for historical characteristics associated with, although not diagnostic, cardiac and noncardiac syncope; Table 4 for short- and long-term risk factors; Table 5 for the type of events, event rates, and study durations from investigations that estimate risk scores; Table 6 for examples of serious conditions associated with syncope which may require inpatient evaluation and “treatment”; Figure 1 for the algorithm on initial evaluation for syncope; and Figure 2 for patient disposition after initial evaluation for syncope. See Online Data Supplements 1 through 4 for data supporting Section 2.

2.1. Definitions: Terms and Classification

Table 2. Relevant Terms and Definitions*

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition/Comments and References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope</td>
<td>A symptom that presents with an abrupt, transient, complete loss of consciousness, associated with inability to maintain postural tone, with rapid and spontaneous recovery. The presumed mechanism is cerebral hypoperfusion.(^{11,12}) There should not be clinical features of other nonsyncope causes of loss of consciousness, such as seizure, antecedent head trauma, or apparent loss of consciousness (i.e., pseudosyncope).(^{11,12})</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>A cognitive state in which one lacks awareness of oneself and one's situation, with an inability to respond to stimuli.</td>
</tr>
<tr>
<td>Transient loss of consciousness</td>
<td>Self-limited loss of consciousness(^{11}) can be divided into syncope and nonsyncope conditions. Nonsyncope conditions include but are not limited to seizures, hypoglycemia, metabolic conditions, drug or alcohol intoxication, and concussion due to head trauma. The underlying mechanism of syncope is presumed to be cerebral hypoperfusion, whereas nonsyncope conditions are attributed to different mechanisms.</td>
</tr>
<tr>
<td>Presyncope (near-syncope)</td>
<td>The symptoms before syncope. These symptoms could include extreme lightheadedness; visual sensations, such as “tunnel vision” or “graying out”; and variable degrees of altered consciousness without complete loss of consciousness. Presyncope could progress to syncope, or it could abort without syncope.</td>
</tr>
<tr>
<td>Unexplained syncope (syncope of undetermined etiology)</td>
<td>Syncope for which a cause is undetermined after an initial evaluation that is deemed appropriate by the experienced healthcare provider. The initial evaluation includes but is not limited to a thorough history, physical examination, and ECG.</td>
</tr>
<tr>
<td>Orthostatic intolerance</td>
<td>A syndrome consisting of a constellation of symptoms that include frequent, recurrent, or persistent lightheadedness, palpitations, tachycardia, generalized weakness, blurred vision, exercise intolerance, and fatigue upon standing. These symptoms can occur with or without orthostatic tachycardia, OH, or syncope.(^{11}) Individuals with orthostatic intolerance have (2) of these symptoms associated with reduced ability to maintain upright posture.</td>
</tr>
<tr>
<td>Orthostatic tachycardia</td>
<td>A sustained increase in heart rate of (\geq20) bpm within (10) min of moving from a recumbent to a quiet (nonexertional) standing position (or (\geq40) bpm in individuals 12–19 y of age).(^{11,13})</td>
</tr>
<tr>
<td>Orthostatic hypotension (OH)</td>
<td>A drop in systolic BP of (\geq20) mm Hg or diastolic BP of (\geq10) mm Hg with assumption of an upright posture.(^{13})</td>
</tr>
<tr>
<td>Initial (immediate) OH</td>
<td>A transient BP decrease within (15) s after standing, with presyncope or syncope.(^{11,14})</td>
</tr>
<tr>
<td>Classic OH</td>
<td>A sustained reduction of systolic BP of (\geq20) mm Hg or diastolic BP of (\geq10) mm Hg within (3) min of assuming upright posture.(^{13})</td>
</tr>
<tr>
<td>Delayed OH</td>
<td>A sustained reduction of systolic BP of (\geq20) mm Hg (or (30) mm Hg in patients with supine hypertension) or diastolic BP of (\geq10) mm Hg that takes &gt;3 min of upright posture to develop. The fall in BP is usually gradual until reaching the threshold.(^{13})</td>
</tr>
<tr>
<td>Neurogenic OH</td>
<td>A subtype of OH that is due to dysfunction of the autonomic nervous system and not solely due to environmental triggers (such as dehydration or drugs).(^{11,14}) Neurogenic OH is due to lesions involving the central or peripheral autonomic nerves.</td>
</tr>
</tbody>
</table>

(Continued)
Table 2. Continued

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition/Comments and References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac (cardiovascular) syncope</td>
<td>Syncope caused by bradycardia, tachycardia, or hypotension due to low cardiac index, blood flow obstruction, vasodilatation, or acute vascular dissection.11,18</td>
</tr>
<tr>
<td>Noncardiac syncope</td>
<td>Syncope due to noncardiac causes, which includes reflex syncope, OH, volume depletion, dehydration, and blood loss.17</td>
</tr>
<tr>
<td>Reflex (neurally mediated) syncope</td>
<td>Syncope due to a reflex that causes vasodilatation, bradycardia, or both.11–13</td>
</tr>
<tr>
<td>Vasovagal syncope (VVS)</td>
<td>The most common form of reflex syncope mediated by the vasovagal reflex. VVS: 1) may occur with upright posture (standing or seated or with exposure to emotional stress, pain, or medical settings); 2) typically is characterized by diaphoresis, warmth, nausea, and pallor; 3) is associated with vasodepressor hypotension and/or inappropriate bradycardia; and 4) is often followed by fatigue. Typical features may be absent in older patients.12 VVS is often preceded by identifiable triggers and/or by a characteristic prodrome. The diagnosis is made primarily on the basis of a thorough history, physical examination, and eyewitness observation, if available.</td>
</tr>
<tr>
<td>Carotid sinus syndrome</td>
<td>Reflex syncope associated with carotid sinus hypersensitivity.11 Carotid sinus hypersensitivity is present when a pause ≥ 3 s and/or a decrease of systolic pressure ≥ 20 mm Hg occurs upon stimulation of the carotid sinus. It occurs more frequently in older patients. Carotid sinus hypersensitivity can be associated with varying degrees of symptoms. Carotid sinus syndrome is defined when syncope occurs in the presence of carotid sinus hypersensitivity.</td>
</tr>
<tr>
<td>Situational syncope</td>
<td>Reflex syncope associated with a specific action, such as coughing, laughing, swallowing, micturition, or defecation. These syncope events are closely associated with specific physical functions.</td>
</tr>
<tr>
<td>Postural (orthostatic) tachycardia syndrome (POTS)</td>
<td>A clinical syndrome usually characterized by all of the following: 1) frequent symptoms that occur with standing (e.g., lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue); and 2) an increase in heart rate of ≥ 40 bpm in those 12–19 years of age; and 3) the absence of OH (&gt;20 mm Hg reduction in systolic BP). Symptoms associated with POTS include those that occur with standing (e.g., lightheadedness, palpitations); those not associated with particular postures (e.g., bloating, nausea, diarrhea, abdominal pain); and those that are systemic (e.g., fatigue, sleep disturbance, migraine headaches).10 The standing heart rate is often ≥ 120 bpm.12,22–24</td>
</tr>
<tr>
<td>Psychogenic pseudosyncope</td>
<td>A syndrome of apparent but not true loss of consciousness that may occur in the absence of identifiable cardiac, reflex, neurological, or metabolic causes.11</td>
</tr>
</tbody>
</table>

*These definitions are derived from previously published definitions from scientific investigations, guidelines, expert consensus statements, and Webster dictionary after obtaining consensus from the WC.

BP indicates blood pressure; ECG, electrocardiogram; OH, orthostatic hypotension; POTS, postural tachycardia syndrome; and VVS, vasovagal syncope.

2.2. Epidemiology and Demographics

Studies of syncope report prevalence rates as high as 41%, with recurrent syncope occurring in 13.5%.25 In a cross section of 1925 randomly selected residents of Olmsted County, Minnesota, with a median age of 62 years (all age > 45 years), 364 reported an episode of syncope in their lifetime; the estimated prevalence of syncope was 19%. Females reported a higher prevalence of syncope (22% versus 15%, P < 0.001).26 The incidence follows a trimodal distribution in both sexes, with the first episode common around 20, 60, or 80 years of age and the third peak occurring 5 to 7 years earlier in males.27 Predictors of recurrent syncope in older adults are aortic stenosis, impaired renal function, atrioventricular or left bundle-branch block, male sex, chronic obstructive pulmonary disorder, heart failure, atrial fibrillation, advancing age, and orthostatic medications;21 with a sharp increase in incidence after 70 years of age.17 Reflex syncope was most common (21%), followed by cardiac syncope (9%) and OH (9%), with the cause of syncope unknown in 37%.17 In patients with New York Heart Association class III–IV heart failure, syncope is present in 12% to 14% of patients.28,29

In older adults, there is a greater risk of hospitalization and death related to syncope. The National Hospital Ambulatory Medical Care Survey reported 6.7 million episodes of syncope in the emergency department, or 0.77% of all ED patients. Among patients > 80 years of age, 58% were admitted to hospital.30 The prevalence of syncope as a presenting symptom to the ED ranged from 0.8% to 2.4% in multiple studies in both academic and community settings.31–37

2.3. Initial Evaluation of Patients With Syncope: Recommendations

2.3.1. History and Physical Examination: Recommendation

<table>
<thead>
<tr>
<th>Recommendation for History and Physical Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>COR</td>
</tr>
<tr>
<td>I</td>
</tr>
</tbody>
</table>

2.3.2. Electrocardiography: Recommendation

<table>
<thead>
<tr>
<th>Recommendation for Electrocardiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>COR</td>
</tr>
<tr>
<td>I</td>
</tr>
</tbody>
</table>
2.3.3. Risk Assessment: Recommendations

Table 3. Historical Characteristics Associated with Increased Probability of Cardiac and Noncardiac Causes of Syncope40,47–55

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>Evaluation of the cause and assessment for the short- and long-term morbidity and mortality risk of syncope are recommended (Table 4)48,57–59</td>
</tr>
<tr>
<td>IIIb</td>
<td>B-NR</td>
<td>Use of risk stratification scores may be reasonable in the management of patients with syncope.47,48,50,51,55,59–62</td>
</tr>
</tbody>
</table>

2.3.4. Disposition After Initial Evaluation: Recommendations

Table 3. Historical Characteristics Associated with Increased Probability of Cardiac and Noncardiac Causes of Syncope40,47–55

<table>
<thead>
<tr>
<th>More Often Associated with Cardiac Causes of Syncope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age (&gt;60 y)</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Presence of known ischemic heart disease, structural heart disease, previous arrhythmias, or reduced ventricular function</td>
</tr>
<tr>
<td>Brief prodrome, such as palpitations, or sudden loss of consciousness without prodrome</td>
</tr>
<tr>
<td>Syncope during exertion</td>
</tr>
<tr>
<td>Syncope in the supine position</td>
</tr>
<tr>
<td>Low number of syncope episodes (1 or 2)</td>
</tr>
<tr>
<td>Abnormal cardiac examination</td>
</tr>
<tr>
<td>Family history of inheritable conditions or premature SCD (&lt;50 y of age)</td>
</tr>
<tr>
<td>Presence of known congenital heart disease</td>
</tr>
<tr>
<td>More Often Associated with Noncardiac Causes of Syncope</td>
</tr>
<tr>
<td>Younger age</td>
</tr>
<tr>
<td>No known cardiac disease</td>
</tr>
<tr>
<td>Syncope only in the standing position</td>
</tr>
<tr>
<td>Positional change from supine or sitting to standing</td>
</tr>
<tr>
<td>Presence of prodrome: nausea, vomiting, feeling warmth</td>
</tr>
<tr>
<td>Presence of specific triggers: dehydration, pain, distressful stimulus, medical environment</td>
</tr>
<tr>
<td>Situational triggers: cough, laugh, micturition, defecation, deglutition</td>
</tr>
<tr>
<td>Frequent recurrence and prolonged history of syncope with similar characteristics</td>
</tr>
</tbody>
</table>

SCD indicates sudden cardiac death.

Figure 1. Syncope Initial Evaluation.

*See relevant terms and definitions in Table 2. Colors correspond to Class of Recommendation in Table 1. This figure shows the general principles for initial evaluation of all patients after an episode of syncope. ECG indicates electrocardiogram.
Table 4. Short- and Long-Term Risk Factors

<table>
<thead>
<tr>
<th>Short-Term Risk Factors (≤30 d)</th>
<th>Long-Term Risk Factors (&gt;30 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History: Outpatient Clinic or ED Evaluation</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>Male sex</td>
</tr>
<tr>
<td>Age (&gt;60 y)</td>
<td>Age</td>
</tr>
<tr>
<td>No prodrome</td>
<td>Absence of nausea/vomiting preceding syncope event</td>
</tr>
<tr>
<td>Palpitations preceding loss of consciousness</td>
<td>VA</td>
</tr>
<tr>
<td>Exertional syncope</td>
<td>Cancer</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>Structural heart disease</td>
</tr>
<tr>
<td>HF</td>
<td>HF</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>Family history of SCD</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Trauma</td>
<td>High CHADS-2 score</td>
</tr>
<tr>
<td>Physical Examination or Laboratory Investigation</td>
<td></td>
</tr>
<tr>
<td>Evidence of bleeding</td>
<td>Abnormal ECG</td>
</tr>
<tr>
<td>Persistent abnormal vital signs</td>
<td>Lower GFR</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td></td>
</tr>
<tr>
<td>Positive troponin</td>
<td></td>
</tr>
</tbody>
</table>

*Definitions for clinical endpoints or serious outcomes vary by study. The specific endpoints for the individual studies in this table are defined in Data Supplements 3 and 4 and summarized in Table 5 for selected studies. This table includes individual risk predictors from history, physical examination, and laboratory studies associated with adverse outcomes from selected studies. CHADS-2 indicates congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke or transient ischemic attack; ECG, electrocardiogram; ED, emergency department; GFR, glomerular filtration rate; HF, heart failure; SCD, sudden cardiac death; and VA, ventricular arrhythmias.

3. ADDITIONAL EVALUATION AND DIAGNOSIS

See Figure 3 for additional evaluation and diagnosis for syncope and Table 7 for a summary of types of ambulatory cardiac rhythm monitoring devices. See Online Data Supplements 7 through 16 for data supporting Section 3.


| Recommendations for Blood Testing |
|-------------------------------|-------------------------------|
| **COR** | **LOE** | **Recommendations** |
| IIa | B-NR | Targeted blood tests are reasonable in the evaluation of selected patients with syncope identified on the basis of clinical assessment from history, physical examination, and ECG.83 |
| IIb | C-LD | Usefulness of brain natriuretic peptide and high-sensitivity troponin measurement is uncertain in patients for whom a cardiac cause of syncope is suspected.83,46 |
| III: No Benefit | B-NR | Routine and comprehensive laboratory testing is not useful in the evaluation of patients with syncope.87,46 |

3.2. Cardiovascular Testing: Recommendations

3.2.1. Cardiac Imaging: Recommendations

| Recommendations for Cardiac Imaging |
|-------------------------------|-------------------------------|
| **COR** | **LOE** | **Recommendations** |
| IIa | B-NR | Transthoracic echocardiography can be useful in selected patients presenting with syncope if structural heart disease is suspected.92,93,94 |
| IIb | B-NR | Computed tomography or magnetic resonance imaging may be useful in selected patients presenting with syncope of suspected cardiac etiology.95 |
| III: No Benefit | B-NR | Routine cardiac imaging is not useful in the evaluation of patients with syncope unless cardiac etiology is suspected on the basis of an initial evaluation, including history, physical examination, or ECG.95,96 |

3.2.2. Stress Testing: Recommendation

| Recommendation for Stress Testing |
|-------------------------------|-------------------------------|
| **COR** | **LOE** | **Recommendation** |
| IIa | C-LD | Exercise stress testing can be useful to establish the cause of syncope in selected patients who experience syncope or presyncope during exertion.93,94 |

3.2.3. Cardiac Monitoring: Recommendations

| Recommendations for Cardiac Monitoring |
|-------------------------------|-------------------------------|
| **COR** | **LOE** | **Recommendations** |
| I | C-EO | The choice of a specific cardiac monitor should be determined on the basis of the frequency and nature of syncope events. |
| IIa | B-NR | To evaluate selected ambulatory patients with syncope of suspected arrhythmic etiology, the following external cardiac monitoring approaches can be useful: 1. Holter monitor95–98 2. Transtelephonic monitor96,100,101 3. External loop recorder96,100–102 4. Patch recorder106,107 5. Mobile cardiac outpatient telemetry.106,107 |
| IIa | B-R | To evaluate selected ambulatory patients with syncope of suspected arrhythmic etiology, an implantable cardiac monitor can be useful.95,108,109,110,111 |

3.2.4. In-Hospital Telemetry: Recommendation

| Recommendation for In-Hospital Telemetry |
|-------------------------------|-------------------------------|
| **COR** | **LOE** | **Recommendation** |
| I | B-NR | Continuous ECG monitoring is useful for hospitalized patients admitted for syncope evaluation with suspected cardiac etiology.95,96,97,108,109,110,111 |
Table 5. Examples of Syncope Risk Scores

<table>
<thead>
<tr>
<th>Study/Reference</th>
<th>Year</th>
<th>Sample N</th>
<th>Events N (%)</th>
<th>Outcome Definition</th>
<th>ED Events*</th>
<th>Predictors</th>
<th>NPV (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin65</td>
<td>1997</td>
<td>252</td>
<td>104 (41%)</td>
<td>1-y death/arrhythmia</td>
<td>Yes</td>
<td>Abnormal ECG; &gt;45 y of age; VA; HF</td>
<td>93</td>
</tr>
<tr>
<td>Sarasin54</td>
<td>2003</td>
<td>175</td>
<td>30 (17%)</td>
<td>Inpatient arrhythmia</td>
<td>Yes</td>
<td>Abnormal ECG; &gt;65 y of age; HF</td>
<td>98</td>
</tr>
<tr>
<td>OESIL47</td>
<td>2003</td>
<td>270</td>
<td>31 (11%)</td>
<td>1-y death</td>
<td>N/A</td>
<td>Abnormal ECG; &gt;65 y of age; no prodiome; cardiac history</td>
<td>100</td>
</tr>
<tr>
<td>SFSR52</td>
<td>2004</td>
<td>684</td>
<td>79 (12%)</td>
<td>7-d serious events§</td>
<td>Yes</td>
<td>Abnormal ECG; dyspnea; hematocrit; systolic BP &lt;90 mm Hg; HF</td>
<td>99</td>
</tr>
<tr>
<td>Boston Syncope Rule50</td>
<td>2007</td>
<td>293</td>
<td>68 (23%)</td>
<td>30-d serious events‖</td>
<td>Yes</td>
<td>Symptoms of acute coronary syndrome; worrisome cardiac history; family history of SCD; VHD; signs of conduction disease; volume depletion; persistent abnormal vital signs; central nervous event</td>
<td>100</td>
</tr>
<tr>
<td>Del Rosso55</td>
<td>2008</td>
<td>260</td>
<td>44 (17%)</td>
<td>Cardiac etiology</td>
<td>N/A</td>
<td>Abnormal ECG/cardiac history; palpitations; exertional; supine; precipitant (a low-risk factor); autonomic prodiome (low-risk factors)</td>
<td>99</td>
</tr>
<tr>
<td>STePS48</td>
<td>2008</td>
<td>676</td>
<td>41 (6%)</td>
<td>10-d serious events¶</td>
<td>Yes</td>
<td>Abnormal ECG; trauma; no prodiome; male sex</td>
<td>–</td>
</tr>
<tr>
<td>Syncope Risk Score51</td>
<td>2009</td>
<td>2584</td>
<td>173 (7%)</td>
<td>30-d serious events§</td>
<td>No</td>
<td>Abnormal ECG; &gt;90 y of age; male sex; positive troponin; history of arrhythmia; systolic BP &gt;160 mm Hg; near-sycope (a low-risk factor)</td>
<td>97</td>
</tr>
<tr>
<td>ROSE53</td>
<td>2010</td>
<td>550</td>
<td>40 (7%)</td>
<td>30-d serious events§</td>
<td>Yes</td>
<td>Abnormal ECG; B-natriuretic peptide; hemoglobin; O₂Sat; fecal occult blood</td>
<td>98</td>
</tr>
</tbody>
</table>

* Did the study include events diagnosed during the ED evaluation?
† NPV: negative predictive value for lowest-risk group for the specific events defined by the study.
‡ Abnormal ECG is defined variably in these studies. In the context of syncope evaluation, an abnormal ECG is any rhythm other than normal sinus rhythm, conduction delays (BBB, type-2 second-degree AVB or third-degree AVB), presence of Q waves, ST abnormalities, or prolonged QT interval.
§ Events: death, MI, arrhythmia, pulmonary embolism, stroke, hemorrhage, or readmission.
¶ Events: death, major therapeutic procedure, MI, arrhythmia, pulmonary embolism, stroke, sepsis, hemorrhage, or life-threatening sequelae of syncope.
‖ Events: death, major therapeutic procedure, or readmission.
# Events: death, arrhythmia, MI, new diagnosis of severe structural heart disease, pulmonary embolism, aortic dissection, stroke/TIA, cerebral hemorrhage, or significant anemia requiring blood transfusion.

3.2.5. Electrophysiological Study: Recommendations

| Recommendations for Electrophysiological Study (EPS) |
|-----------------|--------|----------------|
| COR  | LOE  | Recommendations |
| IIA   | B-NR  | EPS can be useful for evaluation of selected patients with syncope of suspected arrhythmic etiology97,127–134 |
| III: No Benefit | B-NR  | EPS is not recommended for syncope evaluation in patients with a normal ECG and normal cardiac structure and function, unless an arrhythmic etiology is suspected.134–136 |

3.2.6. Tilt-Table Testing: Recommendations

| Recommendations for Tilt-Table Testing |
|-----------------|--------|----------------|
| COR  | LOE  | Recommendations |
| IIA   | B-R   | If the diagnosis is unclear after initial evaluation, tilt-table testing can be useful for patients with suspected vasovagal syncope (VVS).137–142 |
| IIA   | B-NR  | Tilt-table testing can be useful for patients with syncope and suspected delayed OH when initial evaluation is not diagnostic.142–144 |

3.3. Neurological Testing: Recommendations

3.3.1. Autonomic Evaluation: Recommendation

| Recommendation for Autonomic Evaluation |
|-----------------|--------|----------------|
| COR  | LOE  | Recommendation |
| IIA   | C-LD  | Referral for autonomic evaluation can be useful to improve diagnostic and prognostic accuracy in selected patients with syncope and known or suspected neurodegenerative disease.134–135 |
3.3.2. Neurological and Imaging Diagnostics: Recommendations

<table>
<thead>
<tr>
<th>Recommendations for Neurological Diagnostics</th>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iia</td>
<td>C-LD</td>
<td></td>
<td>Simultaneous monitoring of an electroencephalogram and hemodynamic parameters during tilt-table testing can be useful to distinguish among syncope, pseudosyncope, and epilepsy.151,158–160</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>B-NR</td>
<td></td>
<td>Magnetic resonance imaging and computed tomography of the head are not recommended in the routine evaluation of patients with syncope in the absence of focal neurological findings or head injury that support further evaluation.161,162</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>B-NR</td>
<td></td>
<td>Carotid artery imaging is not recommended in the routine evaluation of patients with syncope in the absence of focal neurological findings that support further evaluation.92,161–164</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>B-NR</td>
<td></td>
<td>Routine recording of an electroencephalogram is not recommended in the evaluation of patients with syncope in the absence of specific neurological features suggestive of a seizure.18,92,163–167</td>
</tr>
</tbody>
</table>

4. MANAGEMENT OF CARDIOVASCULAR CONDITIONS

See Online Data Supplements 17 through 24 for data supporting Section 4.

4.1. Arrhythmic Conditions: Recommendations

4.1.1. Bradycardia: Recommendation

<table>
<thead>
<tr>
<th>Recommendation for Bradycardia</th>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-EO</td>
<td></td>
<td>In patients with syncope associated with bradycardia, GDMT is recommended.169</td>
</tr>
</tbody>
</table>

4.1.2. Supraventricular Tachycardia: Recommendations

<table>
<thead>
<tr>
<th>Recommendations for Supraventricular Tachycardia</th>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-EO</td>
<td></td>
<td>In patients with syncope and supraventricular tachycardia, GDMT is recommended.170</td>
</tr>
</tbody>
</table>

4.1.3. Ventricular Arrhythmia: Recommendation

<table>
<thead>
<tr>
<th>Recommendation for Ventricular Arrhythmia (VA)</th>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-EO</td>
<td></td>
<td>In patients with syncope and VA, GDMT is recommended.171</td>
</tr>
</tbody>
</table>

Table 6. Examples of Serious Medical Conditions That Might Warrant Consideration of Further Evaluation and Therapy in a Hospital Setting

<table>
<thead>
<tr>
<th>Cardiac Arrhythmic Conditions</th>
<th>Cardiac or Vascular Nonarrhythmic Conditions</th>
<th>Noncardiac Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained or symptomatic VT</td>
<td>Cardiac ischemia</td>
<td>Severe anemia/ gastrointestinal bleeding</td>
</tr>
<tr>
<td>Symptomatic conduction system disease or Mobitz II or third-degree heart block</td>
<td>Severe aortic stenosis</td>
<td>Major traumatic injury due to syncope</td>
</tr>
<tr>
<td>Symptomatic bradycardia or sinus pauses not related to neurally mediated syncope</td>
<td>Cardiac tamponade</td>
<td>Persistent vital sign abnormalities</td>
</tr>
<tr>
<td>Symptomatic SVT</td>
<td>Pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>Pacemaker/ICD malfunction</td>
<td>Aortic dissection</td>
<td></td>
</tr>
<tr>
<td>Inheritable cardiovascular conditions predisposing to arrhythmias</td>
<td>Acute HF</td>
<td></td>
</tr>
<tr>
<td>HCM</td>
<td>Moderate-to-severe LV dysfunction</td>
<td></td>
</tr>
</tbody>
</table>

HCM indicates hypertrophic cardiomyopathy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LV, left ventricular; SVT, supraventricular tachycardia; and VT, ventricular tachycardia.
4.2. Structural Conditions: Recommendations

4.2.1. Ischemic and Nonischemic Cardiomyopathy: Recommendation

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-EO</td>
<td>In patients with syncope associated with ischemic and nonischemic cardiomyopathy, GDMT is recommended.169,172</td>
</tr>
</tbody>
</table>

4.2.2. Valvular Heart Disease: Recommendation

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-EO</td>
<td>In patients with syncope associated with valvular heart disease, GDMT is recommended.175</td>
</tr>
</tbody>
</table>

4.2.3. Hypertrophic Cardiomyopathy: Recommendation

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-EO</td>
<td>In patients with syncope associated with HCM, GDMT is recommended.170</td>
</tr>
</tbody>
</table>

4.2.4. Arrhythmogenic Right Ventricular Cardiomyopathy: Recommendations

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>Implantable cardioverter-defibrillator (ICD) implantation is recommended in patients with ARVC who present with syncope and have a documented sustained VA.177-181</td>
</tr>
</tbody>
</table>

| Ia   | B-NR | ICD implantation is reasonable in patients with ARVC who present with syncope of suspected arrhythmic etiology.177,178,180-182 |

4.2.5. Cardiac Sarcoidosis: Recommendations

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>ICD implantation is recommended in patients with cardiac sarcoidosis presenting with syncope and documented spontaneous sustained VA.169,180-189</td>
</tr>
</tbody>
</table>

| I    | C-EO | In patients with cardiac sarcoidosis presenting with syncope and conduction abnormalities, GDMT is recommended.169,180-182 |
4.3. Inheritable Arrhythmic Conditions: Recommendations

4.3.1. Brugada Syndrome: Recommendations

**Recommendations for Brugada ECG Pattern and Syncope**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>ICD implantation is reasonable in patients with Brugada ECG pattern and syncope of suspected arrhythmic etiology.196–200</td>
</tr>
<tr>
<td>IIb</td>
<td>B-NR</td>
<td>Invasive EPS may be considered in patients with Brugada ECG pattern and syncope of suspected arrhythmic etiology.192,203,204</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>B-NR</td>
<td>ICD implantation is not recommended in patients with Brugada ECG pattern and reflex-mediated syncope in the absence of other risk factors.192,204</td>
</tr>
</tbody>
</table>

4.3.2. Short-QT Syndrome: Recommendation

**Recommendation for Short-QT Syndrome**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>C-EO</td>
<td>ICD implantation may be considered in patients with short-QT pattern and syncope of suspected arrhythmic etiology.</td>
</tr>
</tbody>
</table>

4.3.3. Long-QT Syndrome: Recommendations

**Recommendations for Long-QT Syndrome (LQTS)**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>Beta-blocker therapy, in the absence of contraindications, is indicated as a first-line therapy in patients with LQTS and suspected arrhythmic syncope.203-206</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>ICD implantation is reasonable in patients with LQTS and suspected arrhythmic syncope who are on beta-blocker therapy or are intolerant to beta-blocker therapy.206,210-214</td>
</tr>
<tr>
<td>IIa</td>
<td>C-LD</td>
<td>Left cardiac sympathetic denervation is reasonable in patients with LQTS and recurrent syncope of suspected arrhythmic mechanism who are intolerant to beta-blocker therapy or for whom beta-blocker therapy has failed.215-217</td>
</tr>
</tbody>
</table>

4.3.4. Catecholaminergic Polymorphic Ventricular Tachycardia: Recommendations

**Recommendations for Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-LD</td>
<td>Exercise restriction is recommended in patients with CPVT presenting with syncope of suspected arrhythmic etiology.178-218</td>
</tr>
<tr>
<td>I</td>
<td>C-LD</td>
<td>Beta blockers lacking intrinsic sympathomimetic activity are recommended in patients with CPVT and stress-induced syncope.197,219,220</td>
</tr>
<tr>
<td>IIa</td>
<td>C-LD</td>
<td>Flecainide is reasonable in patients with CPVT who continue to have syncope of suspected VA despite beta-blocker therapy.212,224</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>ICD therapy is reasonable in patients with CPVT and a history of exercise- or stress-induced syncope despite use of optimal medical therapy or left cardiac sympathetic denervation.177,220,226</td>
</tr>
<tr>
<td>IIb</td>
<td>C-LD</td>
<td>In patients with CPVT who continue to experience syncope or VA, verapamil with or without beta-blocker therapy may be considered.220,221</td>
</tr>
<tr>
<td>IIb</td>
<td>C-LD</td>
<td>Left cardiac sympathetic denervation may be reasonable in patients with CPVT, syncope, and symptomatic VA despite optimal medical therapy.231-233</td>
</tr>
</tbody>
</table>

4.3.5. Early Repolarization Pattern: Recommendations

**Recommendations for Early Repolarization Pattern**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>C-EO</td>
<td>ICD implantation may be considered in patients with early repolarization pattern and suspected arrhythmic syncope in the presence of a family history of early repolarization pattern with cardiac arrest.</td>
</tr>
<tr>
<td>III: Harm</td>
<td>B-NR</td>
<td>EPS should not be performed in patients with early repolarization pattern and history of syncope in the absence of other indications.215</td>
</tr>
</tbody>
</table>

5. REFLEX CONDITIONS: RECOMMENDATIONS

See Figure 4 for the algorithm for treatment of VVS. See Online Data Supplements 25 through 32 for data supporting Section 5.

5.1. Vasovagal Syncope: Recommendations

**Recommendations for Vasovagal Syncope (VVS)**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-EO</td>
<td>Patient education on the diagnosis and prognosis of VVS is recommended.</td>
</tr>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>Physical counter-pressure maneuvers can be useful in patients with VVS who have a sufficiently long prodromal period.210-217</td>
</tr>
</tbody>
</table>
5.2. Pacemakers in Vasovagal Syncope: Recommendation

See the ERC systematic review report “Pacing as a Treatment for Reflex-Mediated (Vasovagal, Situational, or Carotid Sinus Hypersensitivity) Syncope” for the complete systematic evidence review. Recommendations that are based on a body of evidence that includes the systematic review conducted by the ERC are denoted by the superscript SR (eg, LOE B-R-SR).

5.3. Carotid Sinus Syndrome: Recommendations

5.4. Other Reflex Conditions

Situational syncope is defined as syncope occurring only in certain distinct and usually memorable circumstances, including micturition syncope, defecation syncope, cough syncope, laugh syncope, and swallow syncope. Appropriate investigations should be undertaken to determine an underlying etiology, including causes that may be reversible. Evidence for treatment is limited mainly to case reports, small case series, and small observational studies. Treatment of most types of situational syncope relies heavily on avoidance or elimination of a triggering event. This may not always be possible, so increased fluid and salt consumption and reduction or removal of hypotensive drugs and diuretics are encouraged where appropriate and safe.

6. ORTHOSTATIC HYPOTENSION: RECOMMENDATIONS

See Figure 5 for the algorithm for treating orthostatic hypotension (OH). See Online Data Supplements 33 through 37 for data supporting Section 6.
7. ORTHOSTATIC INTOLERANCE

Orthostatic intolerance is a general term referring to frequent, recurrent, or persistent symptoms that develop upon standing (usually with a change in position from sitting or lying to an upright position) and are relieved by sitting or lying.8 Most commonly, the symptoms include lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue. These symptoms may be accompanied by hemodynamic disturbances, including blood pressure decrease, which may or may not meet criteria for OH, and heart rate increase, which may be inadequate or compensatory.8 The pathophysiology is quite varied. One condition of note is Postural Tachycardia Syndrome (POTS), in which upright posture results in an apparently inappropriate tachycardia, usually with heart rates >120 bpm.9

Although syncope occurs in patients with POTS, it is relatively infrequent, and there is little evidence that the syncope is due to POTS.9,10 Treatments that improve symptoms of POTS might decrease the occurrence of syncope.

---

**Table 7. Cardiac Rhythm Monitors**

<table>
<thead>
<tr>
<th>Types of Monitor</th>
<th>Device Description</th>
<th>Patient Selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holter monitor27–30</td>
<td>A portable, battery-operated device Continuous recording for 24–72 h; up to 2 wk with newer models</td>
<td>Symptoms frequent enough to be detected within a short period (24–72 h) of monitoring*</td>
</tr>
<tr>
<td>Patient activated, transtelephonic monitor (event monitor)94,103,101</td>
<td>A recording device that transmits patient-activated data (live or stored) via an analog phone line to a central remote monitoring station (eg, physician office)</td>
<td>Frequent, spontaneous symptoms likely to recur within 2–6 wk Limited use in patients with frank syncope associated with sudden incapacitation</td>
</tr>
<tr>
<td>External loop recorder (patient or auto triggered)96,100,101</td>
<td>A device that continuously records and stores rhythm data over weeks to months Patient activated, or auto triggered (eg, to record asymptomatic arrhythmias) to provide a recording of events antecedent to (3–14 min), during, and after (1–4 min) the triggered event Nearer models are equipped with a cellular phone, which transmits triggered data automatically over a wireless network to a remote monitoring system</td>
<td>Frequent, spontaneous symptoms related to syncope, likely to recur within 2–6 wk</td>
</tr>
<tr>
<td>External patch recorders102–105</td>
<td>Patch device that continuously records and stores rhythm data, with patient-trigger capability to allow for symptom-rhythm correlation No leads or wires, and adhesive to chest wall/sternum Various models record from 2–14 d Offers accurate means of assessing burden of atrial fibrillation Patient activated, or auto triggered (eg, to record asymptomatic arrhythmias) to provide a recording of events antecedent to, during, and after the triggered event</td>
<td>Can be considered as an alternative to external loop recorder Given that it is leadless, can be accurately self-applied, and is largely water resistant, it may be more comfortable and less cumbersome than an external loop recorder, potentially improving compliance Unlike Holter monitors and other external monitors, it offers only 1-lead recording</td>
</tr>
<tr>
<td>Mobile cardiac outpatient telemetry34,107</td>
<td>Device that records and transmits data (up to 30 d) from preprogrammed arrhythmias or patient activation to a communication hub at the patient's home Significant arrhythmias are detected; the monitor automatically transmits the patient's ECG data through a wireless network to the central monitoring station, which is attended by trained technicians 24 h/d This offers the potential for real-time, immediate feedback to a healthcare provider for evaluation</td>
<td>Spontaneous symptoms related to syncope and rhythm correlation In high-risk patients whose rhythm requires real-time monitoring</td>
</tr>
<tr>
<td>Implantable cardiac monitor108,113,121–124</td>
<td>Subcutaneously implanted device, with a battery life of 2–3 y Triggered by the patient (or often family member witness) to store the event Models allow for transtelephonic transmission, as well as automatic detection of significant arrhythmias with remote monitoring</td>
<td>Recurrent, infrequent, unexplained syncope (or suspected atypical reflex syncope) of suspected arrhythmic cause after a nondiagnostic initial workup, with or without structural heart disease</td>
</tr>
</tbody>
</table>

*Includes history, physical examination, and 12-lead ECG; may include nondiagnostic tilt-table test or electrophysiological study.
†Higher yield in patients who are able to record a diary to correlate with possible arrhythmia.

ECG indicates electrocardiogram.

---

**6.2. Dehydration and Drugs: Recommendations**

**Recommendations for Dehydration and Drugs**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-LD</td>
<td>Fluid resuscitation via oral or intravenous bolus is recommended in patients with syncope due to acute dehydration.27–30,327–331</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>Reducing or withdrawing medications that may cause hypotension can be beneficial in selected patients with syncope.102–108</td>
</tr>
<tr>
<td>IIa</td>
<td>C-LD</td>
<td>In selected patients with syncope due to dehydration, it is reasonable to encourage increased salt and fluid intake.24,304,325,330,340,341</td>
</tr>
</tbody>
</table>

---

**7. ORTHOSTATIC INTOLERANCE**
currence of syncope, although this is unknown.\textsuperscript{9–19} For further guidance on the management of POTS, we refer readers to the Heart Rhythm Society consensus statement.\textsuperscript{9}

8. PSEUDOSYNCOPE: RECOMMENDATIONS

See Online Data Supplements 38 and 39 for data supporting Section 8.

9. UNCOMMON CONDITIONS ASSOCIATED WITH SYNCOPE

Table 9 in the full-text guideline\textsuperscript{9} provides a list of less common conditions associated with syncope.

10. AGE, LIFESTYLE, AND SPECIAL POPULATIONS: RECOMMENDATIONS

See Online Data Supplements 40 to 42 for data supporting Section 10.
10.2. Adult Congenital Heart Disease: Recommendations

**Recommendations for Adult Congenital Heart Disease (ACHD)**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>C-EO</td>
<td>For evaluation of patients with ACHD and syncope, referral to a specialist with expertise in ACHD can be beneficial.</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>EPS is reasonable in patients with moderate or severe ACHD and unexplained syncope.</td>
</tr>
</tbody>
</table>

10.3. Geriatric Patients: Recommendations

**Recommendations for Geriatric Patients**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>C-EO</td>
<td>For the assessment and management of older adults with syncope, a comprehensive approach in collaboration with an expert in geriatric care can be beneficial.</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>It is reasonable to consider syncope as a cause of nonaccidental falls in older adults.</td>
</tr>
</tbody>
</table>

10.4. Driving and Syncope: Recommendation

The suggestions in Table 8 provide general guidance for private drivers. Most suggestions are based on expert opinion and supported by limited data. Commercial driving in the United States is governed by federal law and administered by the US Department of Transportation.20

**Recommendation for Driving and Syncope**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>C-EO</td>
<td>It can be beneficial for healthcare providers managing patients with syncope to know the driving laws and restrictions in their regions and discuss implications with the patient.</td>
</tr>
</tbody>
</table>

10.5. Athletes: Recommendations

**Recommendations for Athletes**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-EO</td>
<td>Cardiovascular assessment by a care provider experienced in treating athletes with syncope is recommended prior to resuming competitive sports.</td>
</tr>
<tr>
<td>IIa</td>
<td>C-LD</td>
<td>Assessment by a specialist with disease-specific expertise is reasonable for athletes with syncope and high-risk markers.</td>
</tr>
</tbody>
</table>

Figure 5. Orthostatic Hypotension. Colors correspond to Class of Recommendation in Table 1. BP indicates blood pressure; and OH, orthostatic hypotension.
11. QUALITY OF LIFE AND HEALTHCARE COST OF SYNCOPE

11.1. Impact of Syncope on Quality of Life

QoL is reduced with recurrent syncope, as demonstrated in studies that compared patients with and without syncope. QoL associated with recurrent syncope was equivalent to severe rheumatoid arthritis and chronic low-back pain in an adult population. Similarly, pediatric patients with recurrent syncope reported worse QoL than individuals with diabetes mellitus and equivalent QoL to individuals with asthma, end-stage renal disease, and structural heart disease.

11.2. Healthcare Costs Associated with Syncope

High healthcare costs are associated with the evaluation and management of syncope. These high costs have been estimated both in the United States and abroad.

12. EMERGING TECHNOLOGY, EVIDENCE GAPS, AND FUTURE DIRECTIONS

The writing committee created a list of key areas in which knowledge gaps are present in the evaluation and management of patients presenting with syncope. These knowledge gaps present opportunities for future research to ultimately improve clinical outcomes and effectiveness of healthcare delivery.

12.1. Definition, Classification, and Epidemiology

Reported incidence and prevalence of syncope vary significantly because of several confounders: variable definitions for syncope versus transient loss of consciousness, different populations, different clinical settings, and different study methodologies. Definition and classification of syncope provided in this document will set the standard for future research. Standardized national registries and large sample databases are needed to gather data on a continuous basis to understand the true incidence and prevalence of syncope, understand patient risk, inform driving policies, improve patient outcomes, and improve and streamline health service delivery.

Table 8. Avoidance of Private Driving After an Episode of Syncope: Suggested Symptom-Free Waiting Times for Various Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Symptom-Free Waiting Time*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td>1 month</td>
</tr>
<tr>
<td>VVS, no syncope in prior year</td>
<td>No restriction</td>
</tr>
<tr>
<td>VVS, 1–6 syncope per year</td>
<td>1 month</td>
</tr>
<tr>
<td>VVS, &gt;6 syncope per year</td>
<td>Not fit to drive until symptoms resolved</td>
</tr>
<tr>
<td>Situational syncope other than cough syncope</td>
<td>1 month</td>
</tr>
<tr>
<td>Cough syncope, untreated</td>
<td>Not fit to drive</td>
</tr>
<tr>
<td>Cough syncope, treated with cough suppression</td>
<td>1 month</td>
</tr>
<tr>
<td>Carotid sinus syncope, untreated</td>
<td>Not fit to drive</td>
</tr>
<tr>
<td>Carotid sinus syncope, treated with permanent pacemaker</td>
<td>1 week</td>
</tr>
<tr>
<td>Syncope due to nonreflex bradycardia, untreated</td>
<td>Not fit to drive</td>
</tr>
<tr>
<td>Syncope due to nonreflex bradycardia, treated with permanent pacemaker</td>
<td>1 week</td>
</tr>
<tr>
<td>Syncope due to SVT, untreated</td>
<td>Not fit to drive</td>
</tr>
<tr>
<td>Syncope due to SVT, pharmacologically suppressed</td>
<td>1 month</td>
</tr>
<tr>
<td>Syncope due to SVT, treated with ablation</td>
<td>1 week</td>
</tr>
<tr>
<td>Syncope with LVEF &lt;35% and a presumed arrhythmic etiology without an ICD</td>
<td>Not fit to drive</td>
</tr>
<tr>
<td>Syncope with LVEF &lt;35% and presumed arrhythmic etiology with an ICD</td>
<td>3 months</td>
</tr>
<tr>
<td>Syncope presumed due to VT/VF, structural heart disease and LVEF ≥35%, untreated</td>
<td>Not fit to drive</td>
</tr>
<tr>
<td>Syncope presumed due to VT/VF, structural heart disease and LVEF ≥35%, treated with an ICD and guideline-directed drug therapy</td>
<td>3 months</td>
</tr>
<tr>
<td>Syncope presumed due to VT with a genetic cause, untreated</td>
<td>Not fit to drive</td>
</tr>
<tr>
<td>Syncope presumed due to VT with a genetic cause, treated with an ICD or guideline-directed drug therapy</td>
<td>3 months</td>
</tr>
<tr>
<td>Syncope presumed due to a nonstructural heart disease VT, such as RVOT or LVOT, untreated</td>
<td>Not fit to drive</td>
</tr>
<tr>
<td>Syncope presumed due to a nonstructural heart disease VT, such as RVOT or LVOT, treated successfully with ablation or suppressed pharmacologically</td>
<td>3 months</td>
</tr>
<tr>
<td>Syncope of undetermined etiology</td>
<td>1 month</td>
</tr>
</tbody>
</table>

*It may be prudent to wait and observe for this time without a syncope spell before resuming driving.

ICD indicates implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; OH, orthostatic hypotension; RVOT, right ventricular outflow tract; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; and VVS, vasovagal syncope.
12.2. Risk Stratification and Clinical Outcomes

- Studies are needed to determine whether syncope is an independent predictor of nonfatal or fatal outcomes in selected patient populations.
- Studies are needed to develop risk scores to be prospectively validated in a given clinical setting with predefined endpoints from short- and long-term follow-up.
- Prospective and well-designed studies are needed to define relevant clinical outcomes with regard to recurrent syncope, nonfatal outcomes such as injury, and fatal outcomes. Future studies should incorporate quality of life, work loss, and functional capacity as additional clinical endpoints.
- Prospective studies are needed to differentiate cardiac and noncardiac clinical outcomes in different clinical settings and with different follow-up durations.
- Among patients without identifiable causes of syncope, studies are needed to determine short- and long-term outcomes to guide the overall management of these patients.

12.3. Evaluation and Diagnosis

- Studies are needed to better understand the interaction and relationships among the presenting symptom of syncope, the cause of syncope, the underlying disease condition, and their effect on clinical outcomes.
- Investigations are needed to understand the key components of clinical characteristics during the initial evaluation and to develop standardization tools to guide the evaluation by healthcare team.
- RCTs are needed to develop structured protocols to evaluate patients with syncope who are at intermediate risk without an immediate presumptive diagnosis. In addition to the endpoints of diagnostic yield and healthcare utilization, relevant clinical endpoints of nonfatal and fatal outcomes and recurrence of syncope are to be included.
- RCTs are needed to determine the features of syncope-specialized facilities that are necessary to achieve beneficial outcomes for patient care and to improve efficiency and effectiveness of healthcare delivery.
- As technology advances, studies are needed to determine the value of new technology in the evaluation and management of patients with syncope.

12.4. Management of Specific Conditions

- Although potential causes of syncope are multiple, a treatment decision is usually fairly straightforward for patients with cardiac causes of syncope or orthostatic causes. VVS is the most common cause of syncope in the general population. Treatment remains challenging in patients who have recurrences despite conservative therapy. Studies are needed to differentiate “arrhythmic syncope” versus “nonarrhythmic syncope” versus “aborted SCD” in patients with inheritable arrhythmic conditions.
- Prospectively designed multicenter or national registries are needed to gather clinical information from patients with reflex syncope to better our understanding on other associated conditions, plausible mechanisms, effectiveness of therapeutic interventions, and natural history of these uncommon conditions.
- RCTs are needed to continue the identification of effective treatment approaches to patients with recurrent reflex syncope.

12.5. Special Populations

- Questions and research about risk stratification, evaluation, and management outlined above for the adult population are needed in the pediatric population, geriatric population, and athletes.
- Prospective national registries and big databases are needed to determine risk associated with driving among different populations with syncope.
- Prospective and randomized studies are needed to assess the usefulness of specialized syncope units in different clinical settings.

ACC/AHA TASK FORCE MEMBERS

Glenn N. Levine, MD, FACC, FAHA, Chair; Patrick T. O’Gara, MD, MACC, FAHA, Chair-Elect; Jonathan L. Halperin, MD, FACC, FAHA, Immediate Past Chair*; Sana M. Al-Khatib, MD, MHS, FACC, FAHA; Kim K. Birkner, MS, PharmD, AACC; Birgemi Bozkurt, MD, PhD, FACC, FAHA; Ralph G. Brindis, MD, MPH, MACC*; Joaquin E. Cigarroa, MD, FACC; Lesley H. Curr, PhD, FAHA; Lee A. Fleisher, MD, FACC, FAHA; Federico Gentile, MD, FACC; Samuel Gidding, MD, FAHA; Mark A. Hlatky, MD, FACC; John Ikonomidis, MD, PhD, FAHA; José Joglar, MD, FACC, FAHA; Susan J. Pressler, PhD, RN, FAHA; Duminda N. Wijeysundera, MD, PhD

PRESIDENTS AND STAFF

American College of Cardiology

Richard A. Chazal, MD, FACC, President
Shalom Jakobovitz, Chief Executive Officer
William J. Oetgen, MD, MBA, FACC, Executive Vice President
Science, Education, Quality, and Publishing

*Former Task Force member; current member during the writing effort.


121. Palmsiano P, Accogli M, Zaccaria M, et al. Predictive factors for pace-maker implantation in patients receiving an implantable loop recorder for syncope remained unexplained after an extensive cardiac and neurologi-
123. Krahn AD, Klein GJ, Fitzpatrick A, et al. Predicting the outcome of pa-
124. Lombardi F, Calosso E, Mascioli G, et al. Utility of implantable loop re-
126. Lipski DS, Dannehl KN, Silverman ME. Value of radiotelemetry in a com-
128. Lacroix D, Dubuc M, Kus T, et al. Evaluation of arrhythmic causes of syncope: correlation between Holter monitoring, electrophysi-
129. Moazzen F, Peters T, Simonson J, et al. Syncope of unknown origin: clinical, noninvasive, and electrophysiologic determinants of arrhythmia induc-
132. Reiffel JA, Waring P, Bower R, et al. Electrophysiologic testing in patients with recurrent syncope: are results predicted by prior ambulatory moni-
134. Gulamhusein S, Naccarelli GV, Ko PT, et al. Value and limitations of clini-
135. Gaitozulis KA, Karystinos G, Gialerinos T, et al. Correlation of nonin-
136. Gatzoulis KA, Karystinos G, Gialerinos T, et al. Correlation of nonin-
137. Kenny RA, Ingram A, Baylis J, et al. Head-up tilt: a useful test for inves-
143. Morillo CA, Letch JW, Yee R, et al. A placebo-controlled trial of intrave-
145. Kim DH, Zeldenrust SR, Low PA, et al. Quantitative sensation and auton-
146. Krahn AD, Klein GJ, Fitzpatrick A, et al. The incidence of malig-
149. Zaidi A, Crampton S, Clough P, et al. Head-up tilting is a useful provoca-
151. Tannenmaa RT, van Niekerk J, Rejntjes RH, et al. The sensitivity of tilt-
155. Sheldon RS, Koshman ML, Murphy WF. Electroencephalographic find-
158. Schafani JJ, My J, Zacher LL, et al. Intensive education on evidence-
160. Kang GH, Oh JH, Kim JS, et al. Diagnostic patterns in the evaluation of patients presenting with syncope at the emergency or outpatient depart-
165. Deleted in press.
166. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS guide-
168. August 1, 2017 e47

Downloaded from http://circ.ahajournals.org/ by guest on September 15, 2017


Shen et al


Shen et al


Circulation. 2017;136:e25–e59. DOI: 10.1161/CIR.0000000000000498

Downloaded from http://circ.ahajournals.org/ by guest on September 15, 2017

e52 August 1, 2017

### Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope (March 2015)

<table>
<thead>
<tr>
<th>Committee Member</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
<th>Voting Recusals by Section*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Win-Kuang Shen, Chair</td>
<td>Mayo Clinic Arizona—Professor of Medicine; Mayo Clinic College of Medicine—Chair, Department of Cardiovascular Diseases</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Robert S. Sheldon, Vice Chair</td>
<td>University of Calgary, Department of Medicine—Professor</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>David G. Benditt</td>
<td>University of Minnesota Medical School, Cardiovascular Division—Professor of Medicine</td>
<td>• Medtronic†</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>3.2, 3.2.3, 3.2.5, 4.1.1–4.1.3, 4.2.1–4.2.5, 4.3.1–4.3.5, 5.1–5.3, 10.1, 10.2, 10.3, 10.5, 12</td>
</tr>
<tr>
<td>Mitchell I. Cohen</td>
<td>University of Arizona School of Medicine-Phoenix—Clinical Professor of Child Health; Phoenix Children's Heart Center—Co-Director; Phoenix Children's Hospital, Pediatric Cardiology—Chief</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Daniel E. Forman</td>
<td>University of Pittsburgh—Professor of Medicine; University of Pittsburgh Medical Center—Chair, Geriatric Cardiology Section; VA Pittsburg Healthcare Systems—Director, Cardiac Rehabilitation</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Roy Freeman‡</td>
<td>Harvard Medical School—Professor of Neurology; Beth Israel Deaconess Medical Center, Center for Autonomic and Peripheral Nerve Disorders—Director</td>
<td>• Lundbeck†</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>4.3.1–4.3.5, 5.1, 6.1, 10.1, 10.3, 10.5, 12</td>
</tr>
<tr>
<td>Zachary D. Goldberger</td>
<td>University of Washington School of Medicine, Harborview Medical Center Division of Cardiology—Assistant Professor of Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Blair P. Grubb</td>
<td>University of Toledo Medical Center, Medicine and Pediatrics—Professor</td>
<td>• Biotronik</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>3.2, 3.2.3, 3.2.5, 4.1.1–4.1.3, 4.2.1–4.2.5, 4.3.1–4.3.5, 5.1–5.3, 10.1, 10.2, 10.3, 10.5, 12</td>
</tr>
<tr>
<td>Mohamed H. Hamdan</td>
<td>University of Wisconsin School of Medicine, Cardiovascular Medicine—Professor and Chief of Cardiovascular Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>2.3.3, 2.3.4, 12</td>
</tr>
</tbody>
</table>

(Continued)
This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of \( \geq 5\% \) of the voting stock or share of the business entity, or ownership of \( \geq \$5000 \) of the fair market value of the business entity; or funds received by the person from the business entity exceed 5% of the person’s gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

According to the ACC/AHA, a person has a relevant relationship IF: a) the relationship or interest relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the document; or b) the company/entity (with whom the relationship exists) makes a drug, drug class, or device addressed in the document, or makes a competing drug or device addressed in the document; or c) the person or a member of the person’s household, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the document.

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply (section numbers correspond to the full-text guideline).

†Significant relationship.

‡Dr. Roy Freeman, the official representative of the American Academy of Neurology, resigned from the writing committee in November 2016, before the final balloting process; recusals noted are from the initial round of balloting. We thank him for his contributions.

ACC indicates American College of Cardiology; AHA, American Heart Association; HRS, Heart Rhythm Society; and VA, Veterans Affairs.
### Appendix 2.Reviewer Relationships With Industry and Other Entities (Comprehensive)—2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope (June 2016)

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Representation</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italo Biaggioni</td>
<td>Official Reviewer—AHA</td>
<td>Vanderbilt University School of Medicine—Professor of Medicine</td>
<td>Lundbeck*&lt;br&gt;Shire Pharmaceuticals*&lt;br&gt;Theravance*</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Joaquin E. Cigarroa</td>
<td>Official Reviewer—ACC/AHA Task Force on Clinical Practice Guideline</td>
<td>Oregon Health &amp; Science University—Clinical Professor of Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Kenneth A. Ellenbogen</td>
<td>Official Reviewer—AHA</td>
<td>VCU Medical Center—Director, Clinical EP Laboratory</td>
<td>AHA&lt;br&gt;Atricure*&lt;br&gt;Biosense Webster*&lt;br&gt;Biotronik*&lt;br&gt;Boston Science*&lt;br&gt;HRS*&lt;br&gt;Janssen Pharmaceuticals&lt;br&gt;Medtronic&lt;br&gt;Pfizer*&lt;br&gt;Sentra Heart&lt;br&gt;St. Jude Medical*</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Rakesh Gopinathannair</td>
<td>Official Reviewer—HRS</td>
<td>University of Louisville School of Medicine and Jewish Hospital Division of Cardiovascular Medicine—Associate Professor of Medicine, Director of Cardiac EP</td>
<td>Boston Scientific&lt;br&gt;Health Trust PG&lt;br&gt;St. Jude Medical*</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Robert Helm</td>
<td>Official Reviewer—HRS</td>
<td>Boston University School of Medicine—Assistant Professor of Medicine, Assistant Professor of Radiology</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dhanunjaya Lakireddy</td>
<td>Official Reviewer—ACC Board of Governors</td>
<td>University of Kansas Medical Center—Professor of Medicine, Center for Excellence in AF and Complex Arrhythmias—Director</td>
<td>Biosense Webster&lt;br&gt;St. Jude Medical*</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Thad Waites</td>
<td>Official Reviewer—ACC Board of Trustees</td>
<td>Forrest General Hospital—Director of Catheterization Laboratory</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

(Continued)
### Appendix 2. Continued

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Representation</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christopher Gibbons</td>
<td>Organizational Reviewer—AAN</td>
<td>Beth Israel Deaconess Medical Center Neuropathy Clinic—Director</td>
<td>Lundbeck</td>
<td>None</td>
<td>None</td>
<td>Astellas Pharma (DSMB)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Kaushal H. Shah</td>
<td>Organizational Reviewer—ACEP/SAEM</td>
<td>The Mount Sinai Hospital—Associate Professor of Emergency Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Janssen Pharmaceuticals (DSMB)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Mike Silka</td>
<td>Organizational Reviewer—PACES</td>
<td>Children’s Hospital Los Angeles—Professor of Pediatrics, Cardiology</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Defendant, SCD in CPVT patient, 2016</td>
</tr>
<tr>
<td>Sana M. Al-Khatib</td>
<td>Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines</td>
<td>Duke Clinical Research Institute—Professor of Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>FDA*</td>
<td>Elsevier*</td>
<td>None</td>
</tr>
<tr>
<td>Kim K. Birtcher</td>
<td>Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines</td>
<td>University of Houston College of Pharmacy—Clinical Professor</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>NHLBI*</td>
<td>AHA</td>
<td>None</td>
</tr>
<tr>
<td>Michele Brignole</td>
<td>Content Reviewer</td>
<td>Arrhythmologic Centre, Ospedali del Tigullio—Head of Cardiology</td>
<td>None</td>
<td>None</td>
<td>F2 Solutions†</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Hugh Calkins</td>
<td>Content Reviewer—ACC EP Section Leadership Council</td>
<td>Johns Hopkins Hospital—Professor of Medicine, Director of EP</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Boehringer Ingelheim†</td>
<td>Abbott Laboratories</td>
<td>Defendant, SCD, 2015</td>
</tr>
<tr>
<td>Coletta Barrett</td>
<td>Content Reviewer—Lay Reviewer</td>
<td>Our Lady of the Lake Regional Medical Center—Vice President</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>St. Jude Medical*</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Lin Yee Chen</td>
<td>Content Reviewer</td>
<td>University of Minnesota Medical School—Associate Professor of Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>NIH*</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Andrew Epstein</td>
<td>Andrew Epstein</td>
<td>University of Pennsylvania Hospital and the Veteran’s Administration Medical Center—Professor of Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Biosense Webster*</td>
<td>St. Jude Medical</td>
<td>None</td>
</tr>
</tbody>
</table>

(Continued)
## Appendix 2. Continued

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Representation</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susan Etheridge</td>
<td>Content Reviewer—ACC EP Section Leadership Council</td>
<td>University of Utah—Training Program Director</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>• SADS Foundation • PACEst</td>
<td>• Up-to-Date†</td>
<td>None</td>
</tr>
<tr>
<td>Marci Farquhar-Snow</td>
<td>Content Reviewer</td>
<td>Mayo Clinic School of Health Sciences—Program Director, Cardiology Nurse Practitioner, Fellowship</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Samuel S. Gidding</td>
<td>Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines</td>
<td>Nemours/Alfred I. duPont Hospital for Children—Chief, Division of Pediatric Cardiology</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>• FH Foundationf International • FH Foundationf</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Bulent Gorenek</td>
<td>Content Reviewer—ACC EP Section Leadership Council</td>
<td>Eskisehir Osmangazi University Cardiology Department—Chair</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Paul LeLorier</td>
<td>Content Reviewer—ACC Heart Failure and Transplant Section Leadership Council</td>
<td>LSU Health Sciences Center—Associate Professor of Medicine and Neurology, EP Service—Director</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>• Medtronic*</td>
<td>• Medtronic*</td>
<td>None</td>
</tr>
<tr>
<td>Patrick McBride</td>
<td>Content Reviewer</td>
<td>University of Wisconsin School of Medicine &amp; Public Health—Professor of Medicine and Family Medicine; Dean for Faculty Affairs—Associate, Prevention Cardiology—Associate Director</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Carlos Morillo</td>
<td>Content Reviewer</td>
<td>Cumming School of Medicine—Professor Department of Cardiac Sciences; University of Calgary—Section Chief Division of Cardiology, Libin Cardiovascular Institute</td>
<td>• Bayer HealthCare • Boehringer Ingelheim • Boston Scientific</td>
<td>None</td>
<td>None</td>
<td>• Biosense Webster • Canadian Institutes of Health Research† • Medtronic • Merck • Pfizer • St. Jude Medical</td>
<td>• Biotronik • Pfizer</td>
<td>None</td>
</tr>
<tr>
<td>Rick Nishimura</td>
<td>Content Reviewer</td>
<td>Mayo Clinic Section of Cardiovascular Disease—Professor of Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

(Continued)
### Appendix 2. Continued

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Representation</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richard Page</td>
<td>Content Reviewer</td>
<td>University of Wisconsin School of Medicine &amp; Public Health—Chair, Department of Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>• FDA</td>
<td>None</td>
</tr>
<tr>
<td>Antonio Raviele</td>
<td>Content Reviewer</td>
<td>Alliance to Fight Atrial Fibrillation—President; Venice Arrhythmias—President</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Marwan Refaat</td>
<td>Content Reviewer—ACC EP Section Leadership Council</td>
<td>American University of Beirut—Faculty of Medicine and Medical Center</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Melissa Robinson</td>
<td>Content Reviewer</td>
<td>University of Washington—Assistant Professor of Medicine; Director, Ventricular Arrhythmia Program</td>
<td>• Medtronic*</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Paola Sandroni</td>
<td>Content Reviewer</td>
<td>Mayo Clinic—Professor of Neurology, Practice Chair of Neurology</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Colette Seifer</td>
<td>Content Reviewer</td>
<td>University of Manitoba—Associate Professor, Section of Cardiology</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Monica Solbiati</td>
<td>Content Reviewer</td>
<td>Fondazione IRCCS CA’ Granda, Ospedale Maggiore Policlinico, Milano—Senior Physician</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Richard Sutton</td>
<td>Content Reviewer</td>
<td>National Heart and Lung Institute, Imperial College London—Emeritus Professor</td>
<td>• Medtronic*</td>
<td>• St. Jude Medical*</td>
<td>• Boston Scientific*</td>
<td>• Edwards Lifesciences*</td>
<td>• Shire Pharmaceuticals</td>
<td>• Medtronic*</td>
</tr>
<tr>
<td>Gaurav Upadhyay</td>
<td>Content Reviewer—ACC EP Section Leadership Council</td>
<td>University of Chicago—Assistant Professor of Medicine</td>
<td>• Biosense Webster</td>
<td>• Biotronik</td>
<td>• Boston Scientific</td>
<td>• Medtronic</td>
<td>• St. Jude Medical</td>
<td>• Zoll Medical</td>
</tr>
</tbody>
</table>

(Continued)
Appendix 2. Continued

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Representation</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paul Varosy</td>
<td>Content Reviewer</td>
<td>University of Colorado Hospital, Clinical Cardiac EP Training program—Associate Program Director; VA Eastern Colorado Healthcare System—Director of Cardiovascular EP</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>• AHA†</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

This table represents the relationships of reviewers with industry and other entities that were disclosed at the time of peer review, including those not deemed to be relevant to this document, at the time this document was under review. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review. Please refer to http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

*Significant relationship.
†No financial benefit.

AAN indicates American Academy of Neurology; ACC, American College of Cardiology; ACEP, American College of Emergency Physicians; AHA, American Heart Association; ASA, American Stroke Association; DSMB, data safety monitoring board; CPVT, catecholaminergic polymorphic ventricular tachycardia; EP, electrophysiology; FDA, US Food and Drug Administration; FH, familial hypercholesterolemia; HRS, Heart Rhythm Society; ICD, implantable cardioverter-defibrillator; JCE, Journal of Cardiovascular Electrophysiology; LSU, Louisiana State University; NHLBI, National Heart, Lung, and Blood Institute; PACE, Partners in Advanced Cardiac Evaluation; PACES, Pediatric and Congenital Electrophysiology Society; PCORI, Patient-Centered Outcomes Research Institute; PI, principal investigator; SADS, Sudden Arrhythmia Death Syndromes Foundation; SAEM, Society for Academic Emergency Medicine; SCAI, Society for Cardiovascular Angiography and Interventions; SCAD, sudden cardiac death; VA, Veterans Affairs; VCU, Virginia Commonwealth University; and VVS, vasovagal syncope.

Appendix 3. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACHD</td>
<td>adult congenital heart disease</td>
</tr>
<tr>
<td>ARVC</td>
<td>arrhythmogenic right ventricular cardiomyopathy</td>
</tr>
<tr>
<td>CPVT</td>
<td>catecholaminergic polymorphic ventricular tachycardia</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram/electrocardiographic</td>
</tr>
<tr>
<td>EPS</td>
<td>electrophysiological study</td>
</tr>
<tr>
<td>GDMT</td>
<td>guideline-directed management and therapy</td>
</tr>
<tr>
<td>HCM</td>
<td>hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>ICD</td>
<td>implantable cardioverter-defibrillator</td>
</tr>
<tr>
<td>LQTS</td>
<td>long-QT syndrome</td>
</tr>
<tr>
<td>OH</td>
<td>orthostatic hypotension</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>POTS</td>
<td>postural tachycardia syndrome</td>
</tr>
<tr>
<td>SCD</td>
<td>sudden cardiac death</td>
</tr>
<tr>
<td>VA</td>
<td>ventricular arrhythmia</td>
</tr>
<tr>
<td>VVS</td>
<td>vasovagal syncope</td>
</tr>
</tbody>
</table>


_Circulation_. 2017;136:e25-e59; originally published online March 9, 2017;  
doi: 10.1161/CIR.0000000000000498

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
Copyright © 2017 American Heart Association, Inc. All rights reserved.  
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:  
http://circ.ahajournals.org/content/136/5/e25

Data Supplement (unedited) at:  
http://circ.ahajournals.org/content/suppl/2017/03/08/CIR.0000000000000498.DC1  
http://circ.ahajournals.org/content/suppl/2017/03/08/CIR.0000000000000498.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:  
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:  
http://circ.ahajournals.org/subscriptions/
# Table of Contents

Data Supplement 1. Nonrandomized Trials, Observational Studies, and/or Registries for History and Physical Exam – (Section 2.3.1) ................................................................. 5
Data Supplement 2. Nonrandomized Trials, Observational Studies, and/or Registries of Electrocardiography – (Section 2.3.2) ................................................................. 8
Data Supplement 3. Nonrandomized Trials, Observational Studies, and/or Registries of Risk Stratification - Short-Term Outcomes – (Section 2.3.3)................................. 8
Data Supplement 4. Nonrandomized Trials, Observational Studies, and/or Registries of Risk Stratification - Long-Term Outcomes – (Section 2.3.3)......................... 14
Data Supplement 5. Nonrandomized Trials, Observational Studies, and/or Registries of Disposition After Initial Evaluation – (Section 2.3.4)........................................... 16
Data Supplement 6. RCTs for Disposition After Initial Evaluation – Serious Conditions – (Section 2.3.4) ............................................................................................... 18
Data Supplement 7. Nonrandomized Trials, Observational Studies, and/or Registries Comparing Blood Testing – (Section 3.1)................................................................. 19
Data Supplement 8. Nonrandomized Trials, Observational Studies, and/or Registries of Blood Testing – (Section 3.1) ........................................................................... 21
Data Supplement 9. Nonrandomized Trials, Observational Studies, and/or Registries of Cardiac Imaging – (Section 3.2.1) ................................................................. 22
Data Supplement 10. Nonrandomized Trials, Observational Studies, and/or Registries of Stress Testing – (Section 3.2.2) ................................................................. 25
Data Supplement 11. RCTs Comparing Cardiac Monitoring – (Section 3.2.3)....................................................................................................................... 26
Data Supplement 12. Nonrandomized Trials, Observational Studies, and/or Registries of Cardiac Monitoring – (Section 3.2.3)................................................................. 28
Data Supplement 13. Nonrandomized Trials, Observational Studies, and/or Registries of In-Hospital Telemetry – (Section 3.2.4)................................................................. 35
Data Supplement 14. Nonrandomized Trials, Observational Studies, and/or Registries of Electrophysiology Testing – (Section 3.2.5).................................................. 37
Data Supplement 15. Nonrandomized Trials, Observational Studies, and/or Registries of Tilt Table Testing – (Section 3.2.6.)................................................................. 46
Data Supplement 16. Nonrandomized Trials, Observational Studies, and/or Registries of Neurologic Investigation – (Section 3.3)................................................................. 52
Data Supplement 17. Nonrandomized Trials, Observational Studies, and/or Registries of ARVCD – (Section 4.2.4)........................................................................ 58
Data Supplement 18. Nonrandomized Trials, Observational Studies, and/or Registries of Sarcoid Heart Disease – (Section 4.2.5)................................................................. 59
Data Supplement 19. Nonrandomized Trials, Observational Studies, and/or Registries of Brugada Syndrome – (4.3.1)................................................................. 62
Data Supplement 20. Nonrandomized Trials, Observational Studies, and/or Registries of Short-QT Pattern and Syncope – (Section 4.3.2)........................................... 66
Data Supplement 21. Nonrandomized Trials, Observational Studies, and/or Registries of Long-QT Syndrome – (Section 4.3.3)................................................................. 68
Data Supplement 22. Nonrandomized Trials, Observational Studies, and/or Registries of CPVT-Medical Therapy – (Section 4.3.4).................................................. 72
Data Supplement 23. Nonrandomized Trials, Observational Studies, and/or Registries of CPVT- LSCD and ICD Therapy – (Section 4.3.4)........................................... 76
Methodology and Evidence Review

The recommendations listed in this guideline are, whenever possible, evidence based. An extensive evidence review was conducted from July through October 2015, that included literature published through October 2015. Other selected references published through May 2016 were incorporated by the writing committee. Literature included was derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline. Key search words included but were not limited to the following: adverse, aged, aging, ambulatory monitor, arrhythmogenic right ventricular cardiomyopathy, arrhythmogenic right ventricular dysplasia, athletes, AV block, b-blockers, biomarkers, blood pressure, bradycardia, breath-holding, Brugada Syndrome, cardiovascular disease, carotid sinus hypersensitivity, carotid sinus massage, carotid sinus syndrome, catecholaminergic polymorphic ventricular tachycardia, children, consciousness, dehydration, diagnosis, drug, early repolarization syndrome, echocardiogram, echocardiography, electrocardiography, electrocardiograph, electrophysiologic, electrophysiologic, falls, florinef, fludrocortisone, fluoxetine, functional neurologic symptoms, heart rate, holter monitor, holter, hypertrophic cardiomyopathy, hypertension, ICD, idiopathic AV block, implantable cardioverter defibrillator, implantable loop recorder, laboratory testing, left cardiac sympathetic denervation, long QT Syndrome, loop monitor, loop recorder, medication, midodrine, mode of pacing, monitor, non-epileptic pseudo seizures, orthostatic, pacemaker, pacing, pediatrics, postural, pressure counter maneuvers, presyncope, psychogenic non-epileptic seizure, psychogenic pseudoseizures, psychogenic pseudosyncope, psychogenic syncope, rehydration, salt, short QT Syndrome, stress test, syncope, systole, telemetry, tilt table test, tilt table, tilt-test, tilt-training, transient loss of consciousness, vasodepressor syncope, vasovagal syncope, vasovagal, ventricular arrhythmia, ventricular fibrillation and ventricular tachycardia. Terms may have been used alone or in combination.

Abbreviations

The following abbreviations are used in this guideline:

AC, acute coronary syndrome; ACD, atrial extrasystole; ACC, American College of Cardiology; ACS, acute coronary syndrome; ADE, adverse drug events; AF, atrial fibrillation; AMI, acute myocardial infarction; ARVC, arrhythmogenic right ventricular cardiomyopathy; AUC, appropriate use criteria; AV, atrioventricular; AVB, atrioventricular block; BB, beta blocker; BBB, bundle branch block; BID, two times a day; BNP, brain natriuretic peptide; BP, blood pressure; BS, Brugada syndrome; BSC, Boston Syncope Criteria; CA, cardiac arrest; CAA, carotid artery angioplasty; CAD, coronary artery disease; CBT, cognitive behavioral therapy; CCM, cerebrovascular disease; CCHF, chronic cutaneous candidiasis; CHF, congestive heart failure; CHF, congestive heart failure; CI, confidence interval; CLS, closed loop stimulation; CO, cardiac output; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; CPVT, catecholaminergic polymorphic ventricular tachycardia; CS, carotid sinus syndrome; CS, carotid sinus syndrome; CSS, Carotid Sinus Syndrome; CS, carotid sinus syndrome; CS, Carotid Sinus Syndrome; CT, computed tomography; cTnTh, high-sensitivity cardiac troponin T; CV, cardiovascular; CVD, cardiovascular disease; CXR, chest x-ray; DBP, diastolic blood pressure; DDD, dual chamber pacing; DM, diabetes mellitus; DS, defecation syncope; DVI, dual chamber pacing; ECG, electrocardiogram; ED, emergency department; EDD, emergency department observation syncope protocol; EEG, electroencephalogram; EF, ejection fraction; EGSYS, evaluation of guidelines of syncope study; ELR, external loop recorder; EP, electrophysiologic; EPS, electrophysiologic study; ER, early repolarization; ERP, early repolarization pattern; EST, exercise stress test; FINGER, France, Italy, Netherlands, Germany, Registry; GERD, gastroesophageal reflux disease; GFR, glomerular filtration rate; GTN, glyceryl trinitrate; H&P, history and physical exam; HCM, hypertrophic cardiomyopathy; HF, heart failure; HR, hazard ratio; HTN, hypertension; HUTT, head-up tilt test; Hx, history; ICD, implantable cardioverter-defibrillator; ICU, intensive care unit; IDCM, idiopathic dilated cardiomyopathy; ILR, implantable loop recorder; IV, intravenous fluid; IVCD, intraventricular conduction disturbances; KM, Kaplan-Meier; LBBB, left bundle branch block; LBNP, lower body negative pressure; LCM, left cerebral perfusion pressure; LCI, left cerebral ischemia; LCSD, left cardiac sympathetic denervation; LOC, loss of consciousness; LOS, length of stay; QT, long QT syndrome; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVNC, left ventricular non-compaction; MACE, major adverse cardiac event; MAP, mean arterial pressure; MCA, middle cerebral artery blood velocity; MCOT, mobile cardiac outpatient telemetry; MD, doctor of medicine; MI, myocardial infarction; MRI, magnetic resonance imaging; MS, micturition syncope; MSA, multiple systems atrophy; N/A, not available; NICM, nonischemic dilated cardiomyopathy; NMS, neurally mediated syncope; NPV, negative predictive value; NS, not significant; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association classification for heart failure; ODO, sensing without pacing; OESIL, Osservatorio Epidemiologico sulla Sincope nel Lazio; OH, orthostatic hypotension; OHDSAS, Orthostatic Hypotension Daily Activity Scale; OHQ, orthostatic hypotension questionnaire; OHSAS, Orthostatic Hypotension Symptom Assessment; OI, orthostatic intolerance; OR, odds ratio; OT, Oral Fluid and Trendelenburg position; OT, orthostatic tachycardia; PAF, pure autonomic failure; PCA, posterior cerebral artery blood velocity; PCI, percutaneous coronary intervention; PCM,
physical counter pressure maneuvers; PD, Parkinson disease; PE, physical examination; PES, programmed electrical stimulation; PM, pacemaker; PMVT, polymorphic ventricular arrhythmias; PNES, psychogenic nonepileptic seizures; POST, Prevention of Syncope trial; POTS, postural (orthostatic) tachycardia syndrome; PPM, permanent pacemaker; PPS, psychogenic pseudosyncope; PVC, premature ventricular contractions; PVD, peripheral vascular disease; QoL, quality of life; RCT, randomized controlled trials; RDBPCT, randomized, double blind, placebo-controlled trial; ROSE, risk stratification of Syncope in the Emergency Department; RR, relative risk; RRR relative risk ratio; RyR2, Ryanodine receptor type 2; S/P, strategies primary; SA, sinoatrial; SBP, systolic blood pressure; SCD, sudden cardiac death; SCI, spinal cord injury; SD, sudden death; SFSR, San Francisco Syncope Rule; SHD, structural heart disease; SN, sinus node; SND, sinus node dysfunction; SNRT, sinus node recovery time; SNS, sympathetic nervous system; SQTS, short QT syndrome; SUO, syncope of unknown origin; SV, stroke volume; SVT, supraventricular tachycardia; TCA, trichloroacetic acid; TIA, transient ischemic attack; TLOC, transient loss of consciousness; TOF, tetralogy of Fallot; TPR, total peripheral resistance; TST, thermoregulatory sweat test; TTT, tilt-table test; VA, ventricular arrhythmias; VATS, video-assisted thoracic surgery; VF, ventricular fibrillation; VFL, ventricular flutter; VHD, valvular heart disease; VS, vital signs; VT, ventricular tachycardia; VVI, ventricular pacing; VVS, vasovagal syncope; and WPW, Wolff-Parkinson-White.
### Data Supplement 1. Nonrandomized Trials, Observational Studies, and/or Registries for History and Physical Exam – (Section 2.3.1)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Calkins, et al. 1995 7709949 (1)     | **Aim:** Identify +quantitate symptoms assoc. with VVS, AVB, or VT  
**Study type:** Prospective  
**Size:** n=80 pts (16 AVB, 32 VT, 32 VVS) | **Inclusion criteria:** 80 pts with established hx of VT, VVS, or AVB  
**Exclusion criteria:** N/A | **Results:** Features suggestive of AVB or VT  
- Male gender  
- Age >54  
- <2 episodes of syncope  
Features suggestive of VVS  
- Before syncope: blurred vision, nausea, diaphoresis, palpitations  
- After syncope: nausea, warmth, diaphoresis, fatigue | Clinical history is of value in distinguishing pts with these 3 causes of syncope |
| Alboni P, et al. 2001 11401133 (2)   | **Aim:** Establish the historical findings predictive of the cause of syncope  
**Study type:** Prospective study  
**Size:** n=341 pts analyzed  
- Cardiac cause 78 (23%)  
- VVS 199 (58%)  
- Neuro/Psych 4 (1%)  
- Unexplained 60 (18%) | **Inclusion criteria:** Pts with syncope  
**Exclusion criteria:** N/A | **Results:** Only heart disease was an independent predictor of a cardiac cause of syncope (sensitivity: 95%; specificity: 45%) | Absence of heart disease allowed an exclusion of a cardiac cause in 97% |
| Alboni P, et al. 2004 14697727 (3)  | **Aim:** Establish the clinical features of VVS  
**Study type:** Prospective Study  
**Size:** n=461 pts prospectively evaluated. 280 had VVS:  
- Typical VVS n=39  
- HUTT induced n=142  
- Complex (CSH+VVS) n=31 | **Inclusion criteria:** Pts with syncope  
**Exclusion criteria:** N/A | **Results:** VVS differed from other neutrally mediated syncopes in precipitating factors and clinical features, including lower age and prevalence of organic heart disease, higher prevalence and duration of prodrome, Low prevalence of trauma | Considerable overlap between different Neurally medicated syndromes |
<table>
<thead>
<tr>
<th>Reference</th>
<th>Aim</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheldon, et al. 2006 16223744 (4)</td>
<td><strong>Aim:</strong> Establish historical criteria for diagnosis of VVS</td>
<td>Prospective, used a Questioner of 118 items</td>
<td>n=418 pts 235 syncope and positive HUTT n=95 no apparent cause (-HUTT) n=88 pts secondary syncope n=42 pts with CHB n=21 pts with SVT n=6 pts with VT n=5 pts with AS</td>
<td>Pts with syncope and no apparent structural heart disease</td>
<td>N/A</td>
<td>The point score correctly classified 90 % of pts with an 89% sensitivity and 91 % specificity</td>
<td>The point scoring system can distinguish VVS from other causes of syncope with a high sensitivity and specificity</td>
</tr>
<tr>
<td>Sheldon, et al. 2002 12103268 (5)</td>
<td><strong>Aim:</strong> Develop criteria that distinguish syncope due to VT from VVS in pts with SHD</td>
<td>Prospective analysis</td>
<td>n=671 pts with a history of TLOC completed a 118 item historical questionnaire</td>
<td>Pts with syncope and SHD</td>
<td>N/A</td>
<td></td>
<td>The point score based on symptoms alone correctly classified 94% of pts, diagnosing seizures with a 94% sensitivity and 94% specificity</td>
</tr>
<tr>
<td>FAST Van Dijk, et al. 2008 17916139 (6)</td>
<td><strong>Aim:</strong> Assess yield and accuracy of an initial evaluation using : History, PE, and ECG</td>
<td>Prospective analysis then a 2 y follow-up by an expert committee</td>
<td>n=503 pts (with a 2 y follow-up in 99%)</td>
<td>Adults presenting with TLOC to the Academic Medical Center Amsterdam between February 2000 and May 2002</td>
<td>N/A</td>
<td></td>
<td>Attending physicians can make a diagnosis in 63% of pts with TLOC, with a diagnostic accuracy of 88%</td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romme, et al. 2009&lt;br&gt;19687157 (7)</td>
<td><strong>Aim:</strong> Evaluate the Calgary Syncope Symptom Score</td>
<td>Pts with TLOC</td>
<td>N/A</td>
<td>Sensitivity of Calgary score was 87% but the Specificity was 32%</td>
<td>Sensitivity of the Calgary score similar to original study but the specificity less</td>
</tr>
<tr>
<td>Sheldon, et al. 2010&lt;br&gt;20586825 (8)</td>
<td><strong>Aim:</strong> Evaluate evidence based criteria to distinguish syncope due to VT from VVS in pts with structural heart disease</td>
<td>Pts with syncope and SHD</td>
<td>N/A</td>
<td>21 pts with HUTT+VVS</td>
<td>Factors predicting VT were male gender and &gt;35 y of age&lt;br&gt;Factors predicting VVS were Prolonged sitting or standing, pre-syncope preceded by stress, headaches and fatigue after syncope lasting &gt;1 min&lt;br&gt;The point score identified 92% of pts correctly, diagnosing VT with 99% sensitivity and 68% specificity, negative predictive value of &gt;96%</td>
</tr>
<tr>
<td>PLOS&lt;br&gt;Berecki-Gisolf, et al. 2013&lt;br&gt;24223233 (9)</td>
<td><strong>Aim:</strong> Develop a model for symptoms that associate with cardiac causes of syncope</td>
<td>2 Pubmed searches using the following key words:&lt;br&gt;1. Diagnosis; signs and symptoms; vasovagal syncope&lt;br&gt;2. Clinical history; diagnosis; syncope&lt;br&gt;• Pts with ≥1 transient loss of consciousness&lt;br&gt;• A diagnosis of cardiac syncope vs. other causes&lt;br&gt;• Degree of evidence accepted in each paper&lt;br&gt;• Studies reporting ≥2 predictors of cardiac syncope</td>
<td>N/A</td>
<td>A total of 10 variables were found associated with cardiac syncope :&lt;br&gt;1. Age &gt;60 y&lt;br&gt;2. Male gender&lt;br&gt;3. Structural heart disease&lt;br&gt;4. Low number of spells&lt;br&gt;5. Brief or absent prodrome&lt;br&gt;6. Supine syncope&lt;br&gt;7. Effort syncope&lt;br&gt;8. Absence of nausea&lt;br&gt;9. Absence of diaphoresis&lt;br&gt;10. Absence of blurred vision</td>
<td>A model with 5 variables was as effective with moderate accuracy:&lt;br&gt;• &gt;60 y of age&lt;br&gt;• Male gender&lt;br&gt;• Structural heart disease&lt;br&gt;• Low number of spells&lt;br&gt;• Lack of prodromal symptoms</td>
</tr>
</tbody>
</table>
### Data Supplement 2. Nonrandomized Trials, Observational Studies, and/or Registries of Electrocardiography – (Section 2.3.2)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Recchia D, et al. 1995 8770716 (10)  | **Study type:** Retrospective observational  
 **Size:** n=128 pts | **Inclusion criteria:** All pts admitted to hospital due to syncope  
 **Exclusion criteria:** Pts with syncope with known cause, pts with near syncope, vertigo, seizure, or pts referred to EP testing | **1st endpoint:** frequency of use of echocardiogram to evaluate pts admitted with syncope  
 **Results:** 90% of pts underwent cardiac testing; 64% of pts had echocardiogram which did not help elucidate cause of syncope, and echocardiogram; the ECG was normal for 52% of pts | • Hx, physical and ECG provided information to diagnosis a cause of syncope in 77% of pts (33 of 48 pts for whom a cause of syncope was felt to be ultimately determined)  
 • For pts with suspected cardiac disease, echocardiogram confirmed suspected diagnosis for 48% and ruled out suspected cause for remaining 52%. |
| Perez-Rodon J, et al. 2014 24993462 (11) | **Study type:** Multicenter, prospective, observational  
 **Size:** n=524 pts | **Inclusion criteria:** Pts with syncope, readable ECG and 12 mo f/u  
 **Exclusion criteria:** N/A | **1st endpoint:** Mortality  
 **Results:** 344 pts (65.6%) had abnormal ECG, 33 pts (6.3%) died during f/u. AF OR: 6.8; 95% CI: 1.5–26.3 p=0.011. Ventricular pacing: OR: 21.8; 95% CI:4.1–115.3, p=0.001. Left ventricular hypertrophy ECG criteria OR: 6.3; 95% CI:1.5–26.3; p=0.011. Intraventricular conduction disturbances OR: 3.8; 95% CI: 1.7–8.3; p=0.001 | • Only the presence of AF, intraventricular conduction disturbances, left ventricular hypertrophy ECG and ventricular pacing is associated with 1 y all cause mortality |

### Data Supplement 3. Nonrandomized Trials, Observational Studies, and/or Registries of Risk Stratification - Short-Term Outcomes – (Section 2.3.3)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Grossman SA, et al. 2012 | **Study type:** Prospective observational  
**Size:** n=244 ED pts with presyncope |
|-------------------------|------------------------------------------------|
| **Inclusion criteria:** Presyncope, >18 y of age  
**Exclusion criteria:** None |
| **1º endpoint:** Adverse outcomes (death, cardiac arrest, pulmonary embolus, stroke, severe infection/sepsis, ventricular dysrhythmia, atrial dysrhythmia (including SVT and AF with rapid ventricular response), intracranial bleed, hemorrhage, MI, CHF, acute renal failure, or life-threatening sequelae of syncope (i.e., rhabdomyolysis, long bone or cervical spine fractures) |
| Results: 11 pts admitted with 49 adverse outcomes. If BSC had been followed 41 additional pts admitted and 34 pts discharged. |
| · If BSC had been followed strictly, another 41 pts with risk factors would have been admitted and 34 discharged, a 3% increase in admission rate. However, using the modified criteria, only 68 pts would have required admission, a 38% reduction in admission, with no missed adverse outcomes on follow-up. |

| Colivicchi F, et al. 2003 | **Study type:** Prospective observational  
**Size:** Derivation cohort n=270 pts, Validation cohort n=328 pts |
|-------------------------|------------------------------------------------|
| **Inclusion criteria:** Pts >12 y of age presenting for syncope to one of 6 ED's  
**Exclusion criteria:** Seizure, pre-syncope, dizziness, vertigo |
| **1º endpoint:** 1 y all-cause mortality |
| Results: Primary outcome occurred in 31 (11.5%) pts in derivation cohort and 28 (8.5%) in the validation cohort. "OESIL" score predictors include pts >65 y of age; Hx of CV disease; no prodrome; abnormal ECG |
| · No "OESIL" risk factors associated with 0%, 1 y mortality, may identify low-risk subgroup that can be discharged  
· Quantitative, attempts at reproducing difficult |

| Costantino G, et al. 2014 | **Study type:** Patient level meta-analysis  
**Size:** n=3,681 pts |
|-------------------------|------------------------------------------------|
| **Inclusion criteria:** Patient level data from 6 prospective observational studies  
**Exclusion criteria:** N/A |
| **1º endpoint:** 30 d combined death, arrhythmia, severe outflow tract obstruction, MI, CPR, pulmonary embolism, aortic dissection, hemorrhage, syncope resulting in major trauma |
| Results: "OESIL", "SF SR," "EGSYS" risk scores had similar sensitivity and specificity as clinical judgment. |
| · Unclear whether these specific risk scores add value to clinical evaluation  
· Value of risk scores, etiology important to consider |

| Costantino G, et al. 2008 | **Study type:** Prospective observational  
**Size:** n=676 pts |
|-------------------------|------------------------------------------------|
| **Inclusion criteria:** >18 y of age presenting to one of 4 ED's  
**Exclusion criteria:** Dangerous condition identified in ED; head injury as cause of loss of consciousness; nonspontaneous return to consciousness; light-headedness, vertigo, coma, shock, seizure; terminal illness; substance abuse; |
<p>| <strong>1º endpoint:</strong> 10 d combined death, CPR, pacemaker/ICD placement, ICU admission, acute anti-arrhythmic therapy, readmission |
| Results: Predictors of short-term outcomes (n=41 pts; 6.1%) included abnormal ECG, concomitant trauma, no prodrome, and male gender. |
| · These criteria may identify pts who might benefit from hospital admission |</p>
<table>
<thead>
<tr>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>D'Ascenzo F, et al. 2013 22192287 (16)</td>
<td>Study type: Pooled meta-analysis</td>
<td>Inclusion criteria: Presentation of syncope to an ED</td>
<td>1° endpoint: Combined death, hospitalization/intervention related to arrhythmia, ischemic heart disease, or VHD.</td>
<td>Strongest predictors of an adverse outcome included palpitations preceding syncope, exertional syncope, history of HF or ischemic heart disease, evidence of bleeding</td>
<td>These criteria may identify pts who might benefit from hospital admission</td>
</tr>
<tr>
<td>Da Costa A, et al. 2006 15975670 (17)</td>
<td>Study type: Prospective observational</td>
<td>Inclusion criteria: Normal EPS after first onset of syncope or near-syncope</td>
<td>1° endpoint: Combined symptomatic AV block, conduction abnormalities requiring pacemaker therapy, sustained ventricular arrhythmia, sudden death</td>
<td>ECG is only independent predictor of long term adverse events</td>
<td>5% event rate at 2.5 y; normal EPS does not rule out dangerous conduction problems as cause of syncope</td>
</tr>
<tr>
<td>Del Rosso A, et al. 2008 18519550 (18)</td>
<td>Study type: Prospective observational</td>
<td>Inclusion criteria: Presentation of unexplained syncope to one of 14 ED’s</td>
<td>1° endpoint: Cardiac cause of syncope</td>
<td>&quot;EGSYS&quot; risk score predictors include palpitations prior to syncope (+4), heart disease and/or abnormal ECG (+3), exertional syncope (+3), supine syncope (+2), precipitating factors (-1), autonomic prodrome (-1)</td>
<td>Risk of cardiac cause is &lt;3% if EGSYS score &lt;3, and &gt;17% if EGSYS score ≥3</td>
</tr>
<tr>
<td>Derose S, et al. 2012 22594351 (19)</td>
<td>Study type: Retrospective observational</td>
<td>Inclusion criteria: Primary ED diagnosis of syncope or near-syncope in an integrated health system</td>
<td>1° endpoint: 30 d mortality</td>
<td>Predictors of short term mortality included increasing age, male gender, recent visit for syncope, history of HF, DM, seizure, and dementia</td>
<td>Pts without history of HF and &lt;60 y of age had less than 0.2% risk of 30 d mortality</td>
</tr>
<tr>
<td>Dipaola F, et al. 2010 20468221 (20)</td>
<td>Study type: Prospective observational</td>
<td>Inclusion criteria: &gt;18 y of age presenting to one of 2 EDs with syncope of unknown cause</td>
<td>1° endpoint: 10 d combined death, CPR, pacemaker/ ICD placement, ICU admission, acute anti-arrhythmic therapy, readmission</td>
<td>Compared to the &quot;OESIL&quot; and &quot;SFSR&quot; risk scores, unstructured clinical judgment had similar sensitivity and higher specificity.</td>
<td>Unclear whether these specific risk scores add value to clinical evaluation</td>
</tr>
<tr>
<td>Study type</td>
<td>Study title and authors</td>
<td>Year</td>
<td>Reference</td>
<td>Study type</td>
<td>Size</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------------</td>
<td>------</td>
<td>-----------</td>
<td>------------</td>
<td>------</td>
</tr>
<tr>
<td>Prospective observational</td>
<td>Exposito V, et al. 2013</td>
<td>23478089 (21)</td>
<td></td>
<td><strong>Study type:</strong> Prospective observational</td>
<td><strong>Size:</strong> n=180 pts</td>
</tr>
<tr>
<td>Retrospective observational</td>
<td>Gabayan G, et al. 2010</td>
<td>20102895 (22)</td>
<td></td>
<td><strong>Study type:</strong> Retrospective observational</td>
<td><strong>Size:</strong> n=35,330 pts</td>
</tr>
<tr>
<td>Prospective observational</td>
<td>Grossman S, et al. 2007</td>
<td>17976548 (23)</td>
<td></td>
<td><strong>Study type:</strong> Prospective observational</td>
<td><strong>Size:</strong> n=362 pts</td>
</tr>
<tr>
<td>Prospective observational</td>
<td>Kayayurt K, et al. 2012</td>
<td>22520447 (24)</td>
<td></td>
<td><strong>Study type:</strong> Prospective observational</td>
<td><strong>Size:</strong> n=231 pts</td>
</tr>
<tr>
<td>Prospective observational</td>
<td>Martin T, et al. 1997</td>
<td>9095005 (25)</td>
<td></td>
<td><strong>Study type:</strong> Prospective observational</td>
<td><strong>Size:</strong> Derivation n=252, validation n=374l</td>
</tr>
<tr>
<td>Study type: Prospective observational</td>
<td>Study type: Retrospective observational</td>
<td>Study type: Prospective observational</td>
<td>Study type: Prospective observational</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>----------------------------------------</td>
<td>-------------------------------------</td>
<td>-------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size: n=91 pts</td>
<td>Size: n=200 pts</td>
<td>Size: n=275 pts</td>
<td>Size: n=684 visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inclusion criteria:</strong> Syncope of unknown origin referred for EPS</td>
<td><strong>Inclusion criteria:</strong> &gt;18 y of age hospitalized for syncope</td>
<td><strong>Inclusion criteria:</strong> &gt;18 y of age with syncope of unknown origin after initial evaluation</td>
<td><strong>Inclusion criteria:</strong> Presentation of syncope to an ED</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong> None</td>
<td><strong>Exclusion criteria:</strong> None</td>
<td><strong>Exclusion criteria:</strong> None</td>
<td><strong>Exclusion criteria:</strong> None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1° endpoint: Inducible sustained monomorphic VT</td>
<td>1° endpoint: Cardiac cause of syncope</td>
<td>1° endpoint: Arrhythmic syncope</td>
<td>1° endpoint: 7 d combined death, MI, arrhythmia, pulmonary embolism, stroke, subarachnoid hemorrhage, significant hemorrhage, or any condition causing a return ED visit and hospitalization for a related event</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Results:</strong> Risk factors included abnormal signal averaged ECG; abnormal LVEF; prior sustained monomorphic VT</td>
<td><strong>Results:</strong> OESIL score &lt;2 had NPV of 98% to exclude cardiogenic cause. Prior syncope episodes and lack of prodrome were associated with increased risk of cardiogenic cause.</td>
<td><strong>Results:</strong> Risk factors included absence of nausea/vomiting prior to syncope, and ECG abnormalities</td>
<td><strong>Results:</strong> In this derivation study, &quot;SFSR&quot; risk score predictors include abnormal ECG, shortness of breath, hematocrit &lt;30%, SBP &lt;90 mmHg, Hx of CHF.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• These criteria may be used to identify pts who might benefit from EPS.</td>
<td>• These criteria may identify pts who might benefit from hospital admission</td>
<td>• These criteria may identify pts requiring who might benefit from cardiac monitoring</td>
<td>• Using a cutpoint of 0 risk scores, the &quot;SFSR&quot; risk score has 96% sensitivity and 62% specificity. Use of the &quot;SFSR&quot; in the derivation cohort may have reduced hospitalizations by 10%.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Results:</strong> In this validation cohort, the &quot;SFSR&quot; risk score was 98% sensitive and 56% specific.</td>
<td></td>
<td></td>
<td>• Application of the &quot;SFSR&quot; risk score may have decreased hospitalizations by 7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective observational</td>
<td>&gt;16 y of age presenting with syncope to an ED</td>
<td>30 d combined acute MI, dangerous arrhythmia, pacemaker/ICD placement, pulmonary embolus, neurologic event, hemorrhage requiring transfusion, emergent surgical or endoscopic procedure</td>
<td>These criteria may identify pts who might benefit from hospital admission</td>
</tr>
<tr>
<td>Retrospective registry</td>
<td>Discharged from an ED with first time diagnosis of syncope</td>
<td>All-cause mortality</td>
<td>CHADS2=0 is associated with 1.5% 1 y mortality rate</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>External validation study of &quot;SFSR&quot; risk score</td>
<td>Combined serious outcomes, definition varied by specific study</td>
<td><em>SFSR</em> risk score appears to be less sensitive and specific in external validation studies than originally reported</td>
</tr>
<tr>
<td>Prospective observational</td>
<td>Unexplained syncope after ED evaluation</td>
<td>Arrhythmic syncope</td>
<td>Pts without any risk factors had &lt;2% risk of arrhythmic syncope</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>ED cohort study of syncope/ near-syncope study for risk score derivation or validation</td>
<td>Combined serious outcomes, definition varied by specific study</td>
<td>These criteria may identify pts who might benefit from hospital admission</td>
</tr>
<tr>
<td>Study Acronym; Author; Year Published</td>
<td>Study Type/Design; Study Size</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-------------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Sheldon R, et al. 2006 16223744 (4)</td>
<td>Study type: Prospective observational</td>
<td>Inclusion criteria: Prior episode of syncope evaluated in cardiology clinic or hospital cardiology wards</td>
<td>Exclusion criteria: None</td>
</tr>
<tr>
<td>Sule S, et al. 2012 22878409 (36)</td>
<td>Study type: Prospective observational</td>
<td>Inclusion criteria: Hospitalized for syncope</td>
<td>Exclusion criteria: None</td>
</tr>
<tr>
<td>Sun B, et al. 2009 19766355 (37)</td>
<td>Study type: Retrospective observational</td>
<td>Inclusion criteria: &gt;60 y of age with unexplained syncope or near-syncope after ED evaluation</td>
<td>Exclusion criteria: None</td>
</tr>
<tr>
<td>Numeroso F, et al. 2014 24489075 (38)</td>
<td>Study type: Prospective observational</td>
<td>Inclusion criteria: ED syncope</td>
<td>Exclusion criteria: None</td>
</tr>
</tbody>
</table>

Data Supplement 4. Nonrandomized Trials, Observational Studies, and/or Registries of Risk Stratification - Long-Term Outcomes – (Section 2.3.3)
<table>
<thead>
<tr>
<th>Study type: Prospective observational</th>
<th>Study type: Observational</th>
<th>Study type: Observational</th>
<th>Study type: Observational</th>
<th>Study type: Case control</th>
<th>Study type: Observational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type: Observational</td>
<td>Study type: Observational</td>
<td>Study type: Observational</td>
<td>Study type: Observational</td>
<td>Study type: Observational</td>
<td>Study type: Observational</td>
</tr>
<tr>
<td>Size: n=380 pts</td>
<td>Size: n=325 pts</td>
<td>Size: n=208 pts</td>
<td>Size: n=242 pts</td>
<td>Size: n=352 pts</td>
<td>Size: n=3877 pts with syncope; of which 9.8% had syncope while driving</td>
</tr>
<tr>
<td>Inclusion criteria: ED syncope</td>
<td>Inclusion criteria: Hospitalized for syncope</td>
<td>Inclusion criteria: NCS with Positive tilt and &gt; lifetime syncope</td>
<td>Inclusion criteria: Syncope</td>
<td>Inclusion criteria: ED syncope</td>
<td>Inclusion criteria: Syncope</td>
</tr>
<tr>
<td>Exclusion criteria: None</td>
<td>Exclusion criteria: None</td>
<td>Exclusion criteria: None</td>
<td>Exclusion criteria: None</td>
<td>Exclusion criteria: None</td>
<td>Exclusion criteria: None</td>
</tr>
<tr>
<td>1° endpoint: Death</td>
<td>1° endpoint: Recurrent syncope</td>
<td>1° endpoint: Recurrent syncope</td>
<td>1° endpoint: Recurrent syncope</td>
<td>1° endpoint: Recurrent syncope</td>
<td>1° endpoint: Syncope while driving in followup</td>
</tr>
<tr>
<td>Results: Predictors for recurrent syncope were prodromes and palpitations prior to syncope</td>
<td>Results: Associated with recurrent hospitalized syncope were DM, AF and smoking</td>
<td>Results: Number of syncope in prior y better predicted syncope recurrence compared to lifetime syncope episodes</td>
<td>Results: Increased syncope with age and disability</td>
<td>Results: 3% readmitted; CHF and ACS were risk factors</td>
<td>Results: In the syncope while driving group (n=381 pts) 72 pts had recurrent syncope, including 10 while driving.</td>
</tr>
<tr>
<td>Incidence of syncope recurrence not related to mechanism of syncope or EGYSYS score &lt; or ≥3.</td>
<td>• Syncope etiology found in 74%</td>
<td>• Syncope recurred in 22% of those with &lt;2 episodes in the prior y compared to 69% in those with &gt;6 episodes.</td>
<td>• Syncope recurrence was 32.5%</td>
<td>• Etiology of syncope found in 69%</td>
<td>• Etiology of syncope while driving included neutrally mediated (37%) and arrhythmic (12%)</td>
</tr>
</tbody>
</table>
### Data Supplement 5. Nonrandomized Trials, Observational Studies, and/or Registries of Disposition After Initial Evaluation – (Section 2.3.4)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; and 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruwald MH, et al. 2013 24035171 (46)</td>
<td>Study type: Nationwide administrative registries <strong>Size:</strong> n=5141 pts &gt;85 y of age n=23,454 &lt;85 y of age</td>
<td><strong>Inclusion criteria:</strong> Syncope  <strong>Exclusion criteria:</strong> None</td>
<td><strong>1° endpoint:</strong> Recurrent syncope  <strong>Results:</strong> Predictors of recurrent syncope include: AS, kidney disease, AV or LBBB, Male, COPD, CHF, AF, Age, orthostatic medications</td>
<td>• N/A</td>
</tr>
<tr>
<td>Sun, et al. 2012 22687184 (47)</td>
<td><strong>Study type:</strong> Expert consensus  <strong>Size:</strong> n=24 panelists</td>
<td><strong>Aim:</strong> Create standardized reporting guidelines, including serious outcomes, for syncope research</td>
<td><strong>Primary Endpoint</strong> N/A  <strong>Results:</strong> Modified Delphi consensus process identified final guideline elements from 183 candidate elements</td>
<td>• 23 serious conditions identified for research reporting</td>
</tr>
<tr>
<td>Daccarett, et al. 2011 21757485 (48)</td>
<td><strong>Study type:</strong> Retrospective observational  <strong>Size:</strong> n= 254 pts</td>
<td><strong>Inclusion criteria:</strong> ED visit for syncope identified by ICD code 780.2  <strong>Exclusion criteria:</strong> Pts with secondary diagnosis of syncope</td>
<td><strong>1° endpoint:</strong> Admission rate  <strong>Results:</strong> Retrospective application of the Utah Faint-Algorithm would have reduced admissions by 52%. Algorithm explicitly defined conditions or high risk criteria for which admission would be indicated. The 7-d serious event rate in pts who should have been discharged per the algorithm (3%) was similar to those who were actually discharged (4%).</td>
<td>• A standardized evaluation algorithm that explicitly identified serious conditions which requires admission appears to be safe and reduces resource use.</td>
</tr>
<tr>
<td>Framingham Cohort Study Soteriades, et al. 2002 12239256 (49)</td>
<td><strong>Aim:</strong> Describe prognosis of syncope in general population  <strong>Study type:</strong> Prospective cohort  <strong>Exclusion criteria:</strong> N/A</td>
<td><strong>Inclusion criteria:</strong> Participants in the original Framingham Heart Study and the Framingham Offspring Study</td>
<td><strong>All-cause mortality</strong> Over 25 y follow-up period, pts with presumptive VVS had similar risk-adjusted mortality risk as pts without syncope</td>
<td>• Syncope of vasovagal etiology does not appear to increase mortality risk</td>
</tr>
<tr>
<td>Study Type</td>
<td>Size: n=7,814 pts</td>
<td>Inclusion Criteria: ED visit for syncope, undergoing structured evaluation, age ≥ 50</td>
<td>1st Endpoint: Life threatening event or significant therapeutic intervention</td>
<td>Yield of diagnostic admission appears to be low</td>
</tr>
<tr>
<td>------------</td>
<td>------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Morag, et al. 2004</td>
<td><strong>Aim</strong>: Assess diagnostic benefit of admission for unexplained syncope</td>
<td><strong>Exclusion criteria</strong>: Intoxicated with drugs or alcohol, had antecedent head trauma prompting symptoms, had witnessed seizure activity with a history of seizures, or if their loss of consciousness promptly responded to medical management (administration of glucose or naloxone)</td>
<td><strong>Results</strong>: Of 30 admitted pts, none experienced the primary endpoint as inpatient or at 30 d follow up</td>
<td></td>
</tr>
<tr>
<td><strong>Study Type</strong>: Prospective cohort</td>
<td><strong>Size</strong>: n=45 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Size: n=376 pts</th>
<th>Inclusion Criteria: Hospital admission for evaluation of syncope</th>
<th>1st Endpoint: Diagnostic evaluation, costs, 1 y mortality</th>
<th>A significant proportion of pts have an unrevealing evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shiyovich, et al. 2008</td>
<td><strong>Aim</strong>: Assess diagnostic evaluation, costs, and prognosis of pts admitted for syncope</td>
<td><strong>Exclusion criteria</strong>: pre syncope, seizure, malignant arrhythmia</td>
<td><strong>Results</strong>: 38% had no clear diagnosis at discharge.</td>
<td></td>
</tr>
<tr>
<td><strong>Study Type</strong>: Retrospective cohort</td>
<td><strong>Size</strong>: n=376 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Size: n=127 pts</th>
<th>Inclusion Criteria: Hospital admission for evaluation of syncope</th>
<th>1st Endpoint: No patient has inpatient death or recurrent syncope as inpatient. 2% of pts died within 30 days, all from known pre-existing disease</th>
<th>Hospital evaluation had modest diagnostic yield; population had low short term mortality risk.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schillinger, et al. 2000</td>
<td><strong>Aim</strong>: Assess evaluation and prognosis of pts admitted for syncope</td>
<td><strong>Exclusion criteria</strong>: Not admitted after ED evaluation</td>
<td><strong>Results</strong>: Of 376 pts, 48% had no clear diagnosis at discharge. Long term mortality was higher for pts with cardiac and neurologic etiology.</td>
<td></td>
</tr>
<tr>
<td><strong>Study Type</strong>: Retrospective cohort</td>
<td><strong>Size</strong>: n=127 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Size: n=362 pts</th>
<th>Inclusion Criteria: ED evaluation for TLOC</th>
<th>1st Endpoint: Disposition</th>
<th>Presence of ED observation unit and hospital based syncope unit is associated with lower hospitalization rates compared to historical experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ungar, et al. 2015</td>
<td><strong>Study Type</strong>: Observational</td>
<td><strong>Exclusion criteria</strong>: N/A</td>
<td><strong>Results</strong>: Disposition included 29% admitted; 20%</td>
<td></td>
</tr>
<tr>
<td><strong>Size</strong>: n=362 pts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
Shin, et al.  
2013  
23918559  
(54)

**Study type:** Quasi experimental, pre-post w/o control, assess implementation of standard approach including risk stratification, hospital order set, and ED observation unit  

**Inclusion criteria:** >18 y of age with syncope evaluated in ED  

**Exclusion criteria:** inability to consent, prior enrollment in other studies, non-syncope syndromes  

**1° endpoint:** Admission rate  

**Results:** In the 1-y post-period compared to the 1-y pre-period, there were reductions in admissions (8.3%), costs (30%), and LOS (35%)  

- Standardized evaluation, including risk stratification and use of an observation unit, reduced admissions, costs, and LOS  

---

**Data Supplement 6. RCTs for Disposition After Initial Evaluation – Serious Conditions – (Section 2.3.4)**

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| SEEDS  
Shen, et al.  
2004  
15536093  
(55) | **Aim:** Assess whether designated syncope unit in ED improves diagnostic yield and reduces admission  
**Study type:** 1 site RCT  
**Size:** n=103 pts | **Inclusion criteria:** Syncope of undetermined cause after ED evaluation, AND intermediate risk by semi-structured criteria  
**Exclusion criteria:** 1. Identified cause of syncope; 2. Dangerous condition requiring admission; 3. Non-syncope syndrome such as light-headedness  
**Intervention:** Syncope unit: continuous cardiac monitoring up to 6 h; hourly VS/ orthostatic BP; ECG for abnormal heart sounds or ECG; recommended tilt-table testing for selected pts; outpatient EP consult, echocardiogram, tilt-table testing available within 72 h after discharge  
**Comparator:** Standard care (default was admission to hospital) | **1° endpoint:** Admission rate: 43% in intervention, 98% in control  
**1° Safety endpoint (if relevant):** No differences in survival or recurrent syncope |  
- Hospital d: 64 in intervention, 140 in control  
- Presumptive diagnosis: 67% in intervention, 10% in control  
Summary: Structured syncope unit in ED reduced hospital admission and length of stay without affecting mortality or recurrent syncope rates.
**EDOSP**

Sun, et al.  
2014  
24239341 (56)

**Aim**: Assess whether EDOSP reduces resource use without adversely affecting patient oriented outcomes  
**Study type**: 5-site RCT  
**Size**: n=124 pts  
**Inclusion criteria**: Pts >50 y of age, AND intermediate risk for serious short-term events by semi-structured criteria  
**Exclusion criteria**: 1. Dangerous condition requiring admission; 2. non-syncope syndrome such as seizure  
**Intervention**: 12–24 h of cardiac monitoring; echocardiogram for cardiac murmur; serial troponin  
**Comparator**: Admission to inpatient service  
**1° endpoint**: LOS: 29 h in EDOSP, 47 h in control  
**1° Safety endpoint (if relevant)**: No differences in 30 d serious outcome rates, quality-of-life scores, patient satisfaction  
**Summary**: EDOSP reduced resource use with no difference in outcomes, quality-of-life, or patient satisfaction.

---

**Data Supplement 7. Nonrandomized Trials, Observational Studies, and/or Registries Comparing Blood Testing – (Section 3.1)**

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type*; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
**Study type**: Observational cohort  
**Size**: n=61 pts | **Inclusion criteria**: Consecutive pts in the emergency room  
**Exclusion criteria**: None | **Intervention**: None  
**Comparator**: Between subsequently diagnosed groups | **1° endpoint**: NT-pro BNP levels in different etiology of syncope groups  
• Post hoc determination of levels after diagnosis obtained  
• No gold standard for most diagnostic categories |
| Thiruganasambanda moorthy V. et al. 2015 26498335 (58) | **Aim**: Prognostic value of cardiac biomarkers in the risk stratification of syncope  
**Study type**: Systematic review  
**Size**: N/A | **Inclusion criteria**: Adult syncope pts during acute management  
**Exclusion criteria**: Case reports, children | **Intervention**: None  
**Comparator**: None | **1° endpoint**: MACE: death, CPR, MI, structural heart disease, PE, significant hemorrhage, cardiac intervention. High sensitivity Troponin and natriuretic peptides showed good sensitivity and specificity for MACE  
• Relationship of syncope to MACE and biomarkers is unclear |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>1° endpoint</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>GESINUR Pérez-Rodon et al. 2014 24993462 (11)</td>
<td>Determine outcome predictors on resting ECG</td>
<td>Syncope in the ER with 1 y follow-up</td>
<td>None</td>
<td>Mortality: 33 total deaths (6.6%), 1 SCD</td>
<td>AF, IVCD, LVH and ventricular pacing an independent risk factors for mortality</td>
</tr>
<tr>
<td>Chiu DT, et al. 2014 24698512 (59)</td>
<td>Determine the yield of standard diagnostic tests</td>
<td>ER presentation syncope</td>
<td>None</td>
<td>Yield of 3 diagnostic tests in those pts that had the test (no structured indication for why tests were performed).</td>
<td>Diagnosis in 73 pts (8%). Yield: echo 22%, telemetry 3%, troponin 3%.</td>
</tr>
<tr>
<td>SYSTEMA Fedorowski, et al. 2013 23510366 (60)</td>
<td>Determine role of biomarkers in pts with syncope</td>
<td>Unexplained syncope</td>
<td>Tilt with CSM and biomarker analysis</td>
<td>Levels of C-terminal pro-arginine vasopressin (CT-proAVP), C-terminal endothelin-1 precursor fragment (CT-proET-1), midregional fragments of pro-atrial natriuretic peptide (MR-proANP) and pro-adrenomedullin (MR-proADM)</td>
<td>Biomarkers divided into quartiles, CT-proET-1 and MR-proANP were associated with diagnoses of OH, carotid sinus hypersensitivity and VVS.</td>
</tr>
<tr>
<td>Reed, et al. 2012 22962048 (61)</td>
<td>Assess whether plasma troponin concentration can predict 1 mo and 1 y serious outcome, or all-cause death</td>
<td>Admitted pts with syncope</td>
<td>None</td>
<td>The proportion of pts with a composite serious outcome increased across pts stratified into quintiles based on peak troponin concentration at 1 mo (0%, 9%, 13%, 26%, 70%) and at 1 y (10%, 22%, 26%, 52%, 85%).</td>
<td>Troponin concentrations were above the limit of detection in 261 (77%) pts. Peak troponin concentration was associated with increasing risk of serious outcome and death, which increases with higher troponin concentrations.</td>
</tr>
<tr>
<td>Grossman, et al. 2003 14630890 (62)</td>
<td>Determine role of cardiac enzymes in elderly pts with syncope</td>
<td>Consecutive pts 65 y of age and older with syncope in an urban teaching hospital ED</td>
<td>None</td>
<td>3 of 141 pts, or 2.1% (95% CI: 0.04%–6.09%), had positive cardiac enzymes during their hospitalization (CPK, not TpI study)</td>
<td>Cardiac enzymes may be of little additional value if drawn routinely on elderly pts with syncope</td>
</tr>
</tbody>
</table>
review

Size: n= 319 pts

Pfister, R et al. 2009 18237792 (57)  
Aim: determine NT-pro-BNP values between cardiac and non-cardiac syncope  
Study type: Observational cohort  
Size: n=61 pts

Inclusion criteria: ED syncope
Exclusion criteria: none

Intervention: None

1° endpoint: Pts with cardiac syncope had significantly higher NT-pro-BNP values (514 IQR 286–1154 pg/ml) than pts with non-cardiac cause (182 IQR 70–378 pg/ml, p=0.001). NT-pro-BNP at a cut-off of 164 pg/ml identified pts with cardiac syncope with a sensitivity of 90% and 93.8%, a specificity of 48.8% and 46.7% and a negative predictive value of 91% and 95.5%

Summary: NT-pro-BNP assessment was helpful in differentiating cardiac from non-cardiac syncope

Goble MM et al. 2008 18082784 (63)  
Aim: To evaluate ED management of childhood syncope, focusing on diagnostic tests ordered  
Study type: Retrospective chart review  
Size: n=113 pts

Inclusion criteria: <18 y of age, pediatric ED syncope

Intervention: None

1° endpoint: Most commonly ordered tests in the ED in order of decreasing frequency were electrolytes (90%), ECG (85%), complete blood count (80%), urinalysis, urinary drug screen, or urinary human chorionic gonadotropin 76%, head CT, 58%, and chest x-ray 37%

Summary: Nearly 100% admitted because of automated or non-expert ECG interpretation, weak descriptive study.

Data Supplement 8. Nonrandomized Trials, Observational Studies, and/or Registries of Blood Testing – (Section 3.1)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion</th>
<th>Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanimoto K, et al. 2003 14715356 (64)</td>
<td>Study type: Retrospective observational</td>
<td>Inclusion criteria: Pts with syncope</td>
<td>1° endpoint: To evaluate the feasibility of measuring BNP to identify cardiac syncope.</td>
<td>Summary: Limitations: Retrospective study, and &quot;unknown&quot; causes could be cardiac</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Size: n=118 pts</td>
<td>Exclusion criteria: AF; renal failure; and who died within 24 h after admission</td>
<td>Results:</td>
<td>Conclusions:</td>
<td></td>
</tr>
</tbody>
</table>
● BNP concentrations in the cardiac syncope group (118±42 pg/ml) were significantly higher than those with reflex-mediated, neurologic, or unknown causes of syncope (p<0.01).
● At a cut-off value of 40 pg/ml used to determine a cardiac cause of syncope, the sensitivity and specificity identifying cardiac syncope were 82% and 92%, respectively.

Measurement of BNP concentrations may help confirm cardiac causes of syncope.

Study type: Prospective observational
Size: n=360 pts
Inclusion criteria: Consecutive pts presenting to ED with syncope or near syncope
Exclusion criteria: Persistent altered mental status or illicit drug-related loss of consciousness; seizure; coma; hypoglycemia; transient loss of consciousness caused by head injury; no phlebotomy or troponin
1° endpoint: Diagnostic and predictive value of cTnThs in pts with syncope.

Results:
● Cardiac syncope present in 22% of pts.
● Diagnostic accuracy for cTnThs levels AUC: (0.77; CI:0.72–0.83; p<0.001). Comparable AUC (0.78; CI:0.73–0.83; p<0.001) obtained for predictive value of cTnThs levels within 30 d.

Limitations:
● Post hoc analysis of a single-center trial—not all syncopal pts had troponins. Possible bias in selecting pts for whom treating physicians ordered cTnThs

Conclusions:
● cTnThs levels show a limited diagnostic and predictive accuracy for the identification of pts with syncope at high risk.
<table>
<thead>
<tr>
<th>Year</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
<th>Limitations</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>Retrospective observational</td>
<td>n=128 pts</td>
<td>Adult pts (≥18 y of age) presenting with chief complaint of syncope</td>
<td>Syncope of a known cause, near-syncope or vertigo, clinically obvious seizure, or referred for ECG testing</td>
<td>Frequency echocardiography used in evaluation of pts admitted because of syncope and to examine the diagnostic information, over and above that provided by the initial H&amp;P, and electrocardiography</td>
<td>● Echocardiogram normal for 52% pts ● Echocardiograms of pts with syncope and no clinical evidence of heart disease by H&amp;P, or electrocardiography were normal (63%) or provided no useful additional information for arriving at a diagnosis (37%). ● Among pts for whom cardiac disease was suspected after H&amp;P, or ECG, the echocardiogram confirmed the suspected diagnosis for 48% and ruled out a suspected diagnosis for the remaining 52%. ● H&amp;P, and initial ECG provided sufficient information to permit a diagnosis to be made for 37/48 pts (77%) for whom a cause of syncope was ultimately determined.</td>
<td>● Single-center study; small sample size</td>
<td>For pts without suspected cardiac disease after H&amp;P, and ECG, the echocardiogram did not appear to provide additional useful information, suggesting that syncope alone may not be an indication for echocardiography. For pts with suspected heart disease, echocardiography served to confirm or refute the suspicious in equal proportions.</td>
</tr>
<tr>
<td>2002</td>
<td>Prospective observational</td>
<td>n=650 pts</td>
<td>None specified</td>
<td>None specified</td>
<td>To study the role of echocardiography in the stepwise evaluation of syncope</td>
<td>● Severe AS suspected in 20/61 pts with systolic murmur was suspected in 20 of these, confirmed in 8. ● In pts with unexplained syncope (n=155), echocardiography showed no abnormalities that established cause of the syncope. ● Echocardiography was normal or non-relevant in all pts with a negative cardiac Hx and a normal ECG (n=67). ● In pts with positive cardiac history or an abnormal ECG (n=88), echocardiography showed LVEF ≤40% in 24 (27%) and minor non-relevant findings in remaining 64. ● Arrhythmias were diagnosed in 12/24 pts with</td>
<td>● Relatively small sample size of pts with SUO and/or arrhythmias. ● EPS not performed.</td>
<td>Echocardiography is useful for risk stratification—by measuring LVEF, a predictor of arrhythmias—only in pts with SUO and with a positive cardiac history, or abnormal ECG.</td>
</tr>
<tr>
<td>Study type:</td>
<td>Study type:</td>
<td>Inclusion criteria:</td>
<td>1° endpoint:</td>
<td>Results:</td>
<td>Limitations:</td>
<td>Conclusions:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>-------------</td>
<td>---------------------</td>
<td>-------------</td>
<td>----------</td>
<td>-------------</td>
<td>--------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observational cohort</td>
<td>Observational cohort study</td>
<td>ED visits where any of the 3 pts &quot;reasons for visit&quot; included: fainting (syncope); includes blacking out, passing out, fainting spells; excludes unconsciousness” from the ED portion of the National Hospital Ambulatory Medical Care Survey, 2001–2010</td>
<td>To identify temporal trends in syncope-related ED visits and associated trends in imaging, hospital admissions, and diagnostic frequencies.</td>
<td>Admission rates for syncope pts ranged from 27%–35% and showed no significant downward trend (p=0.1). Advanced imaging rates increased from about 21% to 45% and showed a significant upward trend (p&lt;0.001).</td>
<td>Registry study, potential for residual confounding, miscoding syncope diagnoses</td>
<td>Resource utilization associated with ED visits for syncope appears to have increased, with no apparent improvements in diagnostic yield for admissions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=3,500 pts</td>
<td>n=2106 pts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mendu ML, et al. 2009</td>
<td>Probst MA, et al. 2015</td>
<td>Inclusion criteria: Pts ≥65 y of age admitted to an acute care hospital through ED (2002–2006), with an admission or discharge diagnosis of syncope.</td>
<td>Exclusion criteria: None</td>
<td>To determine the frequency, yield, and costs of tests obtained to evaluate older persons with syncope; to calculate the cost per test yield and determined whether the SFSR improved test yield.</td>
<td>Retrospective diagnosis of database of a single-center, with potential for misclassification of diagnosis by ICD codes</td>
<td>Many unnecessary tests are obtained to evaluate syncope. Selecting tests based on Hx and examination and prioritizing less expensive and higher yield tests would ensure a more informed and cost-effective approach to evaluating older pts with syncope</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25943042 (67)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Data Supplement 10. Nonrandomized Trials, Observational Studies, and/or Registries of Stress Testing – (Section 3.2.2)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woelfel, et al. 1983 6875122 (69)</td>
<td>Study type: Small case series Size: n=3 pts</td>
<td>Inclusion criteria: 1:1 AV conduction at rest developed fixed 2:1 or 3:1 AV block during treadmill exercise testing Exclusion criteria: N/A</td>
<td>1° endpoint: Determine mechanism of high grade block during exertion. Results: ● 3 pts with 1:1 AV conduction at rest developed fixed 2:1 or 3:1 AV block during treadmill exercise testing. EPS documented block distal to the AV node in all 3 pts, and suggested that the exercise-induced block occurred because of increased atrial rate and abnormal refractoriness of the His-Purkinje conduction system. Limitations: ● Small case series Conclusions: ● High grade AV block appearing during exercise reflects conduction disease of the His-Purkinje system rather than of the AV node, even in the absence of BBB. Pts with this diagnosis should be considered for permanent cardiac pacing.</td>
<td></td>
</tr>
<tr>
<td>Kapoor WN, et al. 1983 6866032 (70)</td>
<td>Study type: Prospective cohort Size: n=204 pts</td>
<td>Inclusion criteria: Symptoms &quot;comparable with syncope&quot; Exclusion criteria: Tonic-clonic movements; post-ictal state; aura</td>
<td>1° endpoint: To determine how often a cause of syncope could be established and to define the prognosis of such pts. Results: ● A CV cause was established in 53 pts and a nonCV cause in 54. The cause remained unknown in 97 pts. ● At 12 mo, the overall mortality was 14±2.5%. ● The mortality rate (30±6.7%) in pts with a CV cause of syncope was significantly higher than the rate (12±4.4%) in pts with a nonCV cause (p=0.02) and the rate (6.4±2.8 %) in pts with syncope of unknown origin (p&lt;0.0001). ● The incidence of sudden death was 24±6.6 % in pts with a CV cause, as compared with 4±2.7 % in pts with a nonCV cause (p=0.005) and 3 ±1.8 % in pts with syncope of unknown origin (p=0.0002). Limitations: ● Descriptive study. Conclusions: ● Cause of syncope is frequently not established. Pts with a CV cause have a higher incidence of sudden death than pts with a non-CV or unknown cause (VT and SSS most common).</td>
<td></td>
</tr>
</tbody>
</table>
### Data Supplement 11. RCTs Comparing Cardiac Monitoring – (Section 3.2.3)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krahn, et al. 2001 11435336 (71)</td>
<td>Aim: To compare ILR to conventional monitoring in SUO. <strong>Study type:</strong> RCT, cross-over <strong>Size:</strong> n=60 pts</td>
<td><strong>Inclusion criteria:</strong> Recurrent SUO or a single episode of syncope associated with injury that warranted CV investigation. <strong>Exclusion criteria:</strong> LVEF &lt;35%; unlikely to survive for 1 y; unable to provide follow-up or give informed consent.</td>
<td><strong>Intervention:</strong> ILR with one y of monitoring (n=30). <strong>Comparator:</strong> “Conventional testing” with a 2 to 4 wk period of monitoring with an ELR, followed by tilt table, and EPS (n=30).</td>
<td><strong>1° endpoint:</strong> ● Diagnosis achieved in 14/27 pts randomized to prolonged monitoring compared with 6/30 undergoing conventional testing (52% vs. 20%, p=0.012). ● Prolonged monitoring more likely to result in diagnosis than conventional testing (55% vs. 19%, p=0.0014). ● Bradycardia (sinus and AVB) detected in 14 pts undergoing monitoring compared with 3 pts undergoing conventional testing (40% vs. 8%, p=0.005).</td>
<td><strong>Limitations:</strong> ● Single center study, with possible selection bias due to assessment of older population without structural heart disease (excluding pts with a high pretest probability of neurally mediated syncope or VA). <strong>Conclusions:</strong> ● A prolonged monitoring strategy is more likely to provide a diagnosis than conventional testing in pts with unexplained syncope. ● Bradyarrhythmias are a frequent cause of syncope. <strong>Summary:</strong> ● A strategy of primary monitoring is more cost-effective than conventional testing in establishing a diagnosis in recurrent SUO.</td>
</tr>
<tr>
<td>Krahn AD, et al. 2003 12906979 (72)</td>
<td>Aim: To compare cost-effectiveness of ILR to conventional testing. <strong>Study type:</strong> RCT, crossover <strong>Size:</strong> n=60 pts</td>
<td><strong>Inclusion criteria:</strong> Recurrent SUO or a single episode of syncope associated with injury that warranted CV investigation. <strong>Exclusion criteria:</strong> LVEF &lt;35%; unlikely to survive for 1 y; unable to provide follow-up or give informed consent.</td>
<td><strong>Intervention:</strong> ILR with one y of monitoring (n=30). <strong>Comparator:</strong> “Conventional testing” with a 2 to 4 wk period of monitoring with ELR, followed by tilt table, and EPS (n=30).</td>
<td><strong>1° endpoint:</strong> ● 14/30 pts monitored diagnosed at $2,731±$285/pts, $5,852±$610/diagnosis, compared with 6/30 conventional pts diagnosed (20% vs. 47%, p=0.029), at a $1,683±$505/pts (p&lt;0.001) and $8,414 ±$2,527/diagnosis (p&lt;0.0001).</td>
<td><strong>Limitations:</strong> ● Single center study, with possible selection bias due to assessment of older population without structural heart disease (excluding pts with a high pretest probability of neurally mediated syncope or ventricular arrhythmia). Canadian dollars used. <strong>Summary:</strong> ● A strategy of primary monitoring is more cost-effective than conventional testing in establishing a diagnosis in recurrent SUO.</td>
</tr>
<tr>
<td>Farwell, et al. 2006 16314338 (73)</td>
<td>Aim: To investigate the impact of ILR on pts with recurrent SUO.</td>
<td><strong>Inclusion criteria:</strong> Consecutive pts presenting to single center, ≥16 y of age; acute syncope presentation; ≥2 SUO in 12 mo; no</td>
<td><strong>Intervention:</strong> ILR (n=103) <strong>Comparator:</strong> Conventional (n=98)</td>
<td><strong>1° endpoint:</strong> ● Time to diagnosis: 43% vs. 6% HR: 6.5; 95% CI: 3.7–11.4; p=0.001.</td>
<td><strong>Limitations:</strong> ● Single center, non-blinded trial. <strong>Summary:</strong> ● ILR significantly increases diagnostic</td>
</tr>
</tbody>
</table>
**Study type:** RCT, 18 mo follow-up of previous study which reported 6 mo follow-up did not demonstrate a reduction in syncopal events or an improvement in QoL with ILR.

**Size:** n=201 pts

**Inclusion criteria:** indication for pacing; basic workup including Holter, tilt-table unrevealing.

**Exclusion criteria:** None stated

**2° endpoint:**
- Time to first recurrence: HR: 1.03: (0.67–1.6), p=0.9. Time to second recurrence longer with ILR, p=0.04.
- Improved QoL in ILR group (p=0.03) for general wellbeing.
- Overall mortality was 12%, p=NS.

**Limitations:**
- Highly-specific subset of pts
- Small sample size (unavoidable)
- <3 y of follow-up
- Not designed to test impact of cost

**Summary:**
ILR superior to conventional follow-up in detecting recurrent syncope in pts with isolated syncope, BBB, and negative EPS. Supports early monitoring after first event.

---

**Aim:** To compare ILR and conventional follow-up to estimate prevalence of arrhythmia (pause >5 s, 3rd degree AV block, heart rate <30 bpm for 10 m while awake, >10 beats VT, SVT >165 bpm).

**Study type:** Multicenter RCT

**Size:** n=78 pts (11 right BBB, 34 left BBB, 33 bifascicular)

**Inclusion criteria:**
S/P single syncopal episode with BBB (QRS≥120 ms); negative workup (including EPS).

**Exclusion criteria:**
2° or 3° degree AV block; LVEF ≤35%; poor prognosis (<1 y); inability to follow-up; HV interval ≥70 m; inducible VT/SVT; carotid sinus hypersensitivity; subclavian steal; OH.

**Intervention:**
ILR (n=41)

**Comparator:**
Conventional (n=37) (Outpatient visits every 3 mo for 36 mo, diary, 12-lead ECG, 7 d event recorder)

**1° endpoint:**
- 21/78 developed significant arrhythmia: AV block (14), sick sinus syndrome (4), VT (1), SCD (2).
  - Events detectable in 19 pts, with a statistically significant difference found between the ILR and conventional follow-up groups (36.6% vs. 10.8%; p=0.01).
- 18 pts received pacemakers; 1 received ICD.
- No predictors of AV block identified in the ILR group.
<table>
<thead>
<tr>
<th>Study Acronym;</th>
<th>Study Type/Design;</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results</th>
<th>Summary/Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sivakumaran, et al. 2003</td>
<td><strong>Aim:</strong> To compare diagnostic utility of ELR to Holter in determining arrhythmic cause of syncope.</td>
<td><strong>Inclusion criteria:</strong> SUO: index symptoms of syncope, presyncope, or both, referred for ambulatory ECG monitoring.</td>
<td><strong>Intervention:</strong> Initial 48 H Holter (n=51)</td>
<td><strong>1° endpoint:</strong> 63% ELR vs. 24% Holter had arrhythmia identified or excluded, p&lt;0.0001. Arrhythmia identified as cause of syncope in 1 patient with ELR (p=0.3). Probability of obtaining symptom-rhythm correlation 56% for ELR, 22% for Holter (p&lt;0.00001).</td>
</tr>
<tr>
<td></td>
<td><strong>Study type:</strong> RCT</td>
<td><strong>Exclusion criteria:</strong> None stated</td>
<td><strong>Comparator:</strong> Initial 30 d ELR (n=49)</td>
<td><strong>Limitations:</strong> Non-blinding; pre-enrollment evaluation not standardized. <strong>Conclusions:</strong> ELRs have a much higher diagnostic yield for pts with syncope or presyncope as compared with Holter monitors. Utility of loop recorders is limited by some pts' inability to operate them correctly.</td>
</tr>
<tr>
<td></td>
<td><strong>Size:</strong> n=100 pts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rothman SA, et al. 2007</td>
<td><strong>Aim:</strong> To compare the relative value of a MCOT c/w ELR.</td>
<td><strong>Inclusion criteria:</strong> A high clinical suspicion of a malignant arrhythmia; symptoms of syncope, presyncope, or severe palpitations occurring less frequently than once per 24 H; nondiagnostic 24 H Holter or telemetry monitor within 45 d prior to enrollment.</td>
<td><strong>Intervention:</strong> MCOT (n=134)</td>
<td><strong>1° endpoint:</strong> Diagnosis made in 88% of MCOT pts compared with 75% of ELR pts (p=0.008). MCOT superior in confirming diagnosis of clinically significant arrhythmias 41% vs. 15%, p&lt;0.001.</td>
</tr>
<tr>
<td></td>
<td><strong>Study type:</strong> Multicenter RCT</td>
<td><strong>Exclusion criteria:</strong> NYHA Class IV HF; MI within prior 3 mo; unstable angina; candidate for or recent valvular cardiac surgery; history of sustained VT/VF; frequent PVCs; documented LVEF ≤35%; pts &lt;18 y of age, condition prohibiting completion of or compliance with protocol.</td>
<td><strong>Comparator:</strong> Loop (n=132)</td>
<td><strong>Limitations:</strong> Neither patient nor investigator blinded (although independent strip review). Patient compliance not 100%. <strong>Conclusions:</strong> In diagnosis of pts with symptoms of a cardiac arrhythmia, MCOT provides a significantly higher yield than standard ELR. MCOT superior to ELR for detection of clinically significant arrhythmias, with shorter time to diagnosis.</td>
</tr>
<tr>
<td></td>
<td><strong>Size:</strong> n=266 pts, 17 centers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author; Year Published</td>
<td>Study Size</td>
<td>Study type: Prospective observational</td>
<td>(P values; OR or RR; &amp; 95% CI)</td>
<td>Comment(s)</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------</td>
<td>----------------------------------</td>
<td>-----------------------------</td>
<td>-------------</td>
</tr>
</tbody>
</table>
| Krahn AD, et al. 1995 7671366 (77) | **Study type:** Prospective observational  
**Size:** n=16 pts | **Inclusion criteria:** SUO with resting ECG; ambulatory monitoring; myocardial imaging; and TTT. If noninvasive investigations were negative, EPS performed. ILR implanted with negative EPS.  
**Exclusion criteria:** Pre syncope 1° endpoint: Long-term findings in pts with unexplained syncope and negative laboratory investigations.  
**Results:**  
- 16 pts implanted, and 15 pts (94%) had recurrent syncope 4.4±4.2 mo after implantation.  
- Syncope was secondary to sinus arrest in 5, AV block in 2, VT in 1, SVT in 1, nonarrhythmic in 6.  
- Successful therapy in all 15 pts, without recurrence of syncope during 13.0±8.4 mo of follow-up.  
**Limitations:**  
- Small number of implants, and authors comment on minimal incidence of morbidity and mortality.  
**Conclusions:**  
- ILR useful for establishing a diagnosis when symptoms are recurrent but too infrequent for conventional monitoring techniques. | |
| Krahn AD, et al. 1999 9918528 (78) | **Study type:** Prospective observational  
**Size:** n=85 pts | **Inclusion criteria:** 2 syncopal episodes within the previous 12 mo or a single episode with a Hx of presyncope as well.  
**Exclusion criteria:** Unlikely to survive 1 y; unable to give informed consent; had a previously implanted programmable medical device; were pregnant; or were women of childbearing potential not on a reliable form of contraception 1° endpoint: Determine cause of syncope in pts with SUO and recurrent undiagnosed syncope with an ILR  
**Results:**  
- During a mean of 10.5±4.0 mo of follow-up, symptoms recurred in 58 pts (68%) 71±79 days (2.3±2.6 mo) after ILR insertion.  
- Arrhythmia detected in 42% of pts who recorded a rhythm during recurrent symptoms, with bradycardia present in 18 and tachycardia in 3.  
- 5/18 bradycardic pts and 2 additional sinus rhythm pts received a clinical diagnosis of neurally mediated syncope.  
- Pts who experienced presyncope much less likely to record an arrhythmia during symptoms compared with recurrence of syncope (24% v 70%, p=0.0005).  
**Limitations:**  
- Select population and a small proportion of pts were unable to activate the device after a spontaneous event.  
**Conclusions:**  
- The strategy of prolonged monitoring is effective and safe in pts with SUO. | |
| Moya A, et al. 2001 11551877 (79) | **Study type:** Prospective observational  
**Size:** n=111 pts | **Inclusion criteria:** Syncope, absence of significant structural heart disease, and a normal ECG; tilt-testing was negative in 82 (isolated syncope) and positive in 29 (tilt-positive); ≥3 episodes of syncope in the previous 2 ys 1° endpoint: ILR in pts with isolated syncope and in pts with tilt-positive syncope to obtain further information on the mechanism of syncope and to evaluate the natural Hx of these pts.  
**Results:**  
- Syncope recurred in 28 (34%) and 10 pts (34%), respectively, and ECG correlation was found in 24 (23%) and 8 (28%) pts, respectively.  
**Limitations:**  
- Although documentation of bradynrrhythmia concurrent with a syncopal episode is considered diagnostic, unable to discriminate between an intrinsic cardiogenic abnormality and a neurogenic mechanism.  
**Conclusions:**  
- In most pts, the likely cause was neurally |
<table>
<thead>
<tr>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1st endpoint</th>
<th>Limitations</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective observational</td>
<td>n=52 pts</td>
<td>All pts with any type of BBB with QRS &gt;100 ms, no documentation of 2nd or 3rd degree AV block, and a negative EPS, and SUO</td>
<td>None specified</td>
<td>ILR in pts with BBB and negative EPS to evaluate the natural history of these pts and obtain additional information on the mechanism of syncope.</td>
<td>● The results of the present study cannot be generalized to all syncope pts with BBB but apply only to the minority of those with a negative conventional workup that includes electrophysiological study.</td>
<td>● In pts with BBB and negative EPS, most syncopal recurrences have a homogeneous mechanism that is characterized by prolonged asystolic pauses, mainly attributable to sudden-onset paroxysmal AV block.</td>
</tr>
<tr>
<td>Prospective observational</td>
<td>n=184 pts</td>
<td>184 pts with SUO. EPS: Any of presence of structural heart disease or family Hx of SCD; abnormal ECG; significant nonsymptomatic arrhythmia on Holter monitoring; paroxysmal palpitations immediately before or after syncope. If these pts (defined as Group A) had negative EPS, they underwent TTT. 112 pts with initial TTT were defined as Group B.</td>
<td>None</td>
<td>Diagnostic yield of a protocol in which EPS, TTTs, and ILR are selectively used in SUO.</td>
<td>● Authors feel no ATP testing was a limitation. No follow-up of all pts with ILR to confirm diagnosis.</td>
<td>● In SUO, selective use of EPS or TTT leads to positive diagnosis in &gt;70% of cases. ILR can be useful in non-diagnosed cases.</td>
</tr>
<tr>
<td>Prospective observational</td>
<td>&gt;2 syncopal episodes, or significant physical injury with event</td>
<td>Evaluate relative utility of auto-activate ILR based on an arrhythmia grading system in terms of the likelihood that</td>
<td>None</td>
<td></td>
<td>● Small sample, unclear how generalizable scoring system is.</td>
<td></td>
</tr>
</tbody>
</table>
they provide a diagnostic basis for syncope.

**Results:**
- Of 529 recordings, auto activation accounted for 86.9% of all the documented arrhythmia episodes (194/223 episodes from 30 pts).
- Auto activation provided 90.6% (68 of 75 episodes) of all highly likely diagnoses (i.e., grades 0 and I), and 87.1% of all arrhythmia diagnoses (196 of 225 episodes) (i.e., grades 0 to III).

**Conclusions:**
- Study offers strong support for the value of auto-activation ILR systems, as well as a basis for encouraging further development of arrhythmia scoring.

<table>
<thead>
<tr>
<th>Study type:</th>
<th>Inclusion criteria:</th>
<th>Exclusion criteria:</th>
<th>1st endpoint:</th>
<th>Results:</th>
<th>Limitations:</th>
<th>Conclusions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boersma L, et al. 2004 14697729</td>
<td>SUO, ≥3 episodes of syncope within 6 mo</td>
<td>None</td>
<td>Diagnosis of arrhythmia by ILR</td>
<td>ILR able to record arrhythmic event in 12/43. 10 with bradycardia →, 1 PAF → medication, and polymorphic VT → ICD. 3/12 had normal workup. Others had abnormal HUTT, EPS, echo, ECG, Holter.</td>
<td>Not all had full diagnostic workup 18 mo follow-up somewhat limited. Small sample</td>
<td>ILR is a valuable and effective tool to establish an arrhythmic cause for SUO. The results of HUTT and EPS are neither sufficiently sensitive nor specific enough in this pts group.</td>
</tr>
<tr>
<td>Solano A, et al. 2004 15231369</td>
<td>High-risk syncope: (1) were very frequent, or (2) were recurrent and unpredictable or (3) occurred during the prosecution of a ‘high risk’ activity</td>
<td>Presyncope</td>
<td>ECG diagnosis made by analysis of the ECG tracing obtained during the first syncopal episode that was correctly recorded by the device.</td>
<td>During a median follow-up of 13 mo, syncope recorded in 52 pts. Pts with SHD more frequently had paroxysmal AV block and tachyarrhythmias and pts without SHD more frequently had sinus bradycardia/sinus arrest or no arrhythmia.</td>
<td>Limited to high-risk group</td>
<td>Mechanism of SUO is different in pts with and without SHD, though diagnostic yield and safety are similar in both groups.</td>
</tr>
<tr>
<td>Krahn, et al. 2004 15309004</td>
<td>≥30 y, with LVEF ≥35% and SUO (negative 24 h ambulatory/inpatient monitor, echocardiogram) had ILR</td>
<td>Prespecified arrhythmias: pause &gt;5 seconds; 3rd degree AVB &gt;10 seconds; Heart rate &lt;30 beats/min for &gt;10 seconds while awake</td>
<td>Prespecified arrhythmias: pause &gt;5 seconds; 3rd degree AVB &gt;10 seconds; Heart rate &lt;30 beats/min for &gt;10 seconds while awake.</td>
<td>Population likely to have recurrence and arrhythmias. Asymptomatic arrhythmias considered diagnostic.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>1° endpoint</td>
<td>Conclusions</td>
<td>Limitations</td>
<td>Study type</td>
</tr>
<tr>
<td>-------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>Pierre B, et al. 2008 18325892 (86)</td>
<td>SUO: ≥3 episodes of syncope, normal workup including EPS, CSM</td>
<td>LVEF ≤30–35%, candidates for primary ICD</td>
<td>To determine influence of cardiac conduction abnormalities that turn up on resting ECG and the impact of underlying cardiac disease on developments during follow-up.</td>
<td>● Long-term monitoring of pts with unexplained syncope with automatic arrhythmia detection demonstrated that significant asymptomatic arrhythmias were seen more frequently than anticipated, leading to a change in patient treatment. ● Automatic arrhythmia detection provides incremental diagnostic usefulness in long-term monitoring of pts with syncope.</td>
<td>● Relatively small size with extensive negative workup.</td>
<td>Prospective observational</td>
</tr>
<tr>
<td>Pezawas T, et al. 2008 17947364 (87)</td>
<td>SUO (ISSUE classification) with ≥2 episodes, then ILR implanted</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td>Prospective observational</td>
</tr>
<tr>
<td>Study Type</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>1st Endpoint</td>
<td>Results</td>
<td>Limitations</td>
<td>Conclusions</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>--------------</td>
<td>---------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Edvardsson N, et al. 2011</td>
<td>Recurrent SUO or pre-syncope</td>
<td>None specified</td>
<td>To collect information on the use of ILR in the patient care pathway and to investigate its effectiveness in diagnosis of SUO in everyday clinical practice.</td>
<td>Pts evaluated by an average of 3 different specialists for management of their syncope and underwent a median of 13 tests (range 9–20). The percentages of pts with recurrence of syncope were 19, 26, and 36% after 3, 6, and 12 mo, respectively. Of 218 events within the study, ILR-guided diagnosis was obtained in 170 cases (78%), of which 128 (75%) were cardiac.</td>
<td>12% of implanted pts did not have follow-up visit data. Pts with pre-syncope only were admitted into the registry, and they have been analyzed and reported together with pts with syncope, since the subgroup was small.</td>
<td>A large number of diagnostic tests were undertaken in pts with unexplained syncope without providing conclusive data. In contrast, the ILR revealed or contributed to establishing the mechanism of syncope in the vast majority of pts. The findings support the recommendation in current guidelines that an ILR should be implanted early rather than late in the evaluation of unexplained syncope.</td>
</tr>
<tr>
<td>Linker NJ, et al. 2013</td>
<td>Recurrent SUO or pre-syncope</td>
<td>No evidence of “unexplained syncope,” no follow-up data, ILR implanted for another reason</td>
<td>First recurrence of syncope leading to a diagnosis or for at least 1 y after implant</td>
<td>Initial (8 tests [IQR 6–14]) vs. Full (14 tests [IQR 10–21]), p&lt;0.0001. Hospitalization and injury before implant less common in diagnostic yield of ILR high in both protocols. High number of testing in both protocols may have been mitigated by earlier ILR.</td>
<td>“Unexplained,” “initial workup,” or “full evaluation” not defined in protocol</td>
<td></td>
</tr>
</tbody>
</table>
Palmisano P, et al. 2013 *23701932* (90)

| **Study type:** | observational; 2 center study |
| **Size:** | n=56 pts |
| **Inclusion criteria:** | History of syncope of suspected arrhythmic nature, negative cardiac and neurological workup, who underwent ILR. |
| **Exclusion criteria:** | None |
| **1° endpoint:** | Identify predictive factors for pacemaker implantation in pts receiving an ILR |

**Results:**
- Clinically significant bradyarrhythmia was detected in 11 pts (20%), of which 9 cases related to syncopal relapses: predictive factors: >75 y of age (OR: 29.9; p=0.035); a Hx of trauma secondary to syncope (OR: 26.8; p=0.039); and the detection of periods of asymptomatic bradycardia, performed before ILR implantation (OR: 24.7; p=0.045). |

**Limitations:**
- Non-blinded, clear selection bias |

**Conclusions:**
- An advanced age, a history of trauma secondary to syncope, and the detection of periods of asymptomatic bradycardia during conventional ECG monitoring were independent predictive factors for bradyarrhythmias requiring pacemaker implantation in pts receiving an ILR for unexplained syncope.

Gibson TC, et al. 1984 *6702676* (91)

| **Study type:** | Retrospective observational |
| **Size:** | n=1,512 pts with syncope (of 7,364 total) |
| **Inclusion criteria:** | Pts underwent 24 H Holter monitoring |
| **Exclusion criteria:** | None |
| **1° endpoint:** | Diagnostic yield of Holter for syncope diagnosis |

**Results:**
- 31/1512 (2%) of pts had “arrhythmia-related symptom” that could be diagnostic |
- 15 pts had syncope and 7 of the episodes were related to an arrhythmia, usually VT |
- Presyncope was reported in 241 pts, with a related arrhythmia in 24 |

**Limitations:**
- Large sample (registry), many confounders |
- Percentages likely low due to sample |

**Conclusions:**
- 24 H ambulatory monitoring service rarely results in identifying relevant symptom-related arrhythmias in pts with syncope.

Linzer M, et al. 1990 *2371954* (92)

| **Study type:** | Prospective observational |
| **Size:** | n=57 pts |
| **Inclusion criteria:** | ≥1 episode of SUO |
| **Exclusion criteria:** | Prior EPS |
| **1° endpoint:** | Utility of ELR after indeterminate Holter recording |

**Results:**
- In 14 pts, loop recording definitively determined whether an arrhythmia was cause of symptoms (diagnostic yield 25%; 95% CI: 14–38%). |
- Diagnoses included VT (1 patient), high grade AV block (2 pts), SVT (1 patient), asystole or junctional bradycardia from neurally mediated syncope (3 pts) and normal cardiac rhythms (the remaining 7 pts).

**Limitations:**
- Referral bias, small sample. |

**Conclusions:**
- Early study of external LR, shows utility in SUO.
### Study type: Prospective observational, multicenter
### Size: 392 pts; 282 pts (71.9%) enrolled for palpitations and 110 (28.1%) for syncope.

### Inclusion criteria: Recent (within 1 mo) episode of syncope or sustained palpitations (index event), after being discharged from emergency room or hospitalization without a conclusive diagnosis, and a suspected arrhythmic origin

### Exclusion criteria: None specified

### 1° endpoint: To evaluate the role of external 4 wk ECG monitoring in clinical work-up of unexplained syncope and/or sustained palpitations of suspected arrhythmic origin

### Results: For syncope, the 4 wk diagnostic yield was 24.5%, and predictors of diagnostic events were early start of recording (0–15 vs. >15 days after index event) (OR: 6.2, 95% CI: 1.3–29.6, p=0.021) and previous Hx of supraventricular arrhythmias (OR 3.6, 95% CI:1.4–9.7, p=0.018).

- For palpitations, the 4 wk diagnostic yield was 71.6% and predictors of diagnostic events were Hx of recurrent palpitations (p<0.001) and early start of recording (p=0.001).

### Summary/Conclusion
- The 4 wk external ECG monitoring can be considered as first-line tool in the diagnostic work-up of syncope and palpitation. Early recorder use, history of supraventricular arrhythmia, and frequent previous events increased the likelihood of diagnostic events during the 4 wk external ECG monitoring.
- Diary-reported symptoms/events, true etiology of event unknown (despite documented arrhythmia). Authors note the cumulative diagnostic yield observed may be an overestimation of the true clinical benefit.

---

### Study Acronym; Author; Year Published

- **Benezet-Mazuecos, et al. 2007**
- **17965013 (94)**

### Study type: Prospective cohort study
### Size: n=122 pts

### Inclusion criteria: Presumptive diagnosis of unexplained, likely cardiogenic, syncope.

### Exclusion criteria: Syncope and a documented medical condition actually or potentially responsible for the syncope.

### 1° endpoint: To determine the diagnostic value of cardiac remote telemetry in the setting of unexplained syncope is unknown.

### Results:● There were no deaths during the time of monitoring (4.8±2.7 days). Events requiring transfer to the coronary care units occurred in 15 pts (14.7%), principally due to AV block and extreme bradycardia.

- Cardiac remote telemetry was diagnostic in 18 pts (17.6%) in whom the arrhythmic event occurred simultaneously with the syncopal episode.

- ≥86 y of age (p<0.01) and HF on admission (p<0.04) were the strongest predictors of events.

- The best cut-off point as a threshold for

### Limitations:
- Single center study, and CCU protocols not generalizable.

### Conclusions:
- Cardiac remote telemetry appears to be a useful tool in the management of pts with unexplained syncope, especially in those older and presenting HF on admission.
<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1º endpoint</th>
<th>Limitations</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipskis DJ, et al. 1984 6711429 (95)</td>
<td>Prospective observational</td>
<td>Pts admitted to telemetry</td>
<td>To determine the benefits of telemetry in terms of arrhythmia diagnosis and therapy administered.</td>
<td>Older data, not limited to syncope</td>
</tr>
<tr>
<td>Gibson TC, et al. 1984 6702676 (91)</td>
<td>Retrospective observational</td>
<td>Pts underwent 24 H Holter monitoring</td>
<td>Diagnostic yield of Holter for syncope diagnosis</td>
<td>Large sample (registry), many confounders</td>
</tr>
<tr>
<td>Linzer M, et al. 1990 2371954 (92)</td>
<td>Prospective observational</td>
<td>≥ 1 episode of SUO</td>
<td>Utility of ELR after indeterminate Holter recording</td>
<td>Referral bias, small sample.</td>
</tr>
<tr>
<td>Schuchert A, et al. 2003</td>
<td>Prospective observational</td>
<td>≥ 2 SUO within 6 mo, negative TTT,</td>
<td>Assess diagnostic yield of ELR in pts with</td>
<td>Low sample size, all ELR patient triggered.</td>
</tr>
</tbody>
</table>
negative TTT and recurrent syncope.

**Results:**
- ELR was not useful for arrhythmia detection in pts with syncopal events, no overt heart disease, and a negative tilt table test because the cardiac rhythm was stored in only 1 of 8 (13%) pts with recurrent syncope.

**Conclusions:**
- Reasons for ELR were infrequent syncopal events after baseline evaluation, with rare events during the limited monitoring period in particular, and premature termination or unsuccessful recording in 21% of pts.

---

**Data Supplement 14. Nonrandomized Trials, Observational Studies, and/or Registries of Electrophysiology Testing – (Section 3.2.5)**

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; and 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Linzer M, et al. 1997 *9214258* (97) | Study type: Literature review (population studies, referral studies, or case series) | Inclusion criteria: Published papers were selected if they addressed diagnostic testing in syncope, near syncope, or dizziness | 1st endpoint: To review the literature on diagnostic testing in syncope that remains unexplained after initial clinical assessment. | Limitations:  
- Older data, methods unclear.  
Conclusions:  
- After a thorough H&P, and electrocardiography, the cause of syncope remains undiagnosed in 50% of pts. Stepwise testing may be helpful in elucidating cause of syncope. |
| Lacroix D, et al. 1991 *1950999* (98) | Study type: Prospective cohort | Inclusion criteria: Pts with syncope of unclear etiology who underwent EPS. | 1st endpoint: To compare the results of 24 H monitoring and EPS in the evaluation of pts with recurrent syncope, and additionally to analyze the usefulness of the signal-averaged ECG and of body surface potential mapping in predicting the inducibility of VT. | Limitations:  
- Neurologic and TTT not performed.  
Conclusions:  
- EPS had a higher diagnostic yield than Holter monitoring regardless of cardiac pathology. ECG signal-averaging was useful in predicting VT in pts |
presentation and those with Wolff-Parkinson-White syndrome

- CAD was found in 46 pts and other heart disease was found in 19. EPS was diagnostic in 44 pts, while Holter monitoring suggested a diagnosis in only 21 pts.
- Abnormal body surface potential mapping was frequently seen (56%), especially in CAD (70%), or with inducible VT (87%).
- Late potentials were recorded in 13 pts with CAD; 5 had inducible VT. In 7 other pts with VT, they were either absent or BBB was found.
- Thirteen deaths occurred, and EPS guided therapy resulted in a low rate of total cardiac death.

with CAD without BBB. Body surface potential mapping was abnormal in most pts with cardiac disease, but poorly predicted VT.

<table>
<thead>
<tr>
<th>Study type: Prospective cohort</th>
<th>Inclusion criteria: Syncope/near syncope, symptomatic pts with BBB undergoing EPS</th>
<th>First endpoint: To determine the role of invasive EP testing in pts with symptomatic BBB.</th>
<th>Limitations: Older data, limited and specific population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size: n=112 pts</td>
<td>Exclusion criteria: CV collapse, or requiring resuscitation</td>
<td>Results: Cumulative 4 y survival rate and recurrent syncope, respectively: 83% in 16 pts with no therapy (normal study results); 19% 84% in 34 pts with permanent pacing alone; 6% 63% in 39 pts with antiarrhythmic therapy alone; 33% 84% in 21 pts with both antiarrhythmic therapy; 19%</td>
<td>Conclusions: Severe abnormalities were more frequently detected in our patient population by EP testing than by ambulatory monitoring, especially if pts had organic heart disease.</td>
</tr>
</tbody>
</table>

Click RL, et al. 1987 3825942 (99)

<table>
<thead>
<tr>
<th>Study type: Prospective cohort</th>
<th>Inclusion criteria: 24 H ambulatory ECG monitoring and then EP testing for unexplained syncope.</th>
<th>First endpoint: To assess whether findings on ambulatory monitoring not obtained during syncope can be used to indicate the results which are found on EP testing in pts with recurrent syncope.</th>
<th>Limitations: Not a prospective comparison of ambulatory ECG monitoring and EP testing in all pts with syncope, since pts whose workup stopped after ambulatory ECG monitoring were not enrolled in the study. It is, however, a study of EP results as compared to ambulatory ECG monitoring in pts who do undergo EP testing following non diagnostic ambulatory ECG monitoring -a population frequently encountered in clinical EP laboratories. Thus it biases the results toward the detection of abnormalities by EP tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size: n=59 pts</td>
<td>Exclusion criteria: None specified</td>
<td>Results: Although 29 pts had abnormalities on EP testing, 13 of which were severe, in only 6 were the findings suggested by the abnormalities recorded during ambulatory monitoring. 21 pts had concordance between EP testing and ambulatory monitoring results, but in 15 of the 21 results of both tests were normal.</td>
<td>Conclusions: Severe abnormalities were more frequently detected in our patient population by EP testing than by ambulatory monitoring, especially if pts had organic heart disease.</td>
</tr>
</tbody>
</table>

Reiffel JA, et al. 1985 4072872 (100)
<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
<th>Limitations</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gulamhusein S, et al. 1982 7137203 (101)</td>
<td>Study type: Prospective cohort Size: n=34 pts Inclusion criteria: Unexplained syncope/near syncope who underwent PES Exclusion criteria: None specified.</td>
<td>1° endpoint: To assess the value of clinical EPS using intracardiac recording and PES in 34 pts who had unexplained syncope and/or presyncope.</td>
<td>• EPS diagnostic in 4 pts (11.8 percent) and led to appropriate therapy that totally relieved symptoms. • Results were abnormal but not diagnostic in 2 pts (5.8%) and normal in the remaining 28 pts (82.4%). • Over mean follow up of 15 mo, 16 pts (47%) had no further episodes in the absence of any intervention. In 4 pts (11.8%), a definitive diagnosis was made. In 7 pts, permanent pacing was instituted empirically with relief of syncope.</td>
<td>• Empirical permanent pacing in pts with symptoms appeared to be beneficial, but this result is difficult to evaluate because of the high incidence of spontaneous remission in this group.</td>
<td>• The diagnostic yield of EP testing is low in a patient population that has no ECG abnormality or clinical evidence of cardiac disease.</td>
</tr>
<tr>
<td>Sagrista-Sauleda J, et al. 2001 11350095 (102)</td>
<td>Study type: Retrospective cohort Size: n=600 pts Inclusion criteria: Syncope of unknown etiology who underwent TTT, after H&amp;P, ECG, CSM, Holter monitoring, echocardiogram (in selected pts), exercise stress testing (in selected pts), neurological evaluation. EPS was performed if clinically indicated, mostly in pts with organic heart disease, an intraventricular conduction defect or a suspicion of arrhythmia-related syncope. Exclusion criteria: None specified.</td>
<td>1° endpoint: To assess the diagnostic yield of the head-up tilt test (n=600) and electrophysiology (n=247/600) in pts with syncope of unknown origin established according to simple clinical criteria.</td>
<td>• Positive responses to the tilt test were more common in pts who had suffered their first syncope at an age ≤ 65 y (group I) than in older pts (group II) (47% vs. 33%, p&lt;0.05; OR: 1.8; 95% CI: 1.2–2.78), and in pts with a normal ECG and without organic heart disease than in the other subgroups of pts (47% vs. 37%, p&lt;0.008, OR: 1.6). • The lowest rate of positive response was observed in older pts with an abnormal ECG and organic heart disease. Electrophysiology disclosed abnormal findings in group II more often than in group I (23% vs 7%, p&lt;0.001, OR 3.7, 95% CI: 1.7–9.2). • The diagnostic yield from electrophysiology was higher in pts with an abnormal ECG than in those with a normal ECG (22% vs. 3.7%, p&lt;0.0005, OR: 7.1), and it was especially low in pts with a normal ECG and without organic heart disease (2.6%).</td>
<td>• Retrospective study in very specific population of pts undergoing TTT.</td>
<td>• The diagnostic yield of the TTT and electrophysiology differs in groups of pts with syncope of unknown origin, established according to simple clinical criteria. These findings have a bearing on selecting the most appropriate test in a particular patient.</td>
</tr>
<tr>
<td>Gatzoulis KA, et al. 19419396 (103)</td>
<td>Study type: Prospective cohort Inclusion criteria: Syncope of unknown etiology who had an ECG,</td>
<td>1° endpoint: To assess the utility of noninvasive electrocardiographic evaluation (12-lead ECG and 24 h ambulatory</td>
<td></td>
<td>• Specific population, unclear generalizability.</td>
<td></td>
</tr>
<tr>
<td><strong>Size: n=421 pts</strong></td>
<td>an EPS, and 24 H ambulatory monitoring</td>
<td>Electrocardiographic recordings (ECG) to predict electrophysiology study results in pts with undiagnosed syncope.</td>
<td><strong>Results:</strong> Pts were divided into 4 groups: group 1, abnormal ECG and ambulatory monitor; group 2, abnormal ECG only; group 3, abnormal ambulatory monitor; and group 4, normal ECG and ambulatory monitor. The likelihood of finding at least one abnormality during EP testing among the 4 groups was highest in group 1 (82.2%) and lower in groups 2 and 3 (68.1% and 33.7%, respectively). In group 4, any EPS abnormality was low (9.1%). ORs were 35.9 (p&lt;0.001), 17.8 (p&lt;0.001), and 3.5 (p=0.064) for abnormal findings on EPS, respectively (first 3 groups vs. the 4th one). <strong>Conclusions:</strong> Abnormal ECG findings on noninvasive testing are well correlated with potential brady- or/and tachyarrhythmic causes of syncope, in EPS of pts with undiagnosed syncope.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hess DS, et al. 1982 7148707 (104)</td>
<td><strong>Study type:</strong> Prospective observational</td>
<td><strong>Inclusion criteria:</strong> Syncope of unclear etiology</td>
<td><strong>1° endpoint:</strong> Detection of brady and tachyarrhythmias in EPS to elucidate cause of SUO. <strong>Results:</strong> 18/32 pts had definitive EPS diagnosis; 11 pts with inducible VT 5 pts with SND; 1 patient with infra-His AVB; 1 patient with quinidine-related VT</td>
<td><strong>Limitations:</strong> Small study and most pts had organic heart disease (more inducible VT). Older data, medical therapy changed now. <strong>Conclusions:</strong> The study shows some value in EPS in elucidating cause of syncope, in selected population with SUO.</td>
<td></td>
</tr>
<tr>
<td>Gulamshusein S, et al. 1982 7137203 (101)</td>
<td><strong>Study type:</strong> Prospective observational</td>
<td><strong>Inclusion criteria:</strong> SUO; all undergoing EPS; ≥1 syncopal or ≥2 presyncopal episodes; no cause of syncope on exam; normal ECG and 48 H Holter, normal neurologic testing (including EEG and CT-head); normal echo and CXR</td>
<td><strong>1° endpoint:</strong> Assess diagnostic yield of EPS in SUO. <strong>Results:</strong> EPS diagnostic in 4 pts and led to therapy. During mean 15 mo f/u, 16 pts had no further episodes in absence of any intervention</td>
<td><strong>Limitations:</strong> EPS less diagnostic than predicted: some pts required pacing despite normal or nondiagnostic EPS. <strong>Conclusions:</strong> Diagnostic yield of EPS testing is low in a patient population that has no ECG abnormality or clinical evidence of cardiac disease.</td>
<td></td>
</tr>
<tr>
<td>Akhtar M, et al.</td>
<td><strong>Study type:</strong></td>
<td><strong>Inclusion criteria:</strong></td>
<td><strong>1° endpoint:</strong></td>
<td><strong>Limitations:</strong></td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>Study Type</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>Results</td>
<td>Limitations</td>
</tr>
<tr>
<td>------</td>
<td>------------</td>
<td>--------------------</td>
<td>-------------------</td>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>1983</td>
<td>Prospective observational</td>
<td>SUO (≥ 2 episodes in preceding y); negative evaluation</td>
<td>None specified</td>
<td>To assess results of EPS with PES in pts with recurrent syncope</td>
<td>All pts received EPS, high risk group.</td>
</tr>
<tr>
<td>1984</td>
<td>Prospective observational</td>
<td>SUO undergoing EPS</td>
<td>2nd or 3rd degree AV block; symptomatic SVT; VT; evidence of SND; carotid sinus hypersensitivity; or a history consistent with classic vasovagal or vasodepressor syncope</td>
<td>1st endpoint: Diagnostic yield of EPS with PES in pts with SUO</td>
<td>• In treated pts who did not have recurrence of syncope, it is presumed that syncope did not recur because the cause of syncope was correctly identified and effectively treated.</td>
</tr>
<tr>
<td>1985</td>
<td>Prospective observational</td>
<td>SUO undergoing EPS</td>
<td></td>
<td>Results:</td>
<td>Limitations:</td>
</tr>
<tr>
<td>Doherty JU, et al.</td>
<td>1985</td>
<td>Study type: Prospective observational</td>
<td>Inclusion criteria: SUO undergoing EPS</td>
<td>Exclusion criteria:</td>
<td>Results:</td>
</tr>
</tbody>
</table>
| Study | Size: n=119 pts | Known cause of syncope | **Conclusions:**  
● Presence of structural heart disease (p=0.0033) and previous MI (p=0.05) were the only clinical or ECG predictors of a positive EPS.  
● Therapy guided by EPS and pts followed for 27±20 mo. In pts with negative EPS results, 76%±11% symptom free at follow-up, compared to 68%±10% in positive EPS group.  
● No clinical variables helped to predict remission in absence of therapy.  
● One patient in negative EPS response group and 2 pts in EPS positive group died suddenly.  
● Total CV mortality 13% in positive EPS response group, and 4% in negative EPS response group. |
|-------|----------------|-----------------------|--------------------------------------------------|
| Olshansky B, et al. 1985  
3968306 (108) | **Study type:** Prospective observational  
**Size:** n=105 pts | **Inclusion criteria:** SUO undergoing EPS  
**Exclusion criteria:** None specified | **Limitations:**  
● Small number lost to follow up  
● Does not factor in that some pts have remission spontaneously  
● Nontrivial number of pts receiving ineffective therapy had high percentage of recurrence. |
| **1° endpoint:**  
To determine the significance of inducible tachycardia in SUO | **Results:**  
● 65% did not have inducible tachycardia. 12/60 pts followed had recurrent syncope.  
● VT or SVT inducible in 35%, and inducible tachycardia common in pts both with and without heart disease.  
● 7/13 pts receiving ineffective therapy had recurrence of syncope or cardiac arrest (p<0.05).  
● On resumption of effective therapy, no syncope recurred for 15.6 mo (p<0.025). |
| **Conclusions:**  
● Inducible tachycardias found in approximately 30% of pts with SUO, common in pts both with and without heart disease.  
● Adherence to AAD therapy guided by EPS may prevent recurrence. |
| Teichman SL, et al. 1985  
4025122 (109) | **Study type:** Prospective observational  
**Size:** n=150 pts | **Inclusion criteria:** SUO undergoing EPS  
**Exclusion criteria:** None specified | **Limitations:**  
● Observational data, limited sample, no control. |
| **1° endpoint:**  
Diagnostic yield and therapeutic efficacy of EPS in pts with SUO | **Results:**  
● 162 abnormal EPS findings that could explain SUO in 112 pts  
● His-Purkinje disease in 49 pts (30%), inducible ventricular arrhythmias in 36 (22%), AVB in 20 (12%), SND in 19 (12%), inducible supraventricular arrhythmias in 18 (11%), carotid sinus hypersensitivity in 15 (9%), and hypervagotonia in 5 (3%).  
● Follow up data in 137 pts (91%) (mean 31 mo) showed recurrences in 16/34 pts (47%) without and 15/103 pts (15%) with EP findings despite therapy directed by EPS (p<0.0005). |
| **Conclusions:**  
● This study and a review of the literature indicate that EPS useful in elucidating causes of SUO and directing therapy  
● A significant number of pts benefit from EPS, even when only clearly abnormal findings are considered diagnostic, when only a single syncopal event has occurred, or whether or not organic heart disease or an abnormal ECG is present. |
<table>
<thead>
<tr>
<th>Study type</th>
<th>Prospective observational</th>
<th>Size: n=104 pts</th>
<th>≥1 SUO episode</th>
<th>To evaluate whether clinical variables enable stratification of pts with SUO into low and high probability of having abnormal EPS (SNRT ≥3 seconds; HV interval ≥100 ms; infranodal block during atrial pacing; monomorphic VT; and SVT associated with hypotension)</th>
<th>• No episodes of syncope with ECG recorded.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>Sustained VT; high grade AV block; CSH; vasovagal/vasodepressor syncope; QT prolongation; AS; HCM; symptomatic postural hypotension; brady/tachyarrhythmia known to cause syncope</td>
<td>Results:</td>
<td>• 31 pts had positive EPS, inducible VT most common finding (71% of positive studies).</td>
<td>• On the basis of clinical variables, majority of pts with SUO can be predicted to have normal or abnormal EPS. This may lead to cost-effective use of EPS.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td></td>
<td></td>
<td>• LVEF ≤40% most powerful predictor of a positive EPS (p&lt;0.00001), followed by the presence of BBB (p&lt;0.00003), CAD (p&lt;0.0003), remote MI (p&lt;0.00006), use of type 1 AAD (p&lt;0.00003), injury related to LOC (p&lt;0.01) and male sex (p&lt;0.01).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1° endpoint:</td>
<td></td>
<td></td>
<td>• A negative EPS associated with LVEF &gt;40% (p&lt;0.00001), absence of structural heart disease (p&lt;0.00001), normal ECG (p&lt;0.0001) and normal ambulatory ECG monitoring (p&lt;0.0001).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limitations:</td>
<td></td>
<td></td>
<td>• Probability of a negative study increased as number and duration of syncopal episodes increased.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fujimura O, et al. 1989</td>
<td>2594030 (111)</td>
<td>Study type:</td>
<td>Prospective observational</td>
<td>Inclusion criteria: ECG evidence of intermittent AV block (n=13) or sinus pauses (n=8) causing syncope, but whose cardiac rhythm had reverted to normal by the time of referral</td>
<td>Conclusions:</td>
</tr>
<tr>
<td>Size: n=21 pts</td>
<td></td>
<td></td>
<td>Exclusion criteria: None specified</td>
<td>Sensitivity of EPS in detection of transient bradycardia in pts in normal sinus rhythm referred for pacemaker implantation after ECG documentation of transient bradycardia resulting in syncpe.</td>
<td>• Negative EPS in a patient with a normal cardiac rhythm who has experienced syncope does not exclude a transient bradyarrhythmia as a cause of the syncpe.</td>
</tr>
<tr>
<td>1° endpoint:</td>
<td></td>
<td></td>
<td>Results:</td>
<td>Limitations:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 3/8 with documented sinus pauses had abnormal EPS including a prolonged SNRT in 1 and carotid-sinus hypersensitivity in 2 pts.</td>
<td>• Small study limited to pts with transient ECG findings.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 3/8 pts had abnormalities unrelated to syncope.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 2/13 with documented AVB had abnormalities suggesting correct diagnosis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limitations:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moazzez F, et al. 1991</td>
<td>1985382 (26)</td>
<td>Study type:</td>
<td>Prospective observational</td>
<td>Inclusion criteria: SUO undergoing EPS with BBB, unknown data on LVEF or SAECG</td>
<td>Conclusions:</td>
</tr>
<tr>
<td>Size: n=91 pts</td>
<td></td>
<td></td>
<td>Exclusion criteria:</td>
<td>To examine usefulness of clinical and noninvasive variables to predict EPS, and to compare EPS results and therapy with syncope recurrence</td>
<td>• Pts who have inducible sustained monomorphic VT at EPS can be identified using certain clinical and noninvasive variables.</td>
</tr>
<tr>
<td>1° endpoint:</td>
<td></td>
<td></td>
<td>Results:</td>
<td>Limitations:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Multivariate analysis identified +SAECG, LVEF, and history of sustained monomorphic VT as risk factors for induction of</td>
<td>• BBB pts excluded.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Limitations:</td>
<td>• No TTT or isoproterenol infusion performed.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Muller T, et al. 1991      | SUO undergoing EPS, and HUTT if negative.| To determine the clinical characteristics of subgroups of pts with SUO having EPS and HUTT and to assess efficacy of various therapies. | ● 34% had abnormal EPS, with sustained monomorphic VT induced in 72%, with 76% of these pts with structural heart disease.  
● 40% had syncope provoked by HUTT, with 6% of these pts with structural heart disease.  
● The cause of syncope remained unexplained in 26%, with 30% of these pts with structural heart disease.  
● During a median follow-up period of 18.5 mo, syncope recurred in 9 (10%) pts. | ● Small sample, moderate follow-up |
| Denniss AR, et al. 1992    | SUO undergoing EPS                      | Compare incidence of EPS abnormalities in pts with and without heart disease, and the effect of treatment of these abnormalities on recurrence of syncope. | ● Conduction abnormalities and tachyarrhythmia could account for syncope in 40 pts (30%).  
● 37/40 received pacing or antiarrhythmic therapy c/w 23/94 who had a negative study and received empiric therapy (p<0.0001).  
● During a mean follow-up of 22±17 mo, 22 pts had recurrent syncope and 4 died suddenly  
● Men had a higher incidence of recurrent syncope than women (26% vs. 6%, P<0.005). | ● Failure to demonstrate mortality reduction may be due to high-risk group, refractory to treatment.  
● Syncope pts with heart disease more likely to have a |
| Sra JS, et al. 1991        | SUO undergoing EPS                      | To determine the clinical characteristics of subgroups of pts with SUO having EPS and HUTT and to assess efficacy of various therapies. | ● 34% had abnormal EPS, with sustained monomorphic VT induced in 72%, with 76% of these pts with structural heart disease.  
● 40% had syncope provoked by HUTT, with 6% of these pts with structural heart disease.  
● The cause of syncope remained unexplained in 26%, with 30% of these pts with structural heart disease.  
● During a median follow-up period of 18.5 mo, syncope recurred in 9 (10%) pts. | ● Retrospective evaluation  
● The combination of EPS and HUTT can identify the underlying cause of syncope in as many as 74% of pts presenting with SUO.  
● The combination of EPS and HUTT can identify the underlying cause of syncope in as many as 74% of pts presenting with SUO. |
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1º endpoint</th>
<th>Results</th>
<th>Limitations</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Link MS, et al.</td>
<td>1999</td>
<td>Retrospective observational</td>
<td>n=68 pts</td>
<td>Syncope or presyncope and CAD, with unclear etiology</td>
<td>Sudden cardiac death; spontaneous sustained VT; noninvasive testing explained syncope</td>
<td>Long-term outcome of pts with CAD and non-diagnostic work-up, including EPS</td>
<td>Abnormalities detected in 31/73 with heart disease but in only 6/38 with no heart disease (p&lt;0.01). During follow-up, syncope recurred in 2/37 treated because of abnormal findings, compared with a recurrence rate of 18/74 in untreated group (p&lt;0.05). Probability of remaining free from syncope at 2 y was 0.94 in the treated group and 0.72 in the untreated group (p&lt;0.05). Mortality during follow-up was only in heart disease group with 5/30 treated dying compared with 3/43 untreated pts (p=NS). Treatment directed at correction of abnormalities detected at EPS reduced recurrence of syncope but did not significantly affect mortality.</td>
<td>Retrospective, HV ≥90 ms excluded.</td>
<td></td>
</tr>
<tr>
<td>Knight BP, et al.</td>
<td>1999</td>
<td>Prospective observational</td>
<td>n=33 pts</td>
<td>&quot;Syncope Group&quot;: NICM, SUO, and negative EPS who underwent ICD (n=14); &quot;Arrest Group&quot;: NICM with cardiac arrest and ICD (n=33)</td>
<td>None specified.</td>
<td>Determine outcome of pts with NICM, negative EPS, and SUO treated with ICD</td>
<td>50% in Syncope Group vs. 42% in Arrest Group received appropriate shocks (p=0.1). Mean duration from device implant to first appropriate shock in Syncope Group 32±7 mo (95% CI: 18–45) compared to 72±12 mo (95% CI: 48–96, p=0.1).</td>
<td>Small size, unclear “appropriate” shocks in devices without stored EGM.</td>
<td></td>
</tr>
<tr>
<td>Sagristà-Sauleda J, et al.</td>
<td>2001</td>
<td>Observational cohort</td>
<td>n=600 pts</td>
<td>Group I: first syncope at age ≤65 y (n=464 pts) Group II: first syncope at age &gt;65 y (n=136 pts) 4 subgroups in both:</td>
<td>To assess diagnostic yield of TTT and EPS in different groups of pts with SUO established according to simple clinical criteria.</td>
<td>Positive TTT-more common in (group I) than group II (47% vs.</td>
<td>Retrospective, and only TTT pts studied. EPS done at physician discretion.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
A: pts who no organic heart disease and a normal ECG (n=359 pts)
B: pts with no organic heart disease (n=122 pts) and an abnormal ECG;
C: pts with organic heart disease and a normal ECG (n=44 pts)
D: pts with organic heart disease and an abnormal ECG (n=75 pts)

Exclusion criteria:
None specified

33%, p<0.05; OR: 1.8, 95% CI: 1.2–2.78), and subgroup A (49% vs. 37%, p<0.008, OR:1.6).

- EPS disclosed abnormal findings in group II more than in group I (23% vs. 7%; p<0.001, OR: 3.7; CI: 1.7–9.2).
- Diagnostic yield from EPS was higher in pts with an abnormal ECG (subgroups B and D) than in those with a normal ECG (22% vs. 3.7%, p<0.0005, OR: 7.1), and it was low in pts with a normal ECG and without organic heart disease (2.6%).

- EPS disclosed abnormal findings in group II more than in group I (23% vs. 7%; p<0.001, OR: 3.7; CI: 1.7–9.2).
- Diagnostic yield from EPS was higher in pts with an abnormal ECG (subgroups B and D) than in those with a normal ECG (22% vs. 3.7%, p<0.0005, OR: 7.1), and it was low in pts with a normal ECG and without organic heart disease (2.6%).

Mittal S, et al. 2001 11499726 (117)

- Study type: Prospective observational
- Size: n=118 pts

Inclusion criteria:
CAD and unexplained syncope who underwent EPS

Exclusion criteria:
Pts with a documented sustained ventricular arrhythmia or those resuscitated from sudden cardiac death.

1° endpoint:
To determine the incidence and prognostic significance of inducible VF in pts with CAD and unexplained syncope.

Results:
- Sustained monomorphic VT was inducible in 53 (45%) pts; in 20 (17%) pts, VF was the only inducible arrhythmia; and no sustained ventricular arrhythmia was inducible in the remaining 45 (38%) pts.
- There were 16 deaths among during a follow-up period of 25.3±19.6 mo. The overall one and 2 y survival in these pts was 89% and 81%, respectively.
- No significant difference in survival was observed between pts with and without inducible VF.

Limitations:
- All pts had CAD (limited generalizability)
- VF rarely induced with 2 extrastimuli
- Small sample size

Conclusions:
- Induction of VF in pts with CAD and unexplained syncope may be of limited prognostic significance. VF was the only inducible ventricular arrhythmia at EP testing (using up to triple ventricular extrastimuli) in 17% of these pts. ICD implantation in pts with syncope of undetermined origin in whom only sustained VF is induced during EP testing, especially with triple ventricular extrastimuli, may merit reconsideration.

Data Supplement 15. Nonrandomized Trials, Observational Studies, and/or Registries of Tilt Table Testing – (Section 3.2.6.)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; and 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
<th>Limitations</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenny RA, et al. 1986 2872472 (118)</td>
<td>Case-control</td>
<td>n=25 pts (15 test, 10 control)</td>
<td>Syncope of unclear etiology</td>
<td>To investigate the utility of syncope that remained unexplained despite full clinical and electrophysiological assessment.</td>
<td>• In 10 pts and one control VVS developed after 29±19 min (p&lt;0.001). In symptomatic pts SBP fell from 150 ± 32 to 56 ± 9 mm Hg (p&lt;0.001) and heart rate from 62 ± 9 to 38 ± 12 bpm (p&lt;0.01). In each case symptoms during the test reproduced those previously experienced. No clinical findings predicted development of syncope during tilt. Baseline SBP and heart rate did not differ significantly between pts and controls. Pacemakers were implanted in 7 pts who have remained symptom free since implant (follow-up 10 ± 3 mo).</td>
<td>• Small sample, all with EPS</td>
<td>• Reproduction of symptoms during tilt allows identification of the contribution to syncope made by changes in heart rate and BP and therefore permits the selection of pts in whom cardiac pacing may be beneficial.</td>
</tr>
<tr>
<td>Fitzpatrick A, et al. 1991 2040321 (119)</td>
<td>Retrospective cohort</td>
<td>n=322 pts</td>
<td>Recurrent syncope</td>
<td>To utilize TTT to discover the incidence of malignant VVS in pts with recurrent syncope.</td>
<td>• Prolonged 60 degrees head-up tilt was performed in 71/93 pts with unexplained syncope, and reproduced VVS and presenting symptoms in 53 (75%), or 16% of the whole population reported. • Positive tilts were significantly less common in a group of 27 pts of similar age without a Hx of syncope (7%), and a random sample of 37 pts with AVB (n=16), sick sinus syndrome (n=18) and inducible tachyarrhythmia (n=3), (19%, 11% and 0% respectively, p&lt;0.01).</td>
<td>• All pts underwent EPS, with a large percentage (70%) of abnormal findings (limited generalizability).</td>
<td>• TTT is a valuable provocative tool for VVS and may reduce the number of syncopal pts that remain undiagnosed, although these early observations do not allow an exact appraisal of the sensitivity and specificity of the TTT.</td>
</tr>
<tr>
<td>Passman R, et al. 2003 12963568 (120)</td>
<td>Retrospective cohort</td>
<td>n=694 pts</td>
<td>Pts with syncope</td>
<td>To assess the prevalence and type of apparent neurologic events associated with tilt table testing.</td>
<td>• 222/694 with positive TTT. 18 pts (8%) had neurologic events during TTT. 11 pts (5%) had apparent tonic-clonic seizure-like activity and 7 pts (3%) had non-tonic-clonic neurologic events. • The pts with tonic-clonic seizure-like activity had a significantly lower SBP reading at the termination of tilt table testing than all other pts whose TTT results were positive (p=0.04). • The heart rate at the time of test termination was significantly lower in the pts with tonic-clonic seizure-like activity and non-tonic-clonic</td>
<td>• The retrospective nature of this study may have resulted in inadequate documentation of all potential seizure-like or atypical neurologic events at the time of TTT</td>
<td>• Neurologic events are common during episodes of neurocardiogenic syncope, and this diagnosis should be considered in the evaluation of unexplained seizure-like activity.</td>
</tr>
<tr>
<td>Study type</td>
<td>Size</td>
<td>Inclusion criteria</td>
<td>1st endpoint</td>
<td>Results</td>
<td>Limitations</td>
<td>Conclusions</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>------</td>
<td>-------------------</td>
<td>--------------</td>
<td>---------</td>
<td>-------------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>Grubb BP, et al. 1991 1952474 (121)</td>
<td>Prospective cohort</td>
<td>Recurrent unexplained seizure-like episodes, unresponsive to antiseizure medication.</td>
<td>To evaluate the usefulness of head-upright TTT in the differential diagnosis of convulsive syncope from epileptic seizures in pts with recurrent idiopathic seizure-like episodes.</td>
<td>Syncope associated with tonic-clonic seizure-like activity occurred in 6/15 (40%) during the baseline tilt and in 4/15 during isoproterenol infusion (total positive tests, 67%). The EEG showed diffuse brain wave slowing (not typical of epileptic seizures) in 5/5 pts during the convulsive episode. All pts who had positive test results eventually become tilt table negative after therapy, and over a mean follow-up period of 21 ± 2 mo, no further seizure-like episodes have occurred.</td>
<td>Small sample, single center study</td>
<td>Upright TTT combined with isoproterenol infusion may be useful to distinguish convulsive syncope from epileptic seizures</td>
<td></td>
</tr>
<tr>
<td>Song PS, et al. 2010 20046517 (122)</td>
<td>Retrospective cohort</td>
<td>Syncope during HUTT without any other cause of syncope</td>
<td>To assess the incidence and characteristics of seizure-like activities during HUTT-induced syncope in pts with neurally mediated reflex syncope.</td>
<td>13/226 pts showed seizure-like activities, with 5/226 having multifocal myoclonic jerky movements, 5/226 (2.21%) having focal seizure-like activity involving one extremity, and 3/226 having upward deviation of eye ball. Comparison of pts with and without seizure-like activities revealed no significant differences in terms of clinical variables and hemodynamic parameters during HUTT.</td>
<td>Retrospective in design. Of 1,383 pts with positive HUTT, 1,157 pts were excluded from the study because they did not lose consciousness during HUTT.</td>
<td>Seizure-like activities occurred occasionally during HUTT-induced syncope in pts with neurally mediated reflex syncope. The seizure-like activities during HUTT might not be related to the severity of the syncopal episodes or hemodynamic changes during HUTT.</td>
<td></td>
</tr>
<tr>
<td>Zaidi A, et al. 2000 10898432 (123)</td>
<td>Prospective cohort</td>
<td>Diagnosis of epilepsy, with continued attacks despite adequate anticonvulsant drug treatment (n=36 pts) or uncertainty about the</td>
<td>To investigate the value of CV tests to diagnose convulsive syncope in pts with apparent treatment-resistant epilepsy.</td>
<td>An alternative diagnosis was found in 31 pts (41.9%), including 13 (36.1%) of 36 pts taking an anticonvulsant medication.</td>
<td>Small sample, single center; highly unique population</td>
<td>A simple, noninvasive CV evaluation may identify an alternative diagnosis in many pts with</td>
<td></td>
</tr>
</tbody>
</table>
### Diagnosis of Epilepsy

**Inclusion criteria:** Recurrent seizure-like episodes and a clinical diagnosis of nonepileptic attack disorder.

**Exclusion criteria:** None

**1° endpoint:** To assess the value of HUTT as a provocative test for non-epileptic attack disorder

**Results:**
- 19 pts (25.7%) developed profound hypotension or bradycardia during the HUTT, confirming the diagnosis of VVS.
- 1 pt had a typical vasovagal reaction during intravenous cannulation. 2 pts developed psychogenic symptoms during the HUTT. 7 pts had significant ECG pauses during CSM. In 2 pts, episodes of prolonged bradycardia correlated precisely with seizures according to the insertable ECG recorder.

**Limitations:**
- Small sample, select population.

**Conclusions:**
- HUTT with suggestion is a safe, well tolerated, sensitive, provocative EEG test for dissociative seizure-like attacks and should be considered in pts with suspected non-epileptic attack disorder.

---

### Psychogenic Nonepileptic Attack Disorder

**Study type:** Prospective cohort

**Size:** n=21 pts

**Inclusion criteria:** Episodes of apparent TLOC during tilt-table testing without EEG changes and without decreases in heart rate

**1° endpoint:** To provide a detailed semiology to aid the clinical recognition of psychogenic pseudosyncope which concerns episodes of apparent TLOC that mimic syncope.

**Results:**

- Referral bias.
- A clinical suspicion of PNES was not a formal exclusion criterion for tilt-table testing, but referral selection will have excluded the majority of these pts nonetheless. This may have...

---

### Syncope

**Study type:** Retrospective cohort

**Size:** n=986 pts

**Inclusion criteria:** Unexplained syncope

**Exclusion criteria:** None

**1° endpoint:** To assess the ability of HUTT in recognizing a psychiatric disorder in some pts affected by unexplained syncope.

**Results:**
- In 266 pts the test induced bradycardia and/or hypotension resulting in syncope or presyncope, allowing a diagnosis of neurally mediated syncope.
- In 3 other pts (0.3% of the entire population and 1% of the all positive tests) HUTT provoked LOC despite no significant change in heart rate and/or BP. In all 3 cases unconsciousness was prolonged and no pathological finding was present except lack of response. This phenomenon has been defined as ‘pseudosyncope’ and related to psychiatric illness

**Limitations:**
- Retrospective design, limited number of pts with pseudosyncope, lack of followup.

**Conclusions:**
- HUTT may contribute to the recognition of psychiatric disorder in some pts affected by unexplained syncope.

---

### Blackouts

**Study type:** Prospective cohort

**Size:** n=21 pts

**Inclusion criteria:** Recurrent seizure-like episodes and a clinical diagnosis of nonepileptic attack disorder.

**Exclusion criteria:** Suspected psychogenic nonepileptic attack disorder

**1° endpoint:** To assess the value of HUTT as a provocative test for non-epileptic attack disorder

**Results:**
- 19 pts (25.7%) developed profound hypotension or bradycardia during the HUTT, confirming the diagnosis of VVS.
- 1 pt had a typical vasovagal reaction during intravenous cannulation. 2 pts developed psychogenic symptoms during the HUTT. 7 pts had significant ECG pauses during CSM. In 2 pts, episodes of prolonged bradycardia correlated precisely with seizures according to the insertable ECG recorder.

**Limitations:**
- Small sample, select population.

**Conclusions:**
- HUTT with suggestion is a safe, well tolerated, sensitive, provocative EEG test for dissociative seizure-like attacks and should be considered in pts with suspected non-epileptic attack disorder.
or BP. The event had to be recognized by the patient or a relative (present during the test) as typical of the patient's episodes.

**Exclusion criteria:** None specified.

- Of 800 tilt-table tests, 43 (5.4%) resulted in psychogenic pseudosyncope.
- The median duration of apparent TLOC was longer in psychogenic pseudosyncope (44 s) than in VVS (20 s, p<0.05). During the event, the eyes were closed in 97% in psychogenic pseudosyncope but in only 7% in VVS (p<0.0001).
- A sudden head drop or moving down the tilt table was more common in psychogenic pseudosyncope than in VVS (p<0.01), but jerking movements occurred more frequently in VVS (p<0.0001).
- In psychogenic pseudosyncope, both heart rate and BP increased before and during apparent TLOC (p<0.0001).

**Conclusions:**
- Psychogenic pseudosyncope is clinically distinct from VVS and can be diagnosed accurately with tilt-table testing and simultaneous EEG monitoring.

| Moya A, et al. 1995 | **Study type:** Randomized double-blind crossover study | **Inclusion criteria:** Syncope and a baseline positive HUTT. | **1º endpoint:** To assess the efficacy of oral etilefrine in preventing a positive response to HUTT. | **Results:**
| 7798528 (127) | **Size:** n=30 pts | **Exclusion criteria:** Previous hypertension and 11 (11%) because of a cardioinhibitory response to HUTT. | **Limitations:**
|  | **Endpoint:** | **Results:**
|  |  | HUTT results were negative in 13 (43%) pts with etilefrine and 15 (50%) with placebo (p=NS). The rate of positive responses decreased with repeated testing irrespective of the assigned treatment
|  |  | A positive response was obtained during the second HUTT in 20 pts (10 with placebo, 10 with etilefrine) but in only 12 during the third (7 with etilefrine, 5 with placebo) (p<0.05)
|  |  | In the intravenous phase, complete crossover was achieved in 15 pts. HUTT results during this phase were positive in 13 pts (87%) receiving placebo and in 12 pts (80%) receiving disopyramide (p=0.50, 95% CI: -19%–32%) and were positive in all pts receiving their initially randomized drug or placebo.
|  |  | In the oral phase, HUTT results were positive in only 2 pts (18%)
|  |  | ● Only pts who had a positive response were crossed over to alternative therapy.
|  |  | **Conclusions:**
|  |  | ● Intravenous disopyramide was ineffective for the prevention of neurally mediated syncope provoked by HUTT. No significant effect was observed after oral therapy with disopyramide.

| Morillo CA, et al. 1993 | **Study type:** Double-blind randomized trial | **Inclusion criteria:** Recurrent neurally mediated syncope and 2 or more successive positive HUTT responses | **1º endpoint:** To determine the efficacy of intravenous and oral disopyramide phosphate in preventing neurally mediated syncope induced by a HUTT. | **Results:**
| 8245337 (128) | **Size:** n=22 pts, randomly allocated to receive either intravenous disopyramide or placebo | **Exclusion criteria:** Failure to produce syncope or presyncope during testing | **Limitations:**
|  |  | HUTT results were positive for syncope in 12 (75%) of 16 pts receiving intravenous placebo and in 12 (60%) of 20 pts receiving disopyramide (p=0.55, 95% CI: -14%–40%).
|  |  | In the intravenous phase, complete crossover was achieved in 15 pts. HUTT results during this phase were positive in 13 pts (87%) receiving placebo and in 12 pts (80%) receiving disopyramide (p=0.50, 95% CI: -19%–32%) and were positive in all pts receiving their initially randomized drug or placebo.
|  |  | In the oral phase, HUTT results were positive in only 2 pts (18%)
<table>
<thead>
<tr>
<th>Study</th>
<th>Aims</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
<th>Limitations</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibbons, et al. 2006 16832073 (129)</td>
<td>To investigate the prevalence, symptoms, and neurophysiologic features of delayed OH</td>
<td>OH or delayed during a 60° head-up tilt performed for 45 min</td>
<td>None specified</td>
<td>OH or delayed OH</td>
<td>Of 108 pts with OH, 46% had OH within 3 min of HUTT; 15% had OH between 3 and 10 min; and 39% had OH after 10 min of HUTT. Delayed OH was associated with mild sympathetic adrenergic dysfunction evident of autonomic testing</td>
<td>Laboratory study, Referral population</td>
<td>Delayed OH occurred in 54% of tested population. TTT duration should be extended. Underlying mechanism possibly early or mild sympathetic adrenergic failure.</td>
</tr>
<tr>
<td>Podoleanu, et al. 2009 19669396 (130)</td>
<td>To investigated the hemodynamic mechanisms that underlie delayed OH</td>
<td>Pts with delayed OH and (1) symptoms and signs of orthostatic intolerance after 3 mins; and (2) documentation of a delayed decrease in BP pattern during diagnostic tilt testing</td>
<td>The inability of the patient to collaborate and to perform tilt testing</td>
<td>The changes in the SBP, heart rate, cardiac output, SV and TPR (in pts with delayed OH compared to age- and sex-matched controls during a modified version of the Italian tilt protocol.</td>
<td>Laboratory study, Small number of pts, Blinding – not stated</td>
<td>In pts with delayed OH, the progressive decrease in SBP is associated with progressive decrease in TPR, while CO and SV show little change. The compensatory increase in HR is insufficient to compensate the decline in BP. Administration of elastic compression to the legs counteracts the decrease in SBP and TPR.</td>
<td></td>
</tr>
<tr>
<td>Gurevich T, et al. 2014 25531748 (131)</td>
<td>(1) To assess time-related patterns of SBP and DBP responses in pts referred for suspected OH to tilt testing</td>
<td>Syncope during angioplasty</td>
<td>None specified</td>
<td>OH or delayed OH</td>
<td>Referral population, Laboratory study</td>
<td>Tilt table testing to 30 minus identifies most but no all pts with delayed OH.</td>
<td></td>
</tr>
</tbody>
</table>
To assess the percent of delayed OH and factors associated with it.

**Study type:**
Prospective, observational, mechanistic,

**Size:** n=692 pts; 270 with OH or delayed OH

Gibbons, et al. 2015
26400576
(132)

**Aims:**
To define the long-term outcome of delayed OH

**Study type:**
Prospective, longitudinal follow up, observational, mechanistic

**Size:** n=108 pts with OH, 75 age- and sex-matched controls

**"Inclusion criteria":**
OH during a 60° head-up tilt performed for 45 mins

**Exclusion criteria:**
None

**1° endpoint:**
OH, delayed OH and clinical outcome including mortality

**Results:**
- 54% of individuals with delayed OH progressed to OH.
- 31% with delayed OH developed an α-synucleinopathy
- 10-y mortality rate in individuals with delayed OH was 29%; with baseline OH was 64% and in controls was 9%.
- 10-y mortality of individuals who progressed to OH was 50%.

**Limitations:**
- Laboratory study
- Referral population

**Conclusions:**
- Delayed OH frequently progresses to OH
- Delayed OH frequently progresses to an alpha-synucleinopathy (multiple system atrophy, Parkinson’s disease, dementia with Lewy bodies)
- Delayed OH has a high associated mortality particularly when it progresses to OH

---

Data Supplement 16. Nonrandomized Trials, Observational Studies, and/or Registries of Neurologic Investigation – (Section 3.3)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abubakr A, et al. 2005 15820355 (133)</td>
<td>Study type: Retrospective chart review</td>
<td>Inclusion criteria: Syncope pts selected from a larger population of EEG reports</td>
<td>1° endpoint: Classification of EEG findings including variants of normal. Results: 2 (1.5%) abnormal EEGs: one focal slowing, one diffuse slowing</td>
<td>Very few abnormal EEGs, but the larger population of syncope pts is not reported. Rare EEG abnormalities. No epileptiform features</td>
</tr>
<tr>
<td>Reference</td>
<td>Study type</td>
<td>Inclusion criteria</td>
<td>1st endpoint</td>
<td>Results</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Al-Nsoor, et al. 2010</td>
<td>Perhaps prospective cohort</td>
<td>Syncope in ED seen by a neurologist</td>
<td>Abnormality contributing to diagnosis</td>
<td>254 CT scans (87%); 10 (3.9% of ordered) helped.</td>
</tr>
<tr>
<td>Giglio P, et al. 2005</td>
<td>Retrospective chart review</td>
<td>Syncope pts in ED</td>
<td>Proportion with CT scans; proportion abnormal related to syncope</td>
<td>44 had CT; 1 showed old posterior infarction.</td>
</tr>
<tr>
<td>Goyal N, et al. 2006</td>
<td>Retrospective chart review</td>
<td>Syncope diagnosis by ED MD</td>
<td>Any clinically significant finding</td>
<td>117 had CT; 0 (0% of ordered) helped.</td>
</tr>
<tr>
<td>Johnson PC, et al. 2014</td>
<td>Retrospective chart review</td>
<td>Syncope coded in billing records, and after non-syncopal diagnoses excluded on chart review</td>
<td>Test contributed to alleged diagnosis</td>
<td>131 CT scans (78.4%); 0% helped. 18 brain MRI (10.7%); 0% helped. 52 carotid ultrasounds (31.1%); 0% helped.</td>
</tr>
<tr>
<td>Kapoor WN, et al. 1983</td>
<td>Prospective cohort</td>
<td>Diagnosis of syncope after inclusion for TLOC</td>
<td>Diagnosis of cause of syncope</td>
<td>65 CT scans (32%); 0% helped. 101 EEGs (49.5%); 1 (1% of ordered) helped.</td>
</tr>
<tr>
<td>Mecarelli O, et al. 2004</td>
<td>Prospective observational controlled cohort</td>
<td>recurrent syncope, positive tilt test, negative brain MRI</td>
<td>Abnormal EEG</td>
<td>0 (0%) abnormal findings on routine EEG but increased slow wave activity during hyperventilation</td>
</tr>
<tr>
<td>Mendu ML, et al. 2009</td>
<td>Retrospective chart review</td>
<td>ICD 9 in-hospital primary or secondary syncope diagnosis</td>
<td>Chart documentation that the finding contributed to the diagnosis</td>
<td>1327 CT scans (63%); 35 (2.6% of ordered) helped. 154 brain MRI (19%); 23 (15%</td>
</tr>
<tr>
<td>Study type:</td>
<td>Inclusion criteria:</td>
<td>1st endpoint:</td>
<td>Results:</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>---------------------</td>
<td>---------------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>Retrospective chart review</td>
<td>ICD 9 syncope in in-patients</td>
<td>Apparently contributed to diagnosis of etiology.</td>
<td>283 CT scans (41%); 5 (1.8% of ordered) helped. 10 brain MRI (1.3%); 3 (30% of ordered) helped. 185 carotid ultrasounds (29%); 0 (0% of ordered) helped. 253 EEG (39%); 6 (2.4%) helped</td>
<td></td>
</tr>
<tr>
<td>Retrospective chart review</td>
<td>Syncope or falls and EEG ordered</td>
<td>“Yield” of EEGs</td>
<td>0 (0%) EEGs showed epileptiform activity</td>
<td></td>
</tr>
<tr>
<td>Part A retrospective chart review: Part B prospective post-CME cohort</td>
<td>ICD primary or secondary diagnosis of syncope</td>
<td>Causative finding defined as probably contributing to syncope, OR identifying a high risk subject for arrhythmic death</td>
<td>583 CT scans (53%); 14 (2.4% of ordered) helped. 208 brain MRI (19%); 12 (5.8% of ordered) helped. 57 carotid ultrasounds (0%); 0 (0% of ordered) helped.</td>
<td></td>
</tr>
<tr>
<td>Prospective observational</td>
<td>Syncope or presyncope during head up tilt with isoproterenol provocation</td>
<td>EEG changes during syncopal episodes</td>
<td>Limitations:</td>
<td></td>
</tr>
</tbody>
</table>

- Laboratory study
- Unblinded
- Small number of pts

Conclusions:
- Presyncope and syncope are associated with EEG abnormalities
- No single EEG pattern is pathognomonic of presyncope of syncope
- The transition from presyncope to syncope is marked by abrupt EEG changes.
<table>
<thead>
<tr>
<th>Study</th>
<th>Authors</th>
<th>Year</th>
<th>Journal</th>
<th>Study Type</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Results</th>
<th>Limitations</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low PA, et al. 2004</td>
<td>Aims: To estimate autonomic symptoms and deficits using a laboratory evaluation of autonomic function and a validated self-report measure of autonomic symptoms in pts and matched control pts from the population  Study type: Cross-sectional; population based, observational  Size: n=231 pts with DM (type 1, n=83; type 2, n=148) and n=245 control pts</td>
<td>Inclusion criteria: Known diabetes and willingness to complete general medical and neurological evaluations, and a full autonomic reflex laboratory evaluation annually</td>
<td>Exclusion criteria: None specified</td>
<td>“1° endpoint”: Autonomic symptoms and test results  Results:  ● OH in 8.4 and 7.4% of type 1 and type 2 diabetes, respectively (using the criterion of 30 mmHg SBP)  ● OH in 22.9 and 16.2% of type 1 and type 2 diabetes, respectively (using the criterion of 20 mmHg SBP).  ● Autonomic neuropathy, defined using a composite testing score, was present in 54% of type 1 and 73% of type 2 pts</td>
<td>“1° endpoint”: Autonomic symptoms and test results  Results:  ● OH in 8.4 and 7.4% of type 1 and type 2 diabetes, respectively (using the criterion of 30 mmHg SBP)  ● OH in 22.9 and 16.2% of type 1 and type 2 diabetes, respectively (using the criterion of 20 mmHg SBP).  ● Autonomic neuropathy, defined using a composite testing score, was present in 54% of type 1 and 73% of type 2 pts</td>
<td>Limitations:  ● Single region and demographic  Conclusions:  ● Autonomic symptoms and deficits are common in diabetes, but mild in severity  ● The correlation between symptom scores and deficits is overall weak in mild diabetic neuropathy, emphasizing the need to separately evaluate autonomic symptoms and objective tests.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim, et al. 2009</td>
<td>Aims: To assess the value of standard quantitative autonomic and sensation tests in detecting, characterizing, and quantitating the severity of transthyretin amyloid polyneuropathy  Study type: Retrospective, observational  Size: n=36 pts</td>
<td>Inclusion criteria: A diagnosis of transthyretin amyloid polyneuropathy</td>
<td>Exclusion criteria: None specified</td>
<td>“1° endpoint”: Autonomic and sensory test results  Results:  ● Abnormal postganglionic sympathetic sudomotor dysfunction was found in 74%  ● The HRdb was abnormal in 25 (69%)  ● OH present in 13 pts (36%)  ● Median SBP fall of 36 mmHg at 1 min (range 32–80 mm Hg</td>
<td>“1° endpoint”: Autonomic and sensory test results  Results:  ● Abnormal postganglionic sympathetic sudomotor dysfunction was found in 74%  ● The HRdb was abnormal in 25 (69%)  ● OH present in 13 pts (36%)  ● Median SBP fall of 36 mmHg at 1 min (range 32–80 mm Hg</td>
<td>Limitations:  ● Laboratory study  ● Referral population  ● Small number of pts  Conclusions:  ● This study provides a rationale for the use of quantitative autonomic and sensory testing as standard, objective, and quantitative measures for assessing the severity of TTR-A-PN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iodice V, et al. 2012</td>
<td>Aims: To evaluate the autonomic characterization of MSA in autopsy confirmed cases  Study type: Autopsy confirmed cases of MSA who had undergone formal autonomic testing, including adrenergic, sudomotor and cardiovagal functions and Thermoregulatory Sweat Test  Study type: Autopsy confirmed cases of MSA who had undergone formal autonomic testing, including adrenergic, sudomotor and cardiovagal functions and Thermoregulatory Sweat Test</td>
<td>Inclusion criteria: Autopsy confirmed cases of MSA who had undergone formal autonomic testing, including adrenergic, sudomotor and cardiovagal functions and Thermoregulatory Sweat Test</td>
<td>1° endpoint: Autonomic test results, clinical features  Results:  ● OH was present in 21 pts and symptomatic in 19 pts</td>
<td>“1° endpoint”: Autonomic test results, clinical features  Results:  ● OH was present in 21 pts and symptomatic in 19 pts</td>
<td>Limitations: None  Conclusions: Severe and progressive generalized autonomic failure with severe adrenergic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>1st endpoint</td>
<td>Limitations</td>
<td>Conclusions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-----</td>
<td>-------------------</td>
<td>-------------------</td>
<td>--------------</td>
<td>-------------</td>
<td>-------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thaisetthawatkul P, et al. 2004 15159482 (146)</td>
<td>To assess autonomic function in pts with dementia with Lewy bodies</td>
<td>Clinically probable dementia with Lewy bodies and MSA pts and clinically definite PD pts</td>
<td>Coexistent conditions, such as diabetes, that account for the symptoms of dysautonomia.</td>
<td>Autonomic test results, clinical features</td>
<td>Referral bias Clinical diagnoses Autonomic testing in demented pts</td>
<td>Autonomic dysfunction is frequent in dementia with Lewy bodies and the severity is intermediate between that of multiple system atrophy and Parkinson disease.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thieben MJ, et al. 2007 17352367 (147)</td>
<td>To evaluate the prevalence and pathogenetic mechanisms of POTS</td>
<td>Baseline sinus rhythm with no evidence of arrhythmia or cardiac disease, sustained heart rate increment of 30 beats/min or greater in response to 10 mins of head-up tilt, and symptoms of orthostatic intolerance Symptoms present for more than 3 mo.</td>
<td>(1) OH defined as a decline of 30 mm Hg or more in SBP or 20 mm Hg or more in mean BP within 3 mins of standing or HUTT; (2) pregnancy or lactation; (3) presence of another cause of autonomic failure</td>
<td>Autonomic test results, clinical features</td>
<td>Referral population. Laboratory study</td>
<td>Findings suggest a neuropathic basis for at least half the cases of POTS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>1st endpoint</td>
<td>Limitations</td>
<td>Conclusions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-----</td>
<td>--------------------</td>
<td>--------------</td>
<td>-------------</td>
<td>-------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gibbons C, et al. 2013</td>
<td>To define the neuropathology, clinical phenotype, autonomic physiology and differentiating features in individuals with neuropathic and non-neuropathic POTS.</td>
<td>POTS was defined as an increase in heart rate of &gt;30 beats per min upon standing with symptoms of orthostatic intolerance, without any known medical condition or medication causing the tachycardia</td>
<td>Autonomic test results, clinical features, nerve density from skin biopsy</td>
<td>Referral population, Laboratory study</td>
<td>POTS subtypes may be distinguished using small fiber and autonomic structural and functional criteria.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study type: Observational, mechanistic</td>
<td>Exclusion criteria: DM, impaired glucose tolerance, vitamin deficiencies, heavily metal toxicity, thyroid disorders, pheochromocytoma, hypoadrenalism, anxiety, cardiac disease, volume depletion, drug abuse and medication side effect</td>
<td>Name:</td>
<td>Referral population.</td>
<td>POTS subtypes may be distinguished using small fiber and autonomic structural and functional criteria.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Size: n=24 pts and 10 controls</td>
<td>Results:</td>
<td>1st endpoint:</td>
<td>Laboratory study</td>
<td>Syncope is common in pts undergoing CAA and can be misdiagnosed as frontal seizures, cardio-inhibitory response most frequent mechanism of syncope.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martinez-Fernandez, et al. 2008</td>
<td>Study type: Prospective Registry</td>
<td>Symptomatic pts with TIA or non-invalidating stroke, asymptomatic pts. with 85% stenosis, TCD detected microemboli/ exhausted CVR or silent lesions</td>
<td>Occurrence of CSR and/or syncope during internal CAA</td>
<td>Beat to beat analysis of BP was not performed.</td>
<td>Syncope is common in pts undergoing CAA and can be misdiagnosed as frontal seizures, cardio-inhibitory response most frequent mechanism of syncope.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Size: n=359 pts</td>
<td>Exclusion criteria: N/A</td>
<td>Name:</td>
<td>Referral population.</td>
<td>Syncope is common in pts undergoing CAA and can be misdiagnosed as frontal seizures, cardio-inhibitory response most frequent mechanism of syncope.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Results: CSR and syncope occurred in 62.7 % and 18.6% of pts. EEG changes more prominent in pts. with cardio-inhibitory syncope, Syncope is more frequent in cardio-inhibitory CSR (p&lt;0.001), Risk of syncope during CAA in pts with CSR (OR: 4.2; 95% CI:1.9–9.1) Risk of syncope in pts. with cardio-inhibitory CSR and vasodepressor/mixed CSR (OR: 6.9; 95% CI: 3.2–15.0 and OR: 1.4; 95% CI: 0.6–3.7) respectively.</td>
<td>Name:</td>
<td>Referral population.</td>
<td>Syncope is common in pts undergoing CAA and can be misdiagnosed as frontal seizures, cardio-inhibitory response most frequent mechanism of syncope.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Limitation: Beat to beat analysis of BP was not performed.</td>
<td>Laboratory study</td>
<td>Syncope is common in pts undergoing CAA and can be misdiagnosed as frontal seizures, cardio-inhibitory response most frequent mechanism of syncope.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gibbons, et al. 2015</td>
<td>Aims: To define the long-term outcome of delayed OH</td>
<td>“Inclusion criteria”: OH during a 60° HUTT performed for 45 mins</td>
<td>OH, delayed OH and clinical outcome including mortality</td>
<td>Referral population.</td>
<td>Delayed OH frequently progresses to OH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study type: Prospective, longitudinal follow up, observational, mechanistic</td>
<td>Exclusion criteria: None specified</td>
<td>Name:</td>
<td>Laboratory study</td>
<td>Delayed OH frequently progresses to OH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Size: n=108 pts with OH, 75</td>
<td>Results:</td>
<td>Name:</td>
<td>Referral population.</td>
<td>Delayed OH frequently progresses to an alpha-synucleinopathy (multiple system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>● 54% of individuals with delayed OH progressed to OH.</td>
<td>Name:</td>
<td>Laboratory study</td>
<td>Delayed OH frequently progresses to alpha-synucleinopathy (multiple system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>● 31% with delayed OH developed an alpha-synucleinopathy</td>
<td>Name:</td>
<td>Referral population.</td>
<td>Delayed OH frequently progresses to an alpha-synucleinopathy (multiple system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Acronym; Author; Year Published</td>
<td>Study Type/Design; Study Size</td>
<td>Patient Population</td>
<td>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</td>
<td>Summary/Conclusion Comment(s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-------------------------------</td>
<td>--------------------</td>
<td>----------------------------------------------------------</td>
<td>--------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Corrado D, et al. 2003 14638546 (150) | Study type:  Retrospective  
Size: n=132 pts | Inclusion criteria: ARVC pts treated with ICD  
Exclusion criteria: ARVC with only minor criteria, idiopathic RV VT, myocarditis, IDC, Uhl's anomaly | 1st endpoint: ICD treated arrhythmia  
Results: of 132 pts, 64 (48%) had appropriate ICD intervention in FU of 39 mo. Of 21 pts with syncope 8 (38%) had appropriate ICD therapy including 5 with VFL/VF. | Unexplained syncope had an OR of 7.5 for appropriate ICD interventions (p=0.07; 95% CI: 0.84–1.81) |
| Corrado D, et al. 2010 20823389 (151) | Study type:  Retrospective  
Size: n=106 pts | Inclusion criteria: ARVC pts receiving ICDs  
Exclusion criteria: Prior sustained VT or VF | 1st endpoint: Appropriate ICD interventions.  
Results: Of 106 pts 25 (24%) had appropriate ICD interventions in f/u of 58 mo. Pts presenting with syncope had a 9%/y incidence of appropriate ICD intervention. | Syncope independently predicted for an appropriate ICD shock (HR: 2.94; 95% CI: 1.83 to 4.67; p=0.013) and shocks for VF/VFL (HR: 3.16; 95% CI: 1.39–5.63; p=0.005).  
Syncope was not a predictor of appropriate ICD intervention |
| Bhonsale A, et al. 2011 21939834 (152) | Study type:  Retrospective  
Size: n=84 pts | Inclusion criteria: ARVD/C pts receiving ICDs  
Exclusion criteria: Prior sustained VT or VF | 1st endpoint: Appropriate ICD interventions  
Results: Appropriate ICD therapy in 40 (48%) in f/u of 4.7 y. Of 23 pts presenting with syncope 10 (25%) had appropriate ICD interventions | Syncope was not a predictor of appropriate ICD intervention |
Size: n=215 pts | Inclusion criteria: Diagnosed with ARVD/C  
Exclusion criteria: None | 1st endpoint: SCD, sustained arrhythmia, appropriate ICD intervention  
Results: 86 (40%) had primary endpoint in mean f/u of 7 y. Of 41 pts with syncope, the primary endpoint was met in 30 (73%). | Symptomatic pts (syncope, presyncope and palpitation) predicted for ventricular arrhythmias (p<0.001).  
Syncope was not a predictor of VA. |
| Link MS, et al. 2014 | Study type:  Prospective observational | Inclusion criteria: ARVD/C | 1st endpoint: Sustained ventricular arrhythmias  
Results: 86 (40%) had primary endpoint in mean f/u of 7 y. Of 41 pts with syncope, the primary endpoint was met in 30 (73%). | Syncope was not a predictor of VA. |
<table>
<thead>
<tr>
<th>Study Acronym</th>
<th>Author, Year</th>
<th>Study Type/Design*; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25011714</td>
<td>© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Corrado D, et al. 2015

| Size: n=137 pts; 108 with ICDs | Exclusion criteria: Sarcoid cardiac disease | Results: 48 pts with VA. Of 28 pts with syncope 14 (50%) met primary endpoint |

Study type: Consensus statement

| Inclusion criteria: None | 1ª endpoint: None | Results: None |

Exclusion criteria: None

Data Supplement 18. Nonrandomized Trials, Observational Studies, and/or Registries of Sarcoid Heart Disease – (Section 4.2.5)

<table>
<thead>
<tr>
<th>Study Acronym</th>
<th>Author, Year</th>
<th>Study Type/Design*; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Winters SL, et al. 1991 | 1894867 (156) | Study type: Retrospective | Study type: Retrospective Size: n=7 pts | Inclusion criteria: Documented (n=6) or highly suspected (n=1) Sarcoidosis with ECG abnormalities | 1ª endpoint: Findings during EPS

Results: Sustained VT was easily inducible in all pts. Steroid therapy did not prevent spontaneous VT. Despite anti-arrhythmic therapy, 2 pts had SCD and an additional 4 recurrent VT.4 pts received an ICD and all 4 received appropriate therapy.

> Poor response to ant-arrhythmic drug therapy
> ICD therapy is recommended as primary therapy in pts with sarcoidosis and VT |
| Kaplan, et al. 2006 | 16876741 (157) | Study type: Retrospective | Study type: Retrospective Size: n=8 pts | Inclusion criteria: Cardiac sarcoidosis with recurrent VT | 1ª endpoint: To define the clinical characteristics of pts with CS and the EP findings during EPS.

Results: All pts had a reduced LVEF except for 1 pt (Mean 34% ± 15%) and had failed previous anti-arrhythmic drug therapy.

EPS revealed evidence of scar-related reentry with multiple morphologies. Areas of low-voltage scar were present in the RV in all 8 pts. Ablation was only partially helpful. 5 out of 8 pts eventually required cardiac transplantation.

> Sarcoidosis can be misdiagnosed as idiopathic VT or ARVD.
> Catheter ablation is only partially successful. |
| Jefic, et al. 2009 | 19187909 (158) | Study type: Retrospective | Study type: Retrospective Size: n=42 pts | Inclusion criteria: CS | 1ª endpoint: To determine response to medical therapy and radiofrequency ablation

Results: In 9 out of 21 pts with VT/VF recurrence post-ICD implant, drug therapy was ineffective requiring radiofrequency ablation. The most frequent VT circuit was reentry in the per-tricuspid area. All pts had either a decrease (n=4) or complete elimination (n=5) during follow up (19.8 ± 19.6 mo).

> In pts with CS and refractory VT, catheter ablation is effective in eliminating or reducing the VT burden. |
<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective</td>
<td>CS and sustained monomorphic VT</td>
<td>Mechanism and outcome of VT associated with cardiac sarcoidosis</td>
<td>Most VT is due to reentry. The inducibility rate depends on the presence or absence of an active phase. ICD therapy is effective.</td>
<td>• While most VT is due to reentry, inducibility depends on the disease state including response to immunosuppressive therapy.</td>
</tr>
<tr>
<td>n=8 pts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questionnaire</td>
<td>CS treated with steroid therapy</td>
<td>Steroid dose used and pts outcome</td>
<td>The most common initial steroid dose used was 30 mg/day or 60 mg on alternate days. This dose was continued for 1 mo followed by tapering by 5mg every 2 to 4 wk until reaching the maintenance dose of 5–10 mg/d. Steroid therapy was reported to result in improvement in 54%, no change in 40%, and deterioration in 6% of cases.</td>
<td>• There is a fairly uniform use of steroid therapy in the management of CS with clinical improvement in over one-half of the cases.</td>
</tr>
<tr>
<td>n=49 pts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrospective</td>
<td>Unexplained AV block</td>
<td>To determine the prevalence of CS and giant cell myocarditis in young and middle-aged adults undergoing pacemaker implantation for AV block</td>
<td>CS and giant cell myocarditis were found in 14 (19%) and 4 (6%) pts, respectively. The majority (16/18, 89%) were women. Over an average of 48 mo of follow-up, 7 (39%) of 18 pts with CS or giant cell myocarditis vs. 1 of the 54 pts in whom AV block remained idiopathic, experienced either cardiac death, cardiac transplantation, VF, or treated sustained VT (p&lt;0.001).</td>
<td>• CS and giant cell myocarditis account for &gt;25% of young and middle-aged adults presenting with AV block. • These pts are at high risk of having major adverse events.</td>
</tr>
<tr>
<td>n=72 pts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrospective</td>
<td>CS</td>
<td>Clinical characteristics and response to therapy</td>
<td>Cardiac signs were clinical in 63% of cases and electrical in 22%. During an average follow up of 58 m, 87% of pts showed improvement on immunosuppressive therapy and 54% were cured from a clinical and laboratory point of view.</td>
<td>• Most pts with CS respond to immunosuppressive therapy.</td>
</tr>
<tr>
<td>n=41 pts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrospective</td>
<td>CS and VA</td>
<td>Efficacy of corticosteroid therapy in the treatment of VA</td>
<td>Corticosteroid therapy may be effective for VA in the early stage, but</td>
<td></td>
</tr>
<tr>
<td>Study ID</td>
<td>Study type</td>
<td>Size</td>
<td>Inclusion criteria</td>
<td>1st endpoint</td>
</tr>
<tr>
<td>----------</td>
<td>------------</td>
<td>------</td>
<td>-------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>21496164</td>
<td>Retrospective</td>
<td>n=31 pts</td>
<td>CS and ICD for primary or secondary prevention of sudden death</td>
<td>ICD therapy in pts with CS</td>
</tr>
<tr>
<td>Schuller JL, et al. 2012 22812589 (164)</td>
<td>Retrospective</td>
<td>n=112 pts</td>
<td>CS and ICD for primary or secondary prevention of sudden death</td>
<td>To determine the prevalence and incidence of ventricular tachyarrhythmias in pts with CS and to identify predictors of appropriate therapy</td>
</tr>
<tr>
<td>Betensky BP, et al. 2012 22338670 (165)</td>
<td>Retrospective</td>
<td>n=45 pts</td>
<td>CS and ICD for primary or secondary prevention of sudden death</td>
<td>To evaluate the efficacy and safety of ICD therapy in pts with CS</td>
</tr>
<tr>
<td>Kron J, et al. 2013 23002195 (166)</td>
<td>Retrospective</td>
<td>n=235 pts</td>
<td>Consecutive pts with CS and ICD</td>
<td>To evaluate the efficacy and safety of ICD therapy in pts with CS</td>
</tr>
</tbody>
</table>
Pts who received appropriate ICD therapies were more likely to be male (73.8 vs. 59.6%, p=0.0330), have a history of syncope (40.5 vs. 22.5%, p=0.0044), lower LVEF (38.1 ± 15.2 vs. 48.8 ± 14.7%, p≤0.0001), ventricular pacing on baseline ECG (16.1 vs. 2.1%, p=0.0002), and a secondary prevention indication (60.7 vs. 24.5%, p<0.0001) compared with those who did not receive appropriate ICD therapies.

- Predictors of appropriate ICD therapies include a history of syncope, depressed LV function and ventricular pacing.

- Programmed electrical stimulation may help identify pts with CS who are at risk of having ventricular arrhythmias.

### Data Supplement 19. Nonrandomized Trials, Observational Studies, and/or Registries of Brugada Syndrome – (4.3.1)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morita H, et al. 2008 18836701 (168)</td>
<td>Study type: Retrospective Size: n=115 pts</td>
<td>Inclusion criteria: Symptomatic and asymptomatic BS Exclusion criteria: N/A</td>
<td>1st endpoint: Prevalence of fragmented QRS and its prognostic value Results: Fragmented QRS was more prevalent in pts with VF (85%) and syncope (50%) when compared to asymptomatic pts (34%).</td>
<td>• Fragmented QRS appears to be a marker for spontaneous VF and syncope</td>
</tr>
<tr>
<td>Gehi, et al. 2006 16836701 (169)</td>
<td>Study type: Meta-analysis assessing predictors of cardiac events Size: n=1,545 pts</td>
<td>Inclusion criteria: Studies were included if they m, et al. I of the following criteria: 1) prospective cohort studies of the natural history of pts with Brugada-type ECG; 2) studies included &gt;10 pts, 3) primary data on cardiac events was provided</td>
<td>1st endpoint: SCD, syncope and ICD shock Results: The overall rate was 10% over an average of 32 mo. Predictors of adverse events included • Syncope and SCD (RR: 3.24; 95% CI: 2.13–4.93) • Men compared with women (RR: 3.47; 95% CI: 1.58–7.63), and</td>
<td>• Male sex, spontaneous Type I ECG pattern and Hx of SCD and syncope are good predictors of future cardiac events</td>
</tr>
</tbody>
</table>
and 4) stated clearly that structural heart disease was ruled out.

**Exclusion criteria:** If not all inclusion criteria are met

<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective follow up study</td>
<td>Pts with BS</td>
<td>N/A</td>
<td>To assess phenotype and prognosis differences between men and women</td>
<td>Men had greater rates of spontaneous Type 1 ECG, ST elevation and VF inducibility (p&lt;0.001), syncope (18% vs. 14%) and aborted SCD (6% vs. 1%). Conversely, conduction parameters and QTc increased more in women in response to Na channel blocker.</td>
</tr>
<tr>
<td>N/A</td>
<td>Symptomatic and asymptomatic BS</td>
<td>N/A</td>
<td>Prevalence of fragmented QRS and its prognostic value</td>
<td>Fragmented QRS was more prevalent in pts with VF (85%) and syncope (50%) when compared to asymptomatic pts (34%).</td>
</tr>
<tr>
<td>Registry</td>
<td>Type 1 ECG pattern</td>
<td>N/A</td>
<td>Prevalence of family history of SD and its prognostic value</td>
<td>SD was present in 69 out of 157 families (43%). During follow-up VF or SD-free survival rate was not different between pts with or without a family Hx of SD of a first-degree relative, between pts with or without a family Hx of multiple SD of a first-degree relative at any age and between pts with or without a family Hx of SD in first-degree relatives’ ≤35 y of age.</td>
</tr>
<tr>
<td>Registry</td>
<td>Spontaneous or drug-induced type 1 ECG</td>
<td>Hx of cardiac arrest</td>
<td>Arrhythmic events in pts with and without inducible VT/VF</td>
<td>VT/VF inducibility is unable to identify high-risk pts, whereas the presence of a spontaneous type I ECG, Hx of syncope, ventricular effective refractory period &lt;200 ms, and QRS fragmentation seem useful to identify candidates for primary prevention</td>
</tr>
</tbody>
</table>

**Study type:** Prospective follow up study  
**Size:** n=384 pts

**Study type:** Retrospective  
**Size:** n=115 pts

**Study type:** Registry  
**Size:** n=280 consecutive pts

**Study type:** Registry  
**Size:** n=308 pts
<table>
<thead>
<tr>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacher F, et al. 2006 17116772 (173)</td>
<td>n=220 pts including 88 with syncope</td>
<td>BS with ICD implant</td>
<td>N/A</td>
<td>Appropriate shocks and ICD complications including inappropriate shocks</td>
<td>During a mean follow-up of 38±27 mo, no pts died and 18 pts (8%) had appropriate device therapy. The annual event rate was 2.6% with an annual complication rate of 8.9%. In pts with syncope, 10% received an appropriate shock during a 19.5–59 mo FU period. 7% had syncope recurrence without any documented arrhythmia. The HR for asymptomatic vs. syncope pts was 0.43 (CI: 0.24–0.74).</td>
<td>The annual rate of appropriate ICD therapy is low. Appropriate ICD shocks are more frequent in symptomatic than in asymptomatic pts (12% vs. 4%; p=0.05). Not all syncope in pts with BS is arrhythmic.</td>
</tr>
<tr>
<td>Sarkozy, et al. 2007 17251258 (174)</td>
<td>n=47 pts</td>
<td>Spontaneous or drug induced Type 1 ECG pattern BrS with syncope (n=26) and/or + family Hx (n=26) who underwent ICD implant for primary prevention</td>
<td>N/A</td>
<td>Appropriate and inappropriate ICD shocks.</td>
<td>During a median follow up of 47.5 mo, 7 pts (15%) had appropriate shocks. All were male (3 syncope, 3 + family Hx and 1 had both), 4 pts had recurrent syncope with no documented arrhythmia. Spontaneous Type 1 ECG pattern and NSVT were more frequent among pts with appropriate shocks.</td>
<td>The authors could not confirm that syncope was an independent predictor of appropriate ICD shocks. 4 pts had recurrent syncope with no documented arrhythmia suggesting a reflex mediated mechanism.</td>
</tr>
<tr>
<td>Rosso R, et al. 2008 18669142 (175)</td>
<td>n=59 pts</td>
<td>BS pts with ICD implants: Cardiac arrest (18.6%), syncope (52.5%), inducible VF in asymptomatic (23.7%), and positive family Hx of SD (0.5%)</td>
<td>N/A</td>
<td>Efficacy and complications of ICD therapy</td>
<td>During FU (4–160 mo), 5/11 pts with CA had appropriate device therapy. None of the pts without prior CA had appropriate device therapy.</td>
<td>Appropriate device therapy was limited to CA survivors while none of the other pts including those with syncope and/or inducible VF suffered an arrhythmic event.</td>
</tr>
<tr>
<td>FINGER Brugada Syndrome Registry Probst V, et al. 2010</td>
<td>Registry from 11 tertiary centers in 4 European countries: France, Italy, Netherlands,</td>
<td>Pts with spontaneous or drug-induced Type 1 ECG pattern</td>
<td>N/A</td>
<td>SCD</td>
<td>The cardiac event rate per y was 7.7% in pts with aborted SCD, 1.9% in pts with syncope, and Low event rate even in pts with syncope Family Hx, inducibility of VT/VF and the presence of SCN5A mutation were</td>
<td></td>
</tr>
<tr>
<td>Study type</td>
<td>Exclusion criteria</td>
<td>Inclusion criteria</td>
<td>Size</td>
<td>Swiss</td>
<td>( \text{ICD therapy was an effective strategy in BS, treating potentially lethal arrhythmias in} )</td>
<td>Results</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------</td>
<td>--------------------</td>
<td>------</td>
<td>-------</td>
<td>------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Germany Registry (FINGER)</td>
<td>Diseases that mimic BS</td>
<td>n=1029 consecutive pts</td>
<td>Exclusion criteria</td>
<td>not predictive of arrhythmic events.</td>
<td>0.5% in asymptomatic pts.</td>
<td>Symptoms and spontaneous type 1 ECG were predictors of arrhythmic events, whereas sex, familial Hx of SCD, inducibility of VT during EPS, and the presence of an SCN5A mutation were not predictive of arrhythmic events.</td>
</tr>
<tr>
<td>Conte, et al. 2015</td>
<td>Symptom and spontaneous type 1 ECG were predictors of arrhythmic events, whereas sex, familial Hx of SCD, inducibility of VT during EPS, and the presence of an SCN5A mutation were not predictive of arrhythmic events.</td>
<td>n=176 pts</td>
<td>Inclusion criteria</td>
<td>1(^{st}) endpoint: Appropriate and inappropriate shocks and device complications</td>
<td>Inclusion criteria: Pts with spontaneous or drug-induced Type 1 ECG pattern who underwent ICD implantation.</td>
<td>Appropriate ICD shocks occurred in 28 pts (15.9%), and 33 pts (18.7%) had inappropriate shocks. Electrical storm occurred in 4 pts (2.3%). 28 p pts (15.9%) experienced device-related complications.</td>
</tr>
<tr>
<td>Hiraoka, et al. 2013</td>
<td>The presence of SCD or syncope is a risk factor for cardiac events in pts with BS</td>
<td>n=69 pts</td>
<td>Inclusion criteria: BS with age 35 y of age or younger</td>
<td>1(^{st}) endpoint: Cardiac events (VF or SCD)</td>
<td>Study type: Retrospective analysis of the Japan Idiopathic Ventricular Fibrillation registry</td>
<td>Cardiac events including Syncope</td>
</tr>
<tr>
<td>Sacher F, et al.</td>
<td>VA occurred only in pts with syncope</td>
<td>Study type: Prospective</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
registry

**Size:** n=203 pts

Pts diagnosed with BS between 1999 and 2010

**Exclusion criteria:** N/A

**Results:**
- Of 203 pts, 57 (28%) experienced syncope.
- 23 pts with suspected arrhythmic syncope (Group 1), 17 pts with non-arrhythmic syncope (Group 2) and 17 with syncope of doubtful origin (Group 3).
- After mean follow-up of 65 ± 42 mo, 14 pts in Group 1 remained asymptomatic, 4 had recurrent syncope, and 6 had appropriate ICD therapy. In Group 2, 9 pts remained asymptomatic and 7 had recurrent neurocardiogenic syncope. In Group 3, 7 remained asymptomatic and 9 had recurrent syncope.

suspected to be arrhythmic in origin at a rate of 5.5% per y. No sudden death occurred in pts with nonarrhythmic syncope or with syncope of doubtful origin.

---

**Data Supplement 20. Nonrandomized Trials, Observational Studies, and/or Registries of Short-QT Pattern and Syncope – (Section 4.3.2)**

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Gollob, et al. 2011 21310316 (180)   | Study type: Retrospective review of reported cases of SQTS. **Size:** n=15 articles described unique cases of SQTS | **Inclusion criteria:** Reported cases of SQTS in English **Exclusion criteria:** N/A | **1st endpoint:** The creation of formal diagnostic criteria to facilitate the diagnostic evaluation of suspected cases of SQTS  
**Results:** A total of 61 cases were identified with a mean QTc value of 307 ms (range 248–381 ms). Short QT syndrome criteria were developed and consisted of 4 components including ECG, clinical Hx, family and genotype. An overall score of 4 points or greater indicates a high-probability diagnosis of SQTS, whereas 2 points or less makes a diagnosis of SQTS low probability. Pts with a score of 3 points are considered to have an intermediate probability of having SQTS.  
| Diagnostic criteria may lead to a greater recognition of this condition and provoke screening of at-risk family members. |
| Gaita, et al. 2003 12925462 (181)   | Study type: Retrospective **Size:** n=6 pts belonging to 2 families with idiopathic short QT interval | **Inclusion criteria:** Short QT interval with a Hx of syncope, palpitations or resuscitated SD. | **1st endpoint:** Comprehensive EP evaluation  
**Results:** At baseline ECG, all pts exhibited a QT interval ≤280 ms (QTc ≤300 ms). During EPS (n=4),  
<p>| The short QT syndrome is characterized by familiar sudden death, short refractory periods, and inducible VF. |</p>
<table>
<thead>
<tr>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective</td>
<td>3 families</td>
<td>Short QT interval and history of ventricular arrhythmias or SCD</td>
<td>N/A</td>
<td>Characterization of the genetic basis for SQTS</td>
<td>In 2/3 families, the authors identified 2 different missense mutations resulting in the same amino acid change (N588K) in the S5-P loop region of the cardiac I(<em>{Kr}) channel HERG (KCNH2). The mutations dramatically increase I(</em>{Kr}), leading to heterogeneous abbreviation of action potential duration and refractoriness, and reduce the affinity of the channels to I(_{Kr}) blockers.</td>
</tr>
<tr>
<td>Retrospective</td>
<td>n=12,012 pts</td>
<td>Pts who underwent routine medical examination for occupational reasons</td>
<td>N/A</td>
<td>Survival</td>
<td>The shortest QTc encountered was 335 ms. Information about subsequent survival was available for 36 of the 60 pts with the lowest 1/2 centile of QTc values. None of these pts died during the 7.9 ±4.5 y subsequent to the ECG that demonstrated the short QT interval.</td>
</tr>
<tr>
<td>Retrospective</td>
<td>n=10,822 pts</td>
<td>Randomly selected middle-aged pts enrolled in a population study and followed up for 29±10 y</td>
<td>N/A</td>
<td>All cause and CV mortality</td>
<td>In 10,822 randomly selected and followed for 29±10 y. The prevalence of SQTS (&lt;340ms) was 0.4% and (&lt;320ms) 0.1%. There were no SD or aborted CA or documented VA during follow up.</td>
</tr>
<tr>
<td>Retrospective</td>
<td>n=10,984 pts</td>
<td>Pts who had an ECG between February 2003 and May 2004</td>
<td>Irregular rhythms, conduction disturbances and wide QRS</td>
<td>Prevalence of SQTS (&lt;300ms)</td>
<td>In 10,984 pts, the prevalence of SQTS was 1.25% in males and 1.63% in females (2 SD below the mean). Only 3 pts had QTc&lt;300ms. None were symptomatic.</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Swiss male citizen 18–19 y of age.</td>
<td>Swiss male citizen 18–19 y of age.</td>
<td>Prevalence of LQTS and SQTS</td>
<td>Short QT syndrome is a very rare entity in the population of young male adults</td>
<td></td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ouriel K, et al. 1995 8574528 (188)</td>
<td>Study type: Retrospective Size: n=10 pts</td>
<td>Inclusion criteria: LQTS refractory (n=9) or intolerant (n=1) to BB therapy</td>
<td>1st endpoint: Cardiac events Results: No death. 9/10 developed Horner’s syndrome. The frequency of symptoms decreased from a mean of 7.1/y to 0.1/y(p&lt;0.001). During a mean follow up of 1.3 y. All but 1 pts remained symptom- free. The youngest pts died suddenly 10 mo after surgery.</td>
<td>• LCS is associated with significant clinical benefits in pts with long QT syndrome and the procedure should be considered when symptoms are refractory and malignant, or when contraindications to β-blockers are present.</td>
</tr>
<tr>
<td>Priori SG, et al. 2003 12736279 (189)</td>
<td>Study type: Retrospective Size: n=674 pts</td>
<td>Inclusion criteria: 193 consecutively genotyped families with LQTS in Pavia, Italy</td>
<td>1st endpoint: Cumulative probability of cardiac event defined as syncpe, cardiac arrest or SD Results: The incidence of first cardiac event was 30% (LQT1), 46% (LQT2) and 42% (LQT3). QTc was an independent predictor in LQT1 and LQT2 whereas sex was independent predictor in LQT3.</td>
<td>• The probability of having a cardiac event depends on the genotype and sex.</td>
</tr>
<tr>
<td>Study type:</td>
<td>Retrospective</td>
<td>Inclusion criteria:</td>
<td>1st endpoint:</td>
<td>Results:</td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>---------------------</td>
<td>---------------</td>
<td>----------</td>
</tr>
<tr>
<td>Size:</td>
<td>n=479 probands and n=1041 affected family members with LQTS</td>
<td>LQTS pts and affected family members</td>
<td>To evaluate age and sex-related differences</td>
<td>Among LQTS pts, the risk of cardiac events was higher in males until puberty and higher in females during adulthood. The same pattern was evident among LQT1 gene carriers. No age-sex difference in event rate was detected in LQT2 and LQT3 carriers.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study type:</th>
<th>Retrospective</th>
<th>Inclusion criteria:</th>
<th>1st endpoint:</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size:</td>
<td>n=1,059 pts</td>
<td>LQTS pts with QTc&gt;450 ms presenting with syncope as a first symptom were drawn from the International LQTS Registry</td>
<td>To identify risk factors for fatal arrhythmias (aborted CA, appropriate ICD therapy and SCD)</td>
<td>The lowest risk was in pts with 1 syncope episode before the start of BB therapy. Pts with syncope after BB or who were not treated with BB therapy had a 3.6 fold increase in risk.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study type:</th>
<th>Outcome data</th>
<th>Inclusion criteria:</th>
<th>1st endpoint:</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size:</td>
<td>n=286 pts with LQTS; 125 with an ICD and 161 without an ICD</td>
<td>ICD group (n=125): 54 CA, 19 syncope despite BB and 52 for other reasons Non-ICD group (n=161): 89 CA and 72 syncope despite BB</td>
<td>Death during follow up</td>
<td>1 death (1.3%) over 3 y in 73 ICD pts and 26 deaths (16%) in non-ICD pts over 8-y follow up.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study type:</th>
<th>Retrospective</th>
<th>Inclusion criteria:</th>
<th>1st endpoint:</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size:</td>
<td>n=233 pts</td>
<td>LQTS with an ICD in the European LQTS Registry</td>
<td>To determine the characteristics of LQTS pts receiving an ICD, indications and follow up</td>
<td>91% had symptoms including 44% with prior CA. 41% had not been on prior drug therapy. During 4.6±3.2 y, at least 1 shock was received by 28% of pts. Predictors of appropriate ICD therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study type:</th>
<th>Retrospective</th>
<th>Inclusion criteria:</th>
<th>1st endpoint:</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size:</td>
<td>n=233 pts</td>
<td>LQTS with an ICD in the European LQTS Registry</td>
<td>To determine the characteristics of LQTS pts receiving an ICD, indications and follow up</td>
<td>Cohort limited to pts with an ICD Age&lt;20 y, QTc &gt;500ms, prior CA and cardiac events despite medical therapy were strong predictors of appropriate ICD therapy. Absence of these risk factors indicates good prognosis.</td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
<table>
<thead>
<tr>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
<th>Exclusion criteria</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horner JM, et al. 2010</td>
<td>n=459 pts</td>
<td>Genetically confirmed LQTS including 51 pts (14 LQT1, 22 LQT2, and 15 LQT3) who received an ICD from 2000 to 2010</td>
<td>Report outcome</td>
<td>During an average FU of 7.3 y, 12 (24%) of ICD recipients experienced an appropriate shock and none of the no-ICD group died. Predictors of appropriate therapy included secondary prevention indications, non-LQT3 genotype, QTc &gt;500ms, syncope, TDP and negative family Hx.</td>
<td>N/A</td>
<td>Syncope was a predictor of appropriate therapy (p=0.05)</td>
</tr>
<tr>
<td>Priori SG, et al. 2004</td>
<td>n=335 pts</td>
<td>Genotyped LQTs pts treated with BB</td>
<td>Incidence of cardiac events</td>
<td>Cardiac events occurred in 10%, 23% and 32% of pts with LQT1, LQT2 and LQT3. Predictors included non-LQT1 and QTc &gt;500ms and first occurrence &lt;7 y of age.</td>
<td>N/A</td>
<td>Response to BB depend on the genotype</td>
</tr>
<tr>
<td>Vincent GM, et al. 2009</td>
<td>n=216 pts</td>
<td>Genotyped long-QT1 treated with BB and followed for a median of 10 y</td>
<td>Cardiac events on BB therapy</td>
<td>Cardiac events occurred in 157 pts (73%) at a median age of 9 y, with CA in 26 (12%).</td>
<td>N/A</td>
<td>BB are extremely effective in long-QT syndrome type 1 and should be administered at diagnosis and ideally before the preteen years.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• QT-prolonging drugs were used by 17 pts; 9 of 17 (53%) had CA compared with 17 of 199 nonusers (8.5%; OR: 12.0; 95% CI: 4.1–35.3; p&lt;0.001).</td>
<td>• The risk for CA/SD in compliant pts not taking QT-prolonging drugs was dramatically less compared with noncompliant pts on QT-prolonging drugs (OR: 0.03; 95% CI: 0.003–0.22; p=0.001). None of the 26 pts with CA before BB had CA/SD on BB.</td>
<td></td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
<table>
<thead>
<tr>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Long QT registry</td>
<td>n=1,648 pts</td>
<td>QTc ≥ 450 ms and/or documented LQTS-causing mutation and enrolled in registry before the 20 y age.</td>
<td>Recurrence of syncope after the first event</td>
<td>Multivariate analysis demonstrated that QTc ≥ 500 ms was a significant predictor of a first syncope episode (HR: 2.16).</td>
<td>N/A</td>
</tr>
<tr>
<td>Retrospective</td>
<td>n=382 (101 symptomatic) pts with LQT1/LQT2</td>
<td></td>
<td></td>
<td>Pts who experienced ≥ 1 episodes of syncope had a 6- to 12-fold (p&lt;0.001 for all) increase in the risk of subsequent fatal/near-fatal events independently of QTc duration.</td>
<td>Less than 1 y of age at BB initiation</td>
</tr>
<tr>
<td>Retrospective</td>
<td>n=147 pts</td>
<td>LQTS pts who underwent LCSD (99% symptomatic with 75% of those treated with BB remaining symptomatic</td>
<td>Long-term efficacy of LCSD</td>
<td>LCSD is associated with a significant reduction in the incidence of aborted cardiac arrest and syncope in high-risk LQTS pts when compared with pre-LCSD events.</td>
<td>N/A</td>
</tr>
<tr>
<td>Retrospective</td>
<td></td>
<td>Secondary prevention in 11 pts including 8 with LQTS and primary prevention</td>
<td>Outcome with LCSD using video-assisted thoracic surgery</td>
<td>Videoscopic denervation surgery, in addition to traditional LCSD, offers a safe and effective treatment option for the personalized medicine required for pts</td>
<td></td>
</tr>
</tbody>
</table>
### Size: n=20 pts including 12 with LQTS, 2 JLNS, 4 genotype negative LQTS and 2 CPVT

**Exclusion criteria:** N/A

**Results:** There were no perioperative complications. The average length of available follow-up was 16.6 ± 9.5 mo (range 4–40 mo). Among the 18 pts who underwent VATS-LCSD, the average time from operation to dismissal was 2.6 d (range 1–15 d), the majority being next-day dismissals. Among those receiving LCSD as secondary prevention, there has been a marked reduction in cardiac events.

With LQTS/CPVT.

---


**Study type:** Retrospective

**Size:** n=1,530 pts

**Inclusion criteria:** Pts with LQTS who were prescribed common BB (atenolol, metoprolol, propranolol, or nadolol).

**Exclusion criteria:** Prescribed BB after the age of 40 or have an ICD

**1st endpoint:** Compare efficacy of different BB

**Results:** In LQT1, the risk reduction for first cardiac events was similar among the 4 BB (atenolol, metoprolol, propranolol and nadolol), but in LQT2, nadolol provided the only significant risk reduction (HR: 0.40 (95%CI: 0.16 to 0.98).

- Among pts who had a prior cardiac event while taking BB, efficacy for recurrent events differed by drug ($p=0.004$), and propranolol was the least effective compared with the other BB.

- BB efficacy differed by genotype. Nadolol was the only BB associated with a significant risk reduction in pts with LQT2.

- Pts experiencing cardiac events during BB therapy are at high risk for subsequent cardiac events, and propranolol is the least effective drug in this high-risk group.

---

### Data Supplement 22. Nonrandomized Trials, Observational Studies, and/or Registries of CPVT-Medical Therapy – (Section 4.3.4)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Padfield, GJ, et al. 2016 26416620 (202)</td>
<td>Study type: Retrospective Size: n=8 pts</td>
<td>Inclusion criteria: CPVT secondary to mutations in the RyR2 gene who refused (n=1) or were intolerant to BB therapy (n=7)</td>
<td>1st endpoint: Safety of flecainide as mono-therapy in pts with CPVT</td>
<td>Flecainide mono-therapy is an option in pts with CPVT who are intolerant to BB therapy.</td>
</tr>
</tbody>
</table>

**Results:** Flecainide mono-therapy was better than, or at least as effective as, BB mono-therapy in reducing exercise-induced arrhythmia.

- No episodes of arrhythmic pre-syncop, syncope, or CA occurred in pts on flecainide mono-therapy during the follow-up period of 37.1 mo (range 1.4–75.5 mo).
<table>
<thead>
<tr>
<th>Study type:</th>
<th>Inclusion criteria:</th>
<th>1st endpoint:</th>
<th>Results:</th>
<th>Notes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational</td>
<td>Syncope due to documented or suspected VA.</td>
<td>Syncope recurrence and exercise induced VA</td>
<td>On BB therapy, the pts’ symptoms and polymorphic tachyarrhythmias disappeared. During a mean follow-up period of 7 y, 3 syncopal events and 2 sudden deaths occurred, probably due to treatment interruption.</td>
<td>First report of adrenergic-dependent ventricular tachy-arrhythmia in pts with normal QT interval and no structural heart disease. BB help suppress exercise induced arrhythmias.</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Exercise or emotion induced bidirectional VT (n=14), PMVT (n=12) and catecholaminergic idiopathic VF (n=4)</td>
<td>Clinical and genetic characterization</td>
<td>Genotype-phenotype analysis showed that pts with RyR2 CPVT have events at a younger age than do pts with non-genotyped CPVT and that male sex is a risk factor for syncope in RyR2-CPVT (RR:4.2). All 39 clinically affected pts were treated with BB; however, antiadrenergic drugs provided only incomplete protection from recurrence of sustained VT and VF. 18 of 39 pts treated with β-blockers had cardiac arrhythmias. An ICD was recommended and implanted in12/18. Over a follow-up of ≈2 y, 50% of pts with the ICD received an appropriate shock to terminate ventricular tachyarrhythmias.</td>
<td>CPVT is a clinically and genetically heterogeneous disease manifesting beyond pediatric age with a spectrum of polymorphic arrhythmias. BB reduce arrhythmias, but in 30% of pts an implantable defibrillator may be required.</td>
</tr>
<tr>
<td>Questionnaires were sent to major Japanese pediatric centers</td>
<td>1) Exercise or catecholamine induced VA (&gt;3 beats) with at least 2 morphologies 2) absence of known secondary causes including electrolyte abnormalities and structural heart disease and 3) no evidence of long QT or Brugada.</td>
<td>Questionnaire responses and ECG characteristics</td>
<td>The initial CPVT manifestations were syncope (79%), cardiac arrest (7%), and a family Hx (14%). There was 100% inducibility of CPVT by exercise, 75% by catecholamine infusion, and none by programmed stimulation. During a follow up of 6.8 (4.9) y, sudden death occurred in 24% of the pts. BB completely controlled CPVT in only 31% of cases. Calcium antagonists partially suppressed CPVT</td>
<td>Pts with CPVT have a poor prognosis. BB do not always control symptoms thus the need for other pharmacological and non-pharmacological therapies.</td>
</tr>
<tr>
<td>Study type</td>
<td>Inclusion criteria</td>
<td>1st endpoint</td>
<td>Results</td>
<td>Notes</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------</td>
<td>--------------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>Multicenter observational study</td>
<td>Exercise induced polymorphic ventricular arrhythmias or identification of a mutation in the RYR2 or CASQ2 gene</td>
<td>Incidence of cardiac events (exertional or stress induced syncope, aborted CA, appropriate ICD shocks or SCD)</td>
<td>During a mean follow-up of 7.9 y, cardiac events occurred in 27 pts (27%), including 2 mutation carriers with normal exercise tests. The estimated 8 y event rate was 32% in the total population and 27% and 58% in the pts with and without BB, respectively. Absence of BB HR: 5.48; 95% CI: 1.80–16.68) and younger age at diagnosis (HR: 0.54 per decade; 95% CI: 0.33–0.89) were independent predictors. The estimated 8 y event rate for fatal or near fatal events (ACA, SCD) was 13%. Absence of BB (HR: 5.54; 95% CI: 1.17–26.15) and Hx of aborted CA (HR: 13.01; 95% CI: 2.48–68.21) were independent predictors. BB reduce the cardiac event rate in both CPVT pts and affected families; however, they are not completely protective.</td>
<td>Autosomal dominant cases.</td>
</tr>
<tr>
<td>Meta-analysis including 11 studies using BB and review of other therapies</td>
<td>CPVT pts</td>
<td>Arrhythmic, non-fatal and fatal events</td>
<td>Median FU was 20 mo 8 y. 88% of pts were given BB. The estimated overall 4- and 8 y arrhythmic event rates were 18.6% (95% CI: 8.3–28.9) and 37.2% (95% CI: 16.6–57.7), respectively. Estimated 4- and 8 y near-fatal arrhythmic event rates were 7.7% (95% CI: 3.7–11.7) and 15.3% (95% CI: 7.4–23.3), respectively. Fatal events occurred in 3.2% (95% CI: 1.6–4.8) at 4 y and 6.4% (95% CI: 3.2–9.6) at 8 y follow-up. The variability in outcome with BB therapy is due to multiple factors including the dose, compliance and concomitant use of other drugs including flecainide and Verapamil.</td>
<td></td>
</tr>
<tr>
<td>Chart review from 8 tertiary referral centers</td>
<td>1) Exercise induced PMVT or bidirectional VT 2) Mutation in the gene encoding RyR2 or cardiac Calsequestrin</td>
<td>Reduction of VA during exercise testing</td>
<td>Exercise tests comparing flecainide in pts with CPVT not controlled by conventional drug therapy.</td>
<td></td>
</tr>
<tr>
<td>Study Type</td>
<td>Size</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>1st Endpoint</td>
</tr>
<tr>
<td>------------</td>
<td>------</td>
<td>--------------------</td>
<td>-------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Swan, et al. 2005</td>
<td>n=6 pts</td>
<td>Pts with clinical diagnosis of CPVT and carrying a RyR2 mutation</td>
<td>N/A</td>
<td>Effect of verapamil and magnesium on exercise induced VA.</td>
</tr>
<tr>
<td>Rosso, et al. 2007</td>
<td>n=5 pts</td>
<td>CPVT pts with a Hx of syncope or CA and exercise induced ventricular ectopy despite maximally tolerated BB therapy</td>
<td>N/A</td>
<td>Exercise induced arrhythmias and clinical outcome</td>
</tr>
<tr>
<td>Sy R, et al. 2011</td>
<td>n=27 pts</td>
<td>Hx of sudden cardiac arrest or symptoms occurring in the context of physical activity or acute emotion in conjunction with exercise or adrenaline-induced polymorphic or bidirectional VT of ≥ 4 beats.</td>
<td>First-degree relatives of affected individuals</td>
<td>Long-term outcome and relation between age and clinical presentation</td>
</tr>
</tbody>
</table>
were diagnosed with CPVT if polymorphic or bidirectional
• VT was observed during exercise or adrenaline challenge, on Holter monitoring, or if genetic testing was positive for the disease-causing mutation in the family.

**Exclusion criteria:** N/A

- During follow-up of 6.2±5.7 y, 2 pts died despite having an ICD, 4 pts received ICD therapy for VT, and 5 pts had inappropriate therapy for SVT. Pts presenting with late-onset CPVT (>21 y of age; n=10) were often female (80%) and less likely to have RyR2 (Ryanodine receptor type 2) mutations (33%), and fatal events were not observed during follow-up (4.1±3.6 y).

**Roston TM, et al. 2015 25713214 (212)**

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moray A, et al. 2011 21478052 (213)</td>
</tr>
</tbody>
</table>

**Study type:** Retrospective case report

**Size:** n=1 patient

**Inclusion criteria:** 10 y of age boy with CPVT

**Exclusion criteria:** N/A

**1<sup>st</sup> endpoint:** Safety of simultaneous ICD insertion and thoracoscopic sympathectomy

**Results:** The procedure was safe suggesting that it is a better approach than sequential procedures

**Summary/Conclusion**

• Simultaneous ICD insertion and thoracoscopic sympathectomy is feasible and safe in pts with CPVT

---

### Data Supplement 23. Nonrandomized Trials, Observational Studies, and/or Registries of CPVT- LSCD and ICD Therapy – (Section 4.3.4)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Moray A, et al. 2011 21478052 (213)  | **Study type:** Retrospective case report | **Inclusion criteria:** 10 y of age boy with CPVT | **1<sup>st</sup> endpoint:** Safety of simultaneous ICD insertion and thoracoscopic sympathectomy | **Results:** The procedure was safe suggesting that it is a better approach than sequential procedures | **Summary/Conclusion**

• Simultaneous ICD insertion and thoracoscopic sympathectomy is feasible and safe in pts with CPVT
<table>
<thead>
<tr>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective</td>
<td>n=16 children pts</td>
<td>Diagnosis of CPVT</td>
<td>Clinical features, treatment and outcome</td>
<td>The mean age of pts at the onset of symptoms and at the time of diagnosis was 7.8 ± 2.5 y, and 10.6 ± 3.5 y, respectively. Syncope was the main complaint in 11. Treatment included propranolol plus verapamil if VT was still inducible. ICD was implanted in 4 pts. Of the 16 pts, 4 died suddenly, giving a rate of mortality of 25%.</td>
<td>CPVT must be considered in the differential diagnosis of syncope in children without heart disease but with a normal QT interval. Medical treatment with propranolol and verapamil may decrease the incidence of arrhythmia. Implantation of an ICD should be considered in those resistant to drug therapy.</td>
</tr>
<tr>
<td>Retrospective single center experience</td>
<td>n=3 pts</td>
<td>CPVT with symptoms despite BB therapy 3/3 and mexiletine (1/3)</td>
<td>Cardiac events</td>
<td>LCSD resulted in marked reduction in cardiac arrhythmias and improvement in QOL.</td>
<td>First study to provide evidence that left cardiac sympathetic denervation may be an effective alternative treatment, especially for pts whose symptoms are not adequately controlled by means of BB therapy.</td>
</tr>
<tr>
<td>Retrospective including pts from 11 centers worldwide</td>
<td>n=63 pts</td>
<td>Asymptomatic and symptomatic pts</td>
<td>Cardiac events</td>
<td>LCSD was performed in 9 asymptomatic and 54 symptomatic pts including 38 pts (25 syncope) with breakthrough events despite optimal medical therapy. The 1 and 2 y cumulative event-free survival rates were 87% and 81%. The percentage of pts with major cardiac events despite optimal medical therapy (n=38) was reduced from 100% to 32% (p &lt; 0.001) after LCSD.</td>
<td>LCSD is an effective antifibrillatory intervention for pts with CPVT. Whenever syncope occurs despite optimal medical therapy, LCSD could be considered the next step rather than an ICD and could complement ICDs in pts with recurrent shocks.</td>
</tr>
<tr>
<td>Retrospective Survey-based</td>
<td>n=47 pts who underwent LCSD including 40 with LQTS and 7 with CPVT</td>
<td>Underwent video-assisted thoracoscopic LCSD and completion of a telephone survey</td>
<td>Physical and psychological effects of LCSD and pts satisfaction</td>
<td>Side effects were reported by 42 of 44 (95%), 29 (66%) reported left sided dryness, 26 (59%) a Harlequin-type (unilateral) facial flush, 24 (55%) contralateral hyperhidrosis, 17 (39%) differential hand temperatures, 5 (11%) permanent ptosis (4</td>
<td>Despite significant morbidity resulting from LCSD, pts with LQTS and CVPT have high levels of post-operative satisfaction.</td>
</tr>
</tbody>
</table>
(9%) transient ptosis. 5 (11%) have thermoregulation difficulties, 4 (9%) a sensation of left arm paraesthesia and 3 (7%) lost their sympathetic flight/fright response.

- 38 pts (86%) were happy with procedure, 33 (75%) felt safer and 40 (91%) recommend the procedure. 40 (91%) pts were happy with their scar.

- ICD should be recommended in pts refractory to BB therapy.
- These pts may have recurrent ventricular tachycardia storms treated but not terminated by recurrent ICD shocks, without degeneration to ventricular fibrillation.

### Data Supplement 24. Nonrandomized Trials, Observational Studies, and/or Registries of Early Repolarization Pattern – (Section 4.3.5)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahida S, et al. 2015</td>
<td>Study type: Retrospective</td>
<td>Inclusion criteria: ER syndrome with a history of aborted sudden</td>
<td>1° endpoint: Inducibility of VA</td>
<td>• Programmed stimulation protocols do not enhance risk</td>
</tr>
<tr>
<td>Study ID</td>
<td>Study Description</td>
<td>Study Type</td>
<td>Size</td>
<td>Inclusion Criteria</td>
</tr>
<tr>
<td>----------</td>
<td>------------------</td>
<td>------------</td>
<td>------</td>
<td>-------------------</td>
</tr>
<tr>
<td>25593056 (220)</td>
<td>multicenter study</td>
<td>Retrospective</td>
<td>n=81 pts</td>
<td>death due to ventricular fibrillation</td>
</tr>
<tr>
<td>Morady F, et al. 1986 3717024 (221)</td>
<td>Study type: Retrospective</td>
<td>Size: n=109 pts</td>
<td>Inclusion criteria: 52 pts with a Hx of documented, sustained monomorphic VT and inducible VT and 57 pts with non-clinical inducible polymorphic VT or VF.</td>
<td>Exclusion criteria: N/A</td>
</tr>
<tr>
<td>Nunn LM, et al. 2011 21737021 (222)</td>
<td>Study type: Retrospective</td>
<td>Size: n=363 pts</td>
<td>Inclusion criteria: Families of sudden arrhythmic death syndrome probands</td>
<td>Exclusion criteria: N/A</td>
</tr>
<tr>
<td>Haissaguerre M, et al. 2008 18463377 (223)</td>
<td>Study type: Retrospective</td>
<td>Size: n=206 case pts and 412 control pts matched for age, sex, race and level of physical activity</td>
<td>Inclusion criteria: Resuscitated from cardiac arrest due to idiopathic VF</td>
<td>Exclusion criteria: Age &gt;60 y of age</td>
</tr>
</tbody>
</table>
| Rosso, et al. 2008 18926326. (224) | Study type: Case control study | Size: n=45 pts with Idiopathic VF compared with age and sex matched control pts | Inclusion criteria: Idiopathic VF | Exclusion criteria: Age >60 y of age | 1° endpoint: Prevalence of J point and ST elevation **Results:** J-point elevation was more common among pts with idiopathic VF than among matched control pts (42% vs. 13%, p<0.001). | J-point elevation is found more frequently among pts with idiopathic VF than among healthy control pts. The frequency of J-
<table>
<thead>
<tr>
<th>Study type</th>
<th>Exclusion criteria</th>
<th>Inclusion criteria</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merchant FM et al. 2009 19892058 (225)</td>
<td>Exclusion criteria: The presence of an etiology for the cardiac arrest</td>
<td>Inclusion criteria: Idiopathic VF and ICD implant</td>
<td><strong>1° endpoint:</strong> Prevalence of ER and QRS notching&lt;br&gt;&lt;br&gt;<strong>Results:</strong> ER was present in 9/39 (23%) pts. QRS notching was significantly more prevalent among cases when present in leads V4 (44% vs. 5%, p=0.001) and V5 (44% vs. 8%, p=0.006), with a similar trend in lead V6 (33% vs. 5%, p=0.013).&lt;br&gt;&lt;br&gt;<strong>•</strong> Left precordial terminal QRS notching is more prevalent in malignant variants of ER than in benign cases.</td>
</tr>
<tr>
<td>Tikkanen et al. 2009 19917913 (226)</td>
<td>Exclusion criteria: Structural heart disease, CAD or the presence of an arrhythmia susceptibility syndrome (LQTS, SQTS, WPW, BS or ARVD)</td>
<td>Inclusion criteria: Community based general population</td>
<td><strong>1° endpoint:</strong> Prevalence and prognostic significance of ER including death from cardiac cause, death from arrhythmia and death from any causes&lt;br&gt;&lt;br&gt;<strong>Results:</strong> ER was present in 630 pts (5.8%): 384 (3.5%) in inferior leads and 262 (2.4%) in lateral leads, with elevations in both leads in 16 pts (0.1%).&lt;br&gt;&lt;br&gt;<strong>•</strong> J-point elevation of at least 0.1 mV in inferior leads was associated with an increased risk of death from cardiac causes (adjusted RR: 1.28; 95% CI: 1.04–1.59; p=0.03).&lt;br&gt;&lt;br&gt;<strong>•</strong> J-point elevation of more than 0.2 mV in inferior leads (n=26; 0.3%) had a markedly elevated risk of death from cardiac causes (adjusted RR: 2.98; 95% CI: 1.85–4.92; p&lt;0.001) and from arrhythmia (adjusted RR: 2.92; 95% CI: 1.45–5.89; p=0.01).&lt;br&gt;&lt;br&gt;<strong>•</strong> An ER pattern in the inferior leads of a standard ECG is associated with an increased risk of death from cardiac causes in middle-aged pts.</td>
</tr>
<tr>
<td>Patel et al. 2010 20657030 (227)</td>
<td>Exclusion criteria: Pts who had an acute MI during follow up, suspected BS and pts with QRS ≥120 ms</td>
<td>Inclusion criteria: CAD + ICD implant + sustained arrhythmic events&lt;br&gt;&lt;br&gt;<strong>1° endpoint:</strong> Prevalence of ER&lt;br&gt;&lt;br&gt;<strong>Results:</strong> Overall, early repolarization in 2 or more leads was more common in cases than control pts (32% vs. 8%, P=0.005). Early repolarization was noted more commonly in inferior leads (23% vs. 8%, p=0.03), and a trend was noted in leads V4 through V6 (12% vs. 3%, p= 0.11).&lt;br&gt;&lt;br&gt;<strong>•</strong> ER and, in particular, notching in the inferior leads is associated with increased risk of life-threatening VA in pts with CAD, even after adjustment for LVEF.</td>
<td></td>
</tr>
<tr>
<td>Tikkanen et al.</td>
<td>Inclusion criteria: Pts participating&lt;br&gt;&lt;br&gt;<strong>1° endpoint:</strong> Mortality over a 30±11 y follow up period</td>
<td><strong>•</strong> ST-segment morphology</td>
<td></td>
</tr>
</tbody>
</table>
in the Finnish Social Insurance Institution’s Coronary Heart Disease Study who had undergone clinical baseline examinations between 1966 and 1972.

Exclusion criteria: Pts with missing data

Results: Pts with ER ≥ 0.1 mV and horizontal/descending ST variant (n=412) had an increased HR of arrhythmic death (RR: 1.43; 95% CI: 1.05–1.94).

- When modeled for higher amplitude ER (>0.2 mV) in inferior leads and horizontal/descending ST-segment variant, the HR of arrhythmic death increased to HR: 3.14 (95% CI: 1.56–6.30).

- However, in pts with ascending ST variant, the relative RR for arrhythmic death was not increased (RR: 0.89; 95% CI: 0.52–1.55).

variants associated with ER separates pts with and without an increased risk of arrhythmic death in middle-aged pts.

- Rapidly ascending ST segments after the J-point, the dominant ST pattern in healthy athletes, seems to be a benign variant of ER

---

Sinner, et al. 2010

Study type: Population based study applying a case-cohort design

Size: n=1,945 pts representing a source population of 6,213 individuals, were analyzed

Inclusion criteria: 25-74 y of age

Exclusion criteria: N/A

1° endpoint: Prevalence of ERP and its association with cardiac and all-cause mortality

Results: Prevalence of ERP was 13.1%. ERP was associated with cardiac and all-cause mortality, most pronounced in those of younger age and male sex; a clear ERP-age interaction was detected (p=0.005).

- Age-stratified analyses showed HRs for cardiac mortality of 1.96 (95% CI: 1.05–3.68, p=0.035) for both sexes and 2.65 (95% CI: 1.21–5.83, p=0.015) for men between 35–54 y of age. An inferior localization of ERP further increased ERP-attributable cardiac mortality to HRs of 3.15 (95% CI: 1.58–6.28, p=0.001) for both sexes and to 4.27 (95% CI: 1.90–9.61, p<0.001) for men between 35-54 y of age.

- ERP was associated with about a 2- to 4-fold increased risk of cardiac mortality in individuals between 35 and 54 y. An inferior localization of ERP was associated with a particularly increased risk.
<table>
<thead>
<tr>
<th>Study type</th>
<th>Size: n=15 pts</th>
<th>Aim:</th>
<th>Inclusion: Healthy volunteers</th>
<th>Intervention:</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; endpoint:</th>
<th>Safety endpoint:</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schroeder, et al. 2002</td>
<td>12451007 (231)</td>
<td>To assess water drinking on orthostatic tolerance in healthy pts</td>
<td>to room temperature</td>
<td>Drinking 500 mL water prolonged time to presyncope in 11 pts from 31 +/- 3 min to 36 +/- 3 min (P&lt;0.001). Supine heart rate, BP, SV, and cardiac output were not significantly different with 500 mL water drinking. With HUTT, 500 mL water drinking blunted decrease in SV from -45 +/- 2% to -38 +/- 3%, p&lt;0.01</td>
<td>N/A</td>
<td>Water drinking 500 mL increases orthostatic tolerance, with the effect apparently mediated with factors beyond increasing plasma volume. Increase in peripheral resistance and vasoconstrictor tone may have role.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study type</th>
<th>Size: n=13 pts</th>
<th>Aim:</th>
<th>Inclusion: Recurrent syncope without etiology</th>
<th>Intervention:</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; endpoint:</th>
<th>Safety endpoint:</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>El-Sayed, et al. 1996</td>
<td>8673750 (232)</td>
<td>To evaluated salt supplementation in syncope with orthostatic intolerance,</td>
<td></td>
<td>RDBPCT:</td>
<td>RDBPCT: 8 of 10 pts taking salt, vs. 3 of 10 taking placebo showed significant increases in plasma and blood volumes (p=0.05); all pts with increased plasma and blood volumes showed improved tolerance to orthostatic stress (time to presyncope)</td>
<td>N/A</td>
<td>Pts with salt supplementation (increasing plasma volume by &gt;90 mL) had significant increase in orthostatic tolerance. Pts with signs of high salt intake at baseline (by 24 H urinary sodium excretion) did not benefit from additional salt loading.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria:</th>
<th>Intervention:</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Safety endpoint:</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brignole M, et al. 2002</td>
<td>≥1 episode of syncope; ≥1 syncopal episodes preceded by prodromal; syncope reproduced during 2 tilt tests performed on different days</td>
<td>Hand-grip or arm-tensing</td>
<td></td>
<td>63% in the active arm became asymptomatic vs. 11% in control (p=0.02); 5% vs. 47% developed syncope (p=0.01). F/U 9+3m 99% performing maneuver prevented syncope</td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>1° endpoint</th>
<th>1° Safety endpoint</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Dijk, et al. 2006 17045903 (234)</td>
<td>Assess effectiveness of PCM in daily life</td>
<td>Randomized (multicenter)</td>
<td>n=223 pts; standard n=117; standard+PCM n=106</td>
<td>Recurrent syncope and prodome (≥3 syncope episodes in 2 y or (≥1 syncope and ≥3 presyncope in 1 y)</td>
<td>Heart disease, OH, other causes for syncope, life-expectancy &lt;1; unable to follow-up</td>
<td>Conventional therapy+ PCM (leg-crossing, hand grip, arm tensing)</td>
<td>Conventional therapy</td>
<td>Syncope recurrence</td>
<td>N/A</td>
<td>Isometric arm contraction helps to abort impending syncope BP increased</td>
</tr>
<tr>
<td>Foglia-Manzillo, et al. 2004 15121070 (235)</td>
<td>Efficacy of tilt training in preventing tilt-induced syncope</td>
<td>Randomized (multicenter)</td>
<td>n=68 pts; tilt-training n=35; controls n=33</td>
<td>Recurrent syncope; 2 consecutive positive nitrate-potentiated head-up tilt test</td>
<td>Other causes of syncope</td>
<td>Tilt-training (30min standing against wall 6 days a 1 wk x 3 wk).</td>
<td>No tilt-training</td>
<td>Positive tilt test; syncope recurrence</td>
<td>N/A</td>
<td>Tilt-training not effective in reducing tilt-testing positivity because of poor compliance</td>
</tr>
<tr>
<td>On YK, et al. 2007 17461874 (236)</td>
<td>Effectiveness of repeated home orthostatic self-training</td>
<td>Randomized</td>
<td>n=33 pts; tilt-training n=16; control n=17</td>
<td>VVS by positive HUTT</td>
<td>Other causes of syncope after comprehensive evaluation, structural heart disease.</td>
<td>Daily sessions x 4 wk. Standing against wall 1–2 times a day until prodrome of for up to 30 min</td>
<td>No tilt-training</td>
<td>Tilt response at 1 min; syncope recurrence</td>
<td>N/A</td>
<td>56% positive HUT in training group and 53% in control (p=0.85); syncope or pre-syncope occurred in 42.9% vs. 41.5% controls (p=0.82) during 16.9 m of F/U.</td>
</tr>
<tr>
<td>Duygu, et al. 2008</td>
<td>Effectiveness of repeated orthostatic self-</td>
<td></td>
<td></td>
<td>Recurrent syncope (≥2 events in 6m)</td>
<td></td>
<td>Conventional+tilt-training (Standing against wall 1-</td>
<td></td>
<td></td>
<td>Follow up 12±2 m; syncope recurrence 56% control and</td>
<td></td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
<table>
<thead>
<tr>
<th><strong>18439174</strong> (237)</th>
<th>training</th>
<th>Study type: Randomized</th>
<th>Size: n=82 pts; 1:1</th>
<th>and + HUTT</th>
<th>Exclusion criteria: Other causes of syncope after comprehensive evaluation</th>
<th>Intervention: 2X a d until prodrome of for up to 30 min x 1m; then every other day x2 m then 2x a wk</th>
<th>Comparator: Conventional</th>
<th>1° Safety endpoint: N/A</th>
<th>37% tilt-training (p=0.1); frequency of recurrence similar in all types of VVS; rate of episodes higher in vasodepressor type.</th>
<th>Summary: Tilt-training did not reduce syncope recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salim, et al. 2005 15708690 (238)</strong></td>
<td><strong>Aim:</strong> Effectiveness of salt and fludrocortisone in prevention of VVS in children</td>
<td>Study type: Randomized (pediatric)</td>
<td>Size: n=32 pts; florinef 0.1mg/day and salt 1g/d n=18; control n=14</td>
<td>Inclusion criteria: ≥3 syncope in 2 y; prodrome in 80% episodes; +HUTT</td>
<td>Completion criteria: No structural heart disease</td>
<td>Intervention: florinef 0.1mg/day and salt 1g/d</td>
<td>Comparator: Placebo</td>
<td>1° endpoint: Syncope or pre-syncope recurrence</td>
<td>1° Safety endpoint: N/A</td>
<td>• Follow up 176+117d; recurrence 36% in controls and 55% active arm (p&lt;0.04).</td>
</tr>
<tr>
<td><strong>Romme JJ, et al. 2011 21752826 (239)</strong></td>
<td><strong>Aim:</strong> Effectiveness of midodrine in pts not responding to non-pharmacological treatment (STAND-trial)</td>
<td>Study type: randomized, double-blind crossover (3 m then 1 wk washout)</td>
<td>Size: n=23 pts</td>
<td>Inclusion criteria: ≥3 syncope in 2 y; prodrome in 80% episodes; +HUTT</td>
<td>Exclusion criteria: LOC not due to VVS; already using pharmacotherapy for rx VVS</td>
<td>Intervention: Midodrine</td>
<td>Comparator: Placebo</td>
<td>1° endpoint: Recurrence of syncope or presyncope, side effects and QoL recurrence did not differ between treatment (48 vs. 65% , p=0.22); (74 vs. 78%, p=0.90) • Side effects and QoL did not differ.</td>
<td>1° Safety endpoint: N/A</td>
<td>Summary: Addition of midodrine to non-pharmacological therapy not effective</td>
</tr>
<tr>
<td><strong>Kaufman H, et al. 2002 12205647 (240)</strong></td>
<td><strong>Aim:</strong> Efficacy of midodrine</td>
<td>Study type: Randomized, double-blind cross-over</td>
<td>Size: n=12 (5 mg or placebo day 1 and opposite on day 3)</td>
<td>Inclusion criteria: ≥2 syncope in 1 y; +HUT</td>
<td>Exclusion criteria: N/A</td>
<td>Intervention: Midodrine</td>
<td>Comparator: Placebo</td>
<td>1° endpoint: Recurrence of syncope</td>
<td>1° Safety endpoint: N/A</td>
<td>• Midodrine produced no significant change in BP or heart rate • Response to HUT: NMS 67% on placebo and 17% on midodrine (p&lt;0.02)</td>
</tr>
<tr>
<td>Study Type</td>
<td>Size</td>
<td>Inclusion Criteria</td>
<td>Intervention</td>
<td>Endpoint</td>
<td>Safety Endpoint</td>
<td>Summary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>------</td>
<td>-------------------</td>
<td>--------------</td>
<td>----------</td>
<td>----------------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perez-Lugones, et al. 2001</td>
<td>n=61 pts; midodrine n=31; conventional n=30</td>
<td>≥1 syncope per mo and (2) a positive HUTT.</td>
<td>Midodrine (5 mg po id titrated up to 15 tid if required) q 6 daytime</td>
<td>Syncope recurrence</td>
<td>N/A</td>
<td>Midodrine provides a significant benefit compared to conventional therapy.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ward, et al. 1998</td>
<td>n=16 pts</td>
<td>&gt;2 pre-syncope or syncope; no HTN meds; reproducible syncope with GTN on HUTT</td>
<td>Midodrine x 1 mo</td>
<td>Symptom frequency and hemodynamic response HUTT</td>
<td>N/A</td>
<td>Midodrine associated with reduced symptom frequency; symptom HUTT and improved QoL.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qingyou, et al. 2006</td>
<td>n=26 pts; midodrine+ conventional n=13; conventional n=13</td>
<td>≥3 syncope/y</td>
<td>conventional + midodrine (1.25 mg bid if +HUTT after 1wk then increased 2.5 mg bid then another med added if still +HUTT after 1 wk)</td>
<td>Syncope recurrence</td>
<td>N/A</td>
<td>Midodrine effective in treating VVS in children.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Study Type</td>
<td>Size</td>
<td>Inclusion Criteria</td>
<td>Intervention</td>
<td>Comparator</td>
<td>1st Endpoint</td>
<td>1st Safety Endpoint</td>
<td>Summary</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-----</td>
<td>------------</td>
<td>------</td>
<td>-------------------</td>
<td>--------------</td>
<td>------------</td>
<td>--------------</td>
<td>-----------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Madrid, et al. 2001 11216978 (244)</td>
<td><strong>Aim:</strong> Efficacy of atenolol</td>
<td>Randomized (double-blind and placebo-controlled)</td>
<td>n=50 pts; atenolol n=26; placebo n=24</td>
<td>≥2 syncope 1 y</td>
<td>Atenolol 50 mg/d</td>
<td>Placebo</td>
<td>Time to syncope recurrence</td>
<td>N/A</td>
<td>Recurrence of syncope similar in pts treated with atenolol compared to placebo.</td>
<td></td>
</tr>
<tr>
<td>Flevari, et al. 2002 12142117 (245)</td>
<td><strong>Aim:</strong> Efficacy of propranolol, nadolol and placebo in recurrent VVS</td>
<td>Randomized 3 mo cross-over</td>
<td>n=33</td>
<td>≥2 syncope 3m; +HUTT</td>
<td>Propranolol, nadolol, placebo 3 mo cross-over</td>
<td>See above</td>
<td>Syncope and presyncope recurrence</td>
<td>N/A</td>
<td>Follow up 3m periods syncope and presyncope reduced by all drugs; [ANOVA]: chi-square =67.4; p&lt;0.0001 for syncopal attacks; chi-square =60.1; p&lt;0.0001 for presyncope attacks. B-blockers and placebo equally effective in decreasing syncope and presyncope.</td>
<td></td>
</tr>
<tr>
<td>Brignole, et al. 1992 1632399 (246)</td>
<td><strong>Aim:</strong> Efficacy of medical treatment in preventing VVS</td>
<td>Randomized</td>
<td>n=30 pts; 1:1</td>
<td>Frequent, unexplained syncope or presyncope; 2 +HUTT</td>
<td>Drugs: atenolol n=7; dihydroergotamine n=2; domperidone n=2; cafedrine n=1; stocking ± drug n=3</td>
<td>Placebo</td>
<td>Syncope recurrence</td>
<td>N/A</td>
<td>Follow up 10±7m; absence of syncope recurrence after 20m 70% treatment and 67% placebo. Outcomes similar in either medically treated or placebo groups.</td>
<td></td>
</tr>
<tr>
<td>POST Sheldon, et al. 2006 16505178 (247)</td>
<td><strong>Aim:</strong> Effectiveness of b-blockers in prevention VVS</td>
<td>Randomized (multicenter)</td>
<td>n=208 pts; metoprolol n=108; placebo n=100</td>
<td>≥2 syncope over lifetime or ≥1 syncope 6 mo; ++HUTT</td>
<td>Metoprolol</td>
<td>Placebo</td>
<td>Syncope recurrence</td>
<td>N/A</td>
<td>36% in control and 36% metoprolol (p=0.99). Syncope recurrence did not differ between metoprolol or placebo groups.</td>
<td></td>
</tr>
</tbody>
</table>
| **Theodorakis, et al. 2006**<br>16627439 (248) | **Aim:** Effectiveness of placebo, propranolol, fluoxetine in VVS  
**Study type:** Randomized (multicenter)  
**Size:** n=96 pts; placebo n=22; propranolol n=24; fluoxetine n=30  
**Inclusion criteria:** ≥5 syncope lifetime or ≥2 in 1 y, last 1m prior; no drugs  
**Exclusion criteria:** Other cause of syncope; contraindications to study medications  
**Intervention:** Placebo, propranolol, fluoxetine  
**Comparator:** See above  
**1° endpoint:** Syncope or pre-syncope recurrence  
**1° Safety endpoint:** N/A  
• 41% controls, 51% metoprolol, 22% fluoxetine, log rank p>0.05; well-being improved in the fluoxetine group (p<0.01) before and after treatment.  
**Summary:** Fluoxetine equivalent to propranolol and placebo; effective for reducing pre-syncope; improves well-being. |
| --- | --- | --- | --- |
| **Takata TS, et al. 2002**<br>12234955 (249) | **Aim:** Effect of fluoxetine on CV reflexes  
**Study type:** Randomized (double-blind)  
**Size:** n=19; control n=10; fluoxetine n=9  
**Inclusion criteria:** Healthy; +CSM or LBNP (lower body negative pressure)  
**Exclusion criteria:** Psychiatric, neurological or cardiac disease, prior SSRI or MOI  
**Intervention:** Fluoxetine 20 mg daily  
**Comparator:** Placebo  
**1° endpoint:** Syncope  
**1° Safety endpoint:** N/A  
• Decreases arterial baroreceptor sensitivity but does not prevent presyncope LBNP.  
**Summary:** Prevention of presyncope does not occur in LBNP. |
| **Di Girolamo, et al. 1999**<br>10193720 (250) | **Aim:** Effectiveness of paroxetine in VVS resistant to other drugs  
**Study type:** Randomized  
**Size:** n=68; 1:1  
**Inclusion criteria:** Recurrent syncope; failed conventional therapy; +HUTT  
**Exclusion criteria:** Other causes of syncope after comprehensive evaluation (EPS); depression or panic disorder  
**Intervention:** Paroxetine 20 mg daily  
**Comparator:** Placebo  
**1° endpoint:** Syncope recurrence  
**1° Safety endpoint:** N/A  
• 17.6% paroxetine vs. 52.9% placebo (p<0.0001)  
**Summary:** Paroxetine improves recurrence in pts intolerant to conventional therapy. |
| **Gaggioli, et al. 1997**<br>9352988 (251) | **Aim:** To determine the effect of vasodilator therapy on upright tilt testing for syncope  
**Study type:** Case-control randomized study  
**Inclusion criteria:** 1) ≥1 episodes of syncope occurring during chronic (>6 m) vasodilator treatment with angiotensin-converting enzyme inhibitors, long-acting nitrates, or calcium antagonists, or an association  
**Intervention:** Vasodepressor therapy continued  
**Comparator:** Vasodepressor therapy discontinued  
**1° endpoint:** Vasovagal reaction during upright tilt testing 2 wk after randomization  
**1° safety:** N/A  
**Results:** TTT positive in 85% who continued vasodepressor therapy and 52% who discontinued (p=0.02); type of medication did not influence results  
**Summary:** Chronic vasodilator |
of these or with diuretics, all given within the recommended dosage range; 2) positive response to upright TTT performed during the same treatment which had been administered at the time of the occurrence of the spontaneous syncopal spell(s); and 3) negative work-up for other causes of syncope.

**Exclusion criteria:**
Identifiable causes of syncope
1) OH, which was defined as a decline 220 mm Hg in SBP, or ~10 mm Hg in DBP, within 3 min of standing or using a tilt table in the head-up position, at an angle of ~60°; 2) presence of important clinical conditions contraindicating the interruption of vasodilator therapy, namely, overt HF, severe hypertension, etc; (3) recent (within the previous 6 mo) MI or stroke or other diseases; (4) very severe general diseases; (5) concomitant therapy with BB or any other vasoactive drugs; and (6) intermittent or discontinuous vasodilator administration.

therapy enhances susceptibility to VVS during TTT.
### Data Supplement 26. Nonrandomized Trials, Observational Studies, and/or Registries of Vasovagal Syncope – (Section 5.1.1)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design*; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitt, et al. 2004 15316842 (252)</td>
<td><strong>Study type:</strong> Observational Determine whether syncope pts and control pts show different responses of BP to postural maneuvers; carbohydrate or water <strong>Size:</strong> n=7 pts</td>
<td><strong>Inclusion criteria:</strong> syncope or presyncope related to upright posture; zepisode in prior 6 m; +HUTT: drop in SBP &lt;80 mmHg with symptoms <strong>Exclusion criteria:</strong> Evidence of cardiac or neurological etiology on work-up</td>
<td><strong>1st endpoint:</strong> BP response</td>
<td>• In pts with posturally related syncope unlike in control; carbohydrate ingestion and water result in opposite effects on BP during postural maneuvers.</td>
</tr>
<tr>
<td>Krediet, et al. 2002 12270863 (253)</td>
<td><strong>Study type:</strong> Observational Effects of leg crossing and lower body tensing 30s <strong>Size:</strong> n=21 pts</td>
<td><strong>Inclusion criteria:</strong> Recurrent VVS syncope; positive tilt table <strong>Exclusion criteria:</strong> Other causes of syncope after comprehensive evaluation</td>
<td><strong>1st endpoint:</strong> Syncope or presyncope recurrence after tilt test and use of counter-maneuvers</td>
<td><strong>Counter-maneuvers can help to alleviate prodromal symptoms and can prevent in some recurrent syncope.</strong> • BP increased</td>
</tr>
<tr>
<td>Di Girolamo, et al. 1999 10534467 (254)</td>
<td><strong>Study type:</strong> Controlled Study, standing against wall up to 40 min <strong>Size:</strong> n=47 pts; consent n=24 and refusal (n=23)</td>
<td><strong>Inclusion criteria:</strong> Refractory VVS syncope; positive nitrate-potentiated head-up tilt test <strong>Exclusion criteria:</strong> Other causes of syncope after comprehensive evaluation</td>
<td><strong>1st endpoint:</strong> Syncope recurrence</td>
<td>• Tilt training significantly improves symptoms in those unresponsive or intolerant of medications.</td>
</tr>
<tr>
<td>Reybrouck, et al. 2002 12418741 (255)</td>
<td><strong>Study type:</strong> Observational (long term flu); 1-2m against will <strong>Size:</strong> n=38</td>
<td><strong>Inclusion criteria:</strong> Recurrent VVS syncope and positive tilt without pharmacological provocation <strong>Exclusion criteria:</strong> Other causes of syncope after comprehensive evaluation</td>
<td><strong>1st endpoint:</strong> Syncope recurrence</td>
<td>• Syncope recurrence may improve symptoms.</td>
</tr>
<tr>
<td>Kinay, et al. 2004 15557724 (256)</td>
<td><strong>Study type:</strong> Observational In-hospital training: 3 consecutive session w/o</td>
<td><strong>Inclusion criteria:</strong> Recurrent VVS syncope; positive nitrate-potentiated head-up tilt test</td>
<td><strong>1st endpoint:</strong> Syncope recurrence</td>
<td>• Short-term tilt-training is effective.</td>
</tr>
<tr>
<td>Study Acronym</td>
<td>Author</td>
<td>Year</td>
<td>Aim of Study</td>
<td>Study Type*; Study Size (N)</td>
</tr>
<tr>
<td>---------------</td>
<td>--------</td>
<td>------</td>
<td>--------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Connolly, et al. 1999 9935002 (260)</td>
<td>Aim: Effectiveness of PPM compared with pharmacological therapy in recurrent VVS</td>
<td>Inclusion criteria: ≥6 lifetime syncope; +HUTT Exclusion criteria: Other causes of syncope after comprehensive evaluation</td>
<td>Intervention: PPM with rate drop Comparator: Placebo</td>
<td>1° endpoint: Syncope recurrence</td>
</tr>
</tbody>
</table>

Data Supplement 27. RCTs Comparing Pacemakers in Vasovagal Syncope – (Section 5.1.2)
<table>
<thead>
<tr>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>1st endpoint</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sutton R, et al. 2000 10899092 (261)</td>
<td>n=54;1:1 (terminated early)</td>
<td>≥3 syncope 2 y; + cardio inhibitory response (HUTT)</td>
<td>DDI + hysteresis</td>
<td>placebo</td>
<td>Syncope recurrence</td>
<td>In severely symptomatic, PPM significantly reduces syncope recurrence.</td>
</tr>
<tr>
<td>Ammirati, et al. 2001 11435337 (262)</td>
<td>n=42; PPM n=19; no PPM=23</td>
<td>&gt;35 y of age; ≥3 syncope 2 y; +HUTT with syncope and bradycardia</td>
<td>PPM with rate drop</td>
<td>atenolol</td>
<td>Syncope recurrence</td>
<td>1% (5%) PPM vs. 14 (61%) non-PPM, p&lt;0.0006; KM 1,3,5 y 0%,6%, 6% PPM and 39%, 50%, 75% no PPM (p=0.0004) Mean age no PPM 56 and PPM 64 y of age. In those with cardio-inhibitory response, DDI pacing with hysteresis reduces likelihood of syncope.</td>
</tr>
<tr>
<td>Connolly, et al. 2003 12734133 (263)</td>
<td>n=100 pts; DDD n=48; ODO n=52</td>
<td>≥6 lifetime syncope; 3 in 3 y; +HUTT</td>
<td>DDD with rate drop</td>
<td>ODO</td>
<td>Syncope recurrence</td>
<td>Cumulative risk at 6m 40% (25%–52%) ODO and 31% (~33%–63%) DDD, p=0.14. Pacing did not reduce risk of recurrent syncope.</td>
</tr>
<tr>
<td>Raviele A, et al. 2004 15451153 (264)</td>
<td>n=60 pts; DDD n=30; ODO n=30</td>
<td>≥6 lifetime syncope; 1 in last y; +HUTT (asystole or mixed)</td>
<td>DDD with rate drop</td>
<td>OOO</td>
<td>Syncope recurrence</td>
<td>Follow up med 715d, 8(50%) on vs. 5(38%) off (p=NS); no difference in the mixed and asystole subgroups. Active pacing was not...</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Size</td>
<td>Inclusion Criteria</td>
<td>Intervention</td>
<td>Comparator</td>
<td>1st endpoint</td>
</tr>
<tr>
<td>-------</td>
<td>-----</td>
<td>------</td>
<td>-------------------</td>
<td>--------------</td>
<td>------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Brignole, et al. 2012 <a href="265">22565936</a></td>
<td>Effectiveness of cardiac pacing in NMS and asystole</td>
<td>n=77; on n=16; off n=13</td>
<td>≥40 y of age; ≥3 syncope in 2 y; ILR with ≥3s asystole or &gt;6s asystole w/o syncope</td>
<td>DDD with rate drop</td>
<td>ODO</td>
<td>Syncope recurrence</td>
</tr>
<tr>
<td>Flammang, et al. 1999 <a href="266">11228858</a></td>
<td>Effectiveness of pacing in symptom recurrence with abnormal adenosine 5'-triphosphate</td>
<td>n=20; Dual chamber Pacemaker on n=10; Pacemaker off n=10</td>
<td>VVS and abnormal cardioinhibitory (i.e. electrocardiographic) response during ATP test.</td>
<td>Pacemaker on</td>
<td>Pacemaker off</td>
<td>Syncope recurrence</td>
</tr>
<tr>
<td>Flammang, et al. 2012 <a href="267">22086879</a></td>
<td>Effectiveness of pacing in unexplained syncope and positive adenosine 5'-triphosphate</td>
<td>n=80; active n=39; passive n=41</td>
<td>Syncope of unknown origin; AV or SA block &gt;10s under ATP administration</td>
<td>DDD 70 bpm</td>
<td>back-up 30 bpm</td>
<td>Syncope recurrence</td>
</tr>
</tbody>
</table>
**Occhetta, et al. 2004**

| **Aim:** | To determine whether dual-chamber rate adaptive CLS prevents recurrence of VVS. CLS – tracks variation of intracardiac impedance during systolic phase of cardiac cycle on beat-to-beat basis; activates AV sequential pacing when detecting increased contractility during early phase of VVS. |
| **Study type:** | Randomized (single blind, multicenter) |
| **Size:** | n=26 pts; active n=9; control n=17 |
| **Inclusion criteria:** | >5 syncopal episodes and/or >2 in the last y before enrolment; refractoriness to conventional drug therapy and tilt-training+HUTT with cardio inhibition (+2A or 2B VASIS). |
| **Exclusion criteria:** | previous MI, CHF, severe chronic disease |
| **Intervention:** | DDD |
| **Comparator:** | DDI (40 bpm) |
| **1ª endpoint:** | 2 VVS during 1 y follow-up. |

- Randomization between DDD (9/26) and DDI only during 1ª y
- 24 pts recruited in 2ª y programmed to DDD-CLS

**Summary:** Effectiveness of DDD-CLS in preventing VVS with cardioinhibition

---

**Russo, et al. 2013**

| **Aim:** | The effect of dual-chamber CLS in the prevention of syncope recurrence in refractory VVS |
| **Study type:** | Randomized (single blind, crossover) |
| **Size:** | n=50 pts |
| **Inclusion criteria:** | >40 y of age; sinus rhythm; recurrent unpredictable syncope; no medications that could affect circulatory control; refractoriness to conventional drug therapy and/or tilt-training; +HUTT with cardioinhibition - asystole >3 s (2B VASIS) |
| **Exclusion criteria:** | other causes of syncope after comprehensive evaluation |
| **Intervention:** | DDD CLS on |
| **Comparator:** | DDD CLS off |
| **1ª endpoint:** | Syncope recurrence in the CLS on and off phases |

- Pts with syncope recurrence at 18 mo: Pacemaker CLS ON 1 (2%); Pacemaker CLS OFF 8 (16%)
- Pts with presyncope at 18 mo: Pacemaker CLS ON 4 (8%); Pacemaker CLS OFF 18 (27.8%)

**Summary:** Effectiveness of DDD-CLS in preventing VVS with cardioinhibition

---

**Data Supplement 28. Nonrandomized Trials, Observational Studies, and/or Registries of Pacemakers in Vasovagal Syncope – (Section 5.1.2)**

<table>
<thead>
<tr>
<th><strong>Study Acronym (if applicable)</strong>; <strong>Author; Year</strong></th>
<th><em><em>Study Type/Design</em>; Study Size</em>*</th>
<th><strong>Patient Population</strong></th>
<th><strong>Primary Endpoint and Results (include P value; OR or RR; and 95% CI)</strong></th>
<th><strong>Summary/Conclusion Comment(s)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Deharo, et al. 2013</td>
<td><strong>Study type:</strong> Observational</td>
<td><strong>Inclusion criteria:</strong> Sudden onset syncope without prodrome and normal</td>
<td><strong>1ª endpoint:</strong> Pathophysiology of sudden-onset syncope</td>
<td>Low adenosine plasma levels defines distinct form syncope from...</td>
</tr>
<tr>
<td>Study Acronym</td>
<td>Author</td>
<td>Year</td>
<td>Aim of Study; Study Type*; Study Size (N)</td>
<td>Patient Population</td>
</tr>
<tr>
<td>--------------</td>
<td>--------</td>
<td>------</td>
<td>------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Brignole, et al. 1992 1561975 (273)</td>
<td>Aim: Efficacy of permanent pacing. Study type: RCT  Size: n=60 pts; no pacing=28; pacing 32 (VVI=18, DDD=14)</td>
<td>Inclusion criteria: Recurrent syncope or presyncope causing trauma or future trauma or decreased QoL; cardioinhibitory or mixed symptoms reproducible CSM; no other cause (extensive w/u monitoring, neuro, EPS) Exclusion criteria: SN dysfunction, prolonged HV AV block on EPS</td>
<td>Intervention: Pacing Comparator: No pacing</td>
<td>1° endpoint: Symptom recurrence 1° Safety endpoint: N/A</td>
</tr>
<tr>
<td>Lelonek M, et al. 2007 29 (272)</td>
<td>Study type: Observational  Size: n=34 pts Pacemaker n=22 (DDI +hysteresis) No pacemaker n=12 (pharmacological: midodrine or b-blocker) -all educated on behavior measures</td>
<td>Inclusion criteria: Tilt-induced cardio depressive syncope with asystole &gt;3 s (2B VASIS) Exclusion criteria: Other causes of syncope after comprehensive cardiac and neurological evaluation</td>
<td></td>
<td>1° endpoint: Syncope recurrence Results: Syncope recurrence at 18 mo: Pacemaker 5 (23%); No pacemaker 3 (25%); p&gt;0.05 No injury in either group</td>
</tr>
</tbody>
</table>

### Exclusion criteria

- Other causes of syncope after comprehensive evaluation

### Results

- Study group: lower median adenosine plasmatic level; <0.36 umol/l 73% sensitivity; 93% specificity

- VVS.

- Efficacy of PPM in idiopathic AVB.
| Claesson, et al. 2007 17823136 (274) | **Aim:** Effect of symptoms in cardioinhibitory CCS with and without pacing  
**Study type:** RCT  
**Size:** n=60 pts; no pacing=30 pacing=30 | **Inclusion criteria:** ≥1 episodes of syncope or presyncope; induced cardioinhibitory CSS  
**Exclusion criteria:** N/A | **Intervention:** Pacing  
**Comparator:** No pacing | **1° endpoint:** Syncope (pre-syncope) recurrence  
**1° Safety endpoint:** N/A | ● Rate of syncope in the non-paced group was 40% compared with 10% in the paced group (p=0.008).  
● 10 pts (33%) with recurrent syncope in the NP group later crossed-over to receive a pacemaker implant, and 8 of these 10 pts were asymptomatic at the 12-mo follow-up  
● Pre-syncope occurred in 2 pts (7%) in the NP group and in 8 (27%) in the P group.  
**Summary:** Permanent pacing effective to prevent syncope recurrence in CCS |
| Parry, et al. 2008 19124530 (275) | **Aim:** Effect of falls in CCS with pacing on and off  
**Study type:** RCT(double-blind, cross-over, placebo-controlled)  
**Size:** n=34 | **Inclusion criteria:** ≥ 55 y of age; ≥3 episodes of unexplained falls but no syncope in prior 6 mo; induced cardioinhibitory (>3 s induced 5 s) or mixed (<50 mm Hg with atropine)  
**Exclusion criteria:** Other cause with extensive cardiac, neurological w/u; any Hx of syncope; severe cognitive impairment | **Intervention:** DDD/RDR  
**Comparator:**  
● ODO  
● 6 mo then cross-over | **1° endpoint:** Number of falls  
**2° endpoint:** fall recurrence  
**1° Safety endpoint:** N/A | ● 25 pts completed study  
● Pacing did not affect the number of falls  
● 3 pts cross-over to DDR mode  
● Hx of presentation with falls in ODO mode – unclear bradycardia  
● Pacing did not affect the number of falls |
| Kenny, et al. 2001 11691528 (276) | **Aim:** Whether cardiac pacing reduces falls in older adults with cardioinhibitory carotid sinus hypersensitivity  
**Study type:** RCT; open-label  
**Size:** n=175 Pacemaker=87 No pacemaker=88 | **Inclusion criteria:** ≥ 50 y of age; Cognitively normal pts (MMSE> 23/30 points) who were adults; ED visit for a non-accidental fall.  
**Exclusion criteria:** Cognitive impairment; accidental fall such as a slip or trip, or not attributable to a medical cause such as epilepsy, stroke, alcohol excess, OH, other arrhythmias | **Intervention:** Dual-chamber pacemaker programmed ON  
**Comparator:** No pacing | **1° endpoint:** syncope recurrence  
**2° endpoint:** fall recurrence  
**1° Safety endpoint:** N/A | ● Pts with syncope recurrence at 12 mo: Pacemaker 10 (11%); No pacemaker 19 (22%); p=0.063  
● Syncope recurrent events at 12 mo: Pacemaker 22 events; No pacemaker 47 events; OR 0.53 (Cl: 95%: 0.23–1.2)  
● Pts with no syncope recurrence at 12 mo: Pacemaker 77 (89%); No pacemaker 69 (78%)  
2 outcomes:  
● Fall events at 12 mo: pacemaker 216 events; No pacemaker 699 events  
● Pts with fracture due to fall at 12 mo: pacemaker 3 (3.4%); No pacemaker 4 |
Summary: Pacing associated with less falls and injury; no reduction in syncope events.

Ryan, et al. 2010

Aim: Cardiac pacing for recurrent falls in pts with cardioinhibitory CSH would reduce fall recurrence.

Study type: RCT, open label

Size: n=141; ITT n=129; Pacing on n=68; No pacemaker (ILR) n= 61

Inclusion criteria: ≥ 65 y; symptoms consistent with CSH with a minimum of 2 unexplained falls and/or one syncope in prior 1 y; 3 s of asystole in response to CSM; a MMS >19.

Exclusion criteria: Neoplasm, renal or hepatic failure; and at time of randomization significant HF.

Intervention: Pacing

Comparator: No pacing

1o Endpoint: Number of falls after implant.

2o Endpoint: Time to fall event, presyncope, quality of life and cognitive function

1o Safety endpoint: N/A

2o Endpoints:

• Pts reporting syncope after pacemaker implant RR: 0.47 (95% CI: 0.26–0.86); The number of syncopal events was also significantly less after implant, 0.52 (95% CI: 0.29–0.95).

• Syncope recurrent events at 24 mo: Pacemaker 0.42 mean events; No pacemaker 0.66 mean events; RR: 0.87 (95% CI: 0.3–2.48)

Summary: No difference in falls, syncope and other secondary endpoints between 2 groups.

Data Supplement 30. Nonrandomized Trials, Observational Studies, and/or Registries of Permanent Pacing in Carotid Sinus Hypersensitivity – (Section 5.2.2)

<table>
<thead>
<tr>
<th>Study Acronym (if applicable)</th>
<th>Author, Year</th>
<th>Study Type/Design*; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (include P value; OR or RR; and 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugrue, et al. 1986</td>
<td>Study type: Retrospective, observational study of untreated</td>
<td>Inclusion criteria: ≥1 episodes of syncope or presyncope;</td>
<td>1o Endpoint: Symptom recurrence</td>
<td>• PPM effective in CSS predominately cardioinhibitory</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Study type</td>
<td>Size</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>1° endpoint</td>
</tr>
<tr>
<td>-----------</td>
<td>------------</td>
<td>------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>3941204 (278)</td>
<td>compared to pacing or anticholinergic drugs</td>
<td>n=56 untreated=13 anticholinergic=20 pacing=23</td>
<td>cardioinhibitory, vasodepressor or mixed; no other cause</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Blanc, et al. 1984 6424619 (279)</td>
<td>Study type: Retrospective, observational</td>
<td>n=54 pts; no pacing=33 pacing=21</td>
<td>Inclusion criteria: Cardio inhibitory or mixed; no other cause</td>
<td>N/A</td>
<td>1° endpoint: Symptom recurrence after pacemaker implant</td>
</tr>
<tr>
<td>Morley, et al. 1982 7073901 (280)</td>
<td>Study type: Prospective, observational</td>
<td>n=70 pts; pacing mode (VVI, DVI, DDD, AAI)</td>
<td>Inclusion criteria: Cardioinhibitory with pacemaker</td>
<td>N/A</td>
<td>1° endpoint: Symptom persistence, vasodepressor response, pacemaker effect</td>
</tr>
<tr>
<td>Gaggioli, et al. 1995 7572635 (281)</td>
<td>Study type: Retrospective, observational</td>
<td>n=169 pts; VVI n=59 DDD n=110</td>
<td>Inclusion criteria: Cardioinhibitory or mixed; no other cause</td>
<td>N/A</td>
<td>1° endpoint: Symptom recurrence after pacemaker implant</td>
</tr>
<tr>
<td>Maggi, et al. 2007 17507364 (282)</td>
<td>Study type: case-control (age-sex matched 2:1)</td>
<td>n=18 pts</td>
<td>Inclusion criteria: Cardio inhibitory CSM and spontaneous syncope by ILR Control group: negative CSM, tilt and ATP Exclusion criteria: Structural cardiac disease, conduction, symptomatic OH, non-syncopal cause of LOC</td>
<td>N/A</td>
<td>1° endpoint: Syncope recurrence</td>
</tr>
<tr>
<td>Lopes, et al. 2011 21169606 (283)</td>
<td>Study type: Retrospective observational</td>
<td>n=138 pts</td>
<td>Inclusion criteria: Cardio inhibitory or mixed in whom pacemaker implanted</td>
<td>1° endpoint: Symptom recurrence after pacemaker implant</td>
<td>Results: Syncope recurrence 10.9%; 5.8% minor</td>
</tr>
<tr>
<td>Study type</td>
<td>Size</td>
<td>Exclusion criteria</td>
<td>Inclusion criteria</td>
<td>1st endpoint</td>
<td>Results</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------</td>
<td>--------------------</td>
<td>-------------------------------------</td>
<td>-------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| **Brignole, et al. 2011** 21570228 (271) | **Study type:** Systematic review  
**Size:** 12 studies; n=601 pts with pacing and 305 untreated | **Exclusion criteria:** N/A | **Inclusion criteria:** Cardioinhibitory or mixed | **1st endpoint:** Syncope recurrence; up to 5 y follow-up | • Benefit of cardiac pacing with significant reduction in recurrence;  
lead to reduced morbidity  
• Recurrence 20% of paced pts at 5 y  
Symptoms/presyncope; mixed CSS predicted recurrence (HR: 2.84; 1.20–6.71; p=0.017) |
| **Menozzi, et al. 1993 8237805 (284) | **Study type:** Prospective observational  
**Size:** n=23 pts | **Exclusion criteria:** Case reports | **Inclusion criteria:** Recurrent or severe episodes of syncope and presyncope causing major trauma or risk of death; asystolic response >3 s with CSM or eyeball compression with and without positive head-up tilt test; VVI pacemakers ability to track asystolic episodes. | **1st endpoint:** Occurrence of asystolic episodes | • Asystolic response to vasovagal maneuvers predicts occurrence of spontaneous asystolic episodes.  
Spontaneous episodes are asymptomatic and incidence is low.  
Results: Follow up 15 + 7 mo; asystolic episodes occurred in 74% of pts; actuarial estimate of occurrence of asystolic episodes of >3 and >6 s were 82% and 53% after 2 y. 12 episodes >3–6 s (0.7%) and 20 episodes of >6s (43%) |
| **Striyger, et al. 1986 2429277 (285) | **Study type:** Prospective observational  
**Size:** n=20 pts | **Exclusion criteria:** No other identifiable cause | **Inclusion criteria:** Repeated syncope of unknown cause; CSM asystole of >4 sec; cardioinhibitory based on EPS | **1st endpoint:** Efficacy of VVI pacing in preventing recurrence | • VVI pacing for isolated form of cardioinhibitory syncope results in complete resolution of symptoms.  
Results: Mean 20 mo; no pts had reoccurrence of syncope |
| **Walter, et al. 1978 356576 (286) | **Study type:** Prospective observational  
**Size:** n=21 pts | **Exclusion criteria:** N/A | **Inclusion criteria:** Syncope of unknown cause or pre-syncope; CSM ventricular asystole of >3 sec | **1st endpoint:** N/A | • PPM in cardio inhibitory syncope is associated with less reoccurrences.  
Results: 17 pts had cardio inhibitory, 2 vasodepressor and 2 mixed. 11 pts of these 9 had no further symptoms or rare pre-syncopal events; 2 of the pts with PPM had mixed response on CSM and had pre-syncope or syncope related to drop in BP. |
| **Crilley, et al. 1997 9338027 (287) | **Study type:** Prospective observational  
**Size:** n=42 pts | **Exclusion criteria:** N/A | **Inclusion criteria:** recurrent falls, pre-syncope or syncope and CSM >3 s ventricular asystole | **1st endpoint:** Outcomes of DCH PPM on elderly with falls, pre-syncope and syncope associated with cardioinhibitory syncope | • DCH PPM is effective for hypersensitive cardioinhibitory syncope.  
Results: All pts had DDI pacemaker implant; 84% no longer had further syncope mean follow up 10 mo and |
Data Supplement 31. RCTs for Type of Permanent Pacing in Carotid Sinus Hypersensitivity – (Section 5.2.2)

<table>
<thead>
<tr>
<th>Study Acronym Author Year</th>
<th>Aim of Study; Study Type*; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (include Absolute Event Rates, P value; OR or RR; and 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brignole, et al. 1988 2463565 (288)</td>
<td>Aim: Evaluate importance of atrial synchronism for mixed CSS</td>
<td>Inclusion criteria: Mixed CSS Exclusion criteria: Isolated cardioinhibitory or vasodepressor</td>
<td>Intervention: DVI/DDD Comparator: VVI</td>
<td>1° endpoint: Symptom recurrence; VA conduction, OH, pacemaker effect 1° Safety endpoint: N/A</td>
<td>• DVI vs. VVI, syncope occurred in 0% vs. 13% (p= 0.25); pre-syncope in 48% vs. 74% (p=0.04); DVI was the mode preferred by 64% of pts, remaining 36% did not express any preference (p=0.001). Summary: DVI/DDD pacing effective in 61% compared to VVI. When pacemaker effect, ventriculoatrial conduction and OH are present, VVI failure is possible, therefore DVI/DDD stimulation is indicated</td>
</tr>
<tr>
<td>McLeod, et al. 2012 22548372 (289)</td>
<td>Aim: Investigate impact of pacing modes (DDDR, DDR with sudden brady response and VVI) on syncope recurrence and QoL</td>
<td>Inclusion criteria: Cardioinhibitory/ mixed CSS; symptoms reproducible CSM Exclusion criteria: Isolated vasodepressor response to CSM; another cause for LOC; structural heart disease, PPM</td>
<td>Intervention: DDDR, DDR with sudden brady response and VVI Comparator:</td>
<td>1° endpoint: Syncope and pre-syncope recurrence; QoL 9SF-36 1° Safety endpoint: N/A</td>
<td>• Frequency of V pacing in VVI mode marginally less than any DDDR modes (p=0.04) • For any pacing mode syncope recurrence (29–2; p&lt;0.001) and presyncope (258–17; p&lt;0.001) reduced • Pacing modality found to marginally increase bodily pain and vitality measures in the DDDR mode Summary: No clear superiority of one pacing mode over another; QoL overall did not differ</td>
</tr>
</tbody>
</table>
### Data Supplement 32. Observational studies, for Type of Permanent Pacing in Carotid Sinus Hypersensitivity – (Section 5.2.2)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design*; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Madigan, et al. 1984 6702680 (290)   | Study type: Prospective, observational DVI vs. VVI  
**Size:** n=11 pts  
**Inclusion criteria:** Cardioinhibitory with partial or complete reproduction of symptoms or dizziness, near or syncopal compatible with cardiac origin  
**Exclusion criteria:** N/A | 1<sup>st</sup> endpoint: Changes in BP after CSM in pts paced in DVI mode vs. VVI  
**Results:** Drop in BP in VVI vs. DVI (59 vs. 37 mm Hg; p=0.001) and a higher rate of symptom persistence (91% vs. 27%; p=0.008) | VVI results in significant hemodynamic compromise resulting in increased symptoms |
| Sutton, et al. 1989 (291)            | Study type: Case series  
AAI vs. DVI vs. VVI  
**Size:** n=202 pts  
**Inclusion criteria:** syncope or pre-syncope 98%; positive CSM; pacemaker inserted  
**Exclusion criteria:** N/A | 1<sup>st</sup> endpoint: Syncope recurrence  
**Results:** Failure to control syncope for various modes: AAI 50%, VVI 18% and DVI/DDD 9% | The most effective pacing mode is DVI/DDD compared with other modes |
| Bae MH, et al. 2011 22188510 (292)  | Study type: Retrospective, observational study comparing defecation, micturition and VVS  
**Size:** n= 680 consecutive DS n=38; MS n=38; VVS n=208  
**Inclusion criteria:** DS occurring during or immediately after defecation and during abdominal cramping or urge to defecate; MS - syncope occurring at the beginning of, during, at the termination of, or immediately after urination  
**Exclusion criteria:** Other cause of syncope or unknown not consistent with VVS (clinical & HUTT) | 1<sup>st</sup> endpoint: Clinical characteristics ( using standard statistics to compare btw groups)  
**Results:** DS occurred in older age of diagnosis (p=0.004) and first syncope (p=0.002); younger VVS; male more likely MS (p=0.036); frequency of drinking alcohol higher in MS (<0.001) as was CV risk factor/underlying disease (p=0.031) | DS occurred in older women, MS in middle-age men and drinking alcohol precipitator |

### Data Supplement 33. RCTs for Neurogenic Orthostatic Hypotension – (Section 6.1)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2&lt;sup&gt;nd&lt;/sup&gt; Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| Anley C, et al. 2011 20584756 (293) | **Aim:** To assess which treatment protocol for exercise-associated postural hypotension  
**Inclusion:** All collapsed athletes at 2 Ironman Triathlon competitions and one ultra-distance footrace  
**Intervention:** OT, oral fluid and Trendelenburg position  
**Comparator:** IV, intravenous fluid | **1<sup>st</sup> endpoint:** Time to discharge: no significant difference between IV (52.5 +/- 18 min) and OT group (58+/-23 min), p=0.47  
Secondary: heart rate and BP changes: NS | With no difference in time to discharge, but significantly less fluid given in OT group compared to IV group, the |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion</th>
<th>Intervention</th>
<th>Endpoint</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu CC, et al. 2008</td>
<td>Assess whether glucose water ingestion will reduce orthostatic tolerance in young healthy volunteers</td>
<td>Healthy male</td>
<td>10% glucose water</td>
<td>Orthostatic tolerance (time to presyncope during 70 degree HUTT): 13 of 15 (87%) ingesting pure water were able to complete the full tilt without presyncope, but 7 of 15 (47%) ingesting glucose water could complete the full tilt. Test was terminated sooner in glucose water group (40.0±6.9 min) vs. pure water group (43±5.6 min), p=0.008. There was no difference in symptom scores (p=0.26) between 2 groups.</td>
<td>Abnormal serum sodium</td>
</tr>
<tr>
<td>Raj SR, et al. 2006</td>
<td>To assess if ingestion of salt with water would increase magnitude of acute pressor response compared with water in OH</td>
<td>OH pts with at least 6 mo Hx of orthostatic symptoms and were ≥18 y of age. All medications that could impair BP regulation were withdrawn for ≥5 half-lives before testing.</td>
<td>Distilled water mixed with 2 g of NaCl added,</td>
<td>Hemodynamic response to water: SBP increased from 92±8 mmHg at baseline to 129±9 mmHg 30 min after ingestion (p&lt;0.001), and 110±12 mmHg 60 min after ingestion (p=0.022). Plasma norepinephrine significantly increased at 30 min (p=0.018) after water ingestion</td>
<td>None</td>
</tr>
<tr>
<td>Schroeder C, et al. 2002</td>
<td>To assess water drinking on orthostatic tolerance in healthy pts</td>
<td>Healthy volunteers</td>
<td>500 mL nonsparkling mineral water at room temperature</td>
<td>Drinking 500 mL water prolonged time to presyncope in 11 pts from 31 ±3 min to 36 ±3 min (p&lt;0.001). Supine</td>
<td></td>
</tr>
</tbody>
</table>

results in earlier discharge.

**Study type**: Analytical, Randomized controlled, prospective cohort

**Size**: n=28 pts

In 2006 and 2007

**Exclusion**: Abnormal serum sodium

changes were seen.

- Total volume of fluid in OT group was 204 +/- 149 ml, and was significantly less than IV group 1045+/−185 ml, p<0.001.

probable cause of exercise associated postural hypotension is peripheral vasodilatation resulting in venous pooling.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study type: Analytical, randomized controlled, prospective cohort,</th>
<th>Exclusion: Regular medication except oral contraceptives</th>
<th>Comparator: 50 mL nonsparking mineral water, then 60 degree HUTT for 20 min followed by LBNP for 10 m each at -20, then -40, -60 mmHg</th>
<th>heart rate, BP, SV, and cardiac output were not significantly different with 500 mL water drinking. With HUTT, 500 mL water drinking blunted decrease in SV from -45+/−2% to -38 ±3%, p&lt;0.01</th>
<th>mediated with factors beyond increasing plasma volume. Increase in peripheral resistance and vasoconstrictor tone may have role.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jordan J, et al. 1998 9774366 (296)</td>
<td>Study type: Analytical, Randomized placebo controlled, cross-sectional cohort,</td>
<td>Size: n=9 pts</td>
<td>Inclusion: Idiopathic OI (&gt;30 bpm increase in heart rate within 5 min of standing without a concomitant decrease in SBP/DBP &gt;20/10 mmHg); plasma norepi level &gt;600 pg/mL with standing; at least 6 mo Hx of typical symptoms of OI with standing, which were significantly relieved by lying down</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; endpoint: At 5 m HUTT compared to placebo, volume loading significantly blunted the increased upright heart rate (-20+/−3.2 bpm, p&lt;0.001) as did phenylephrine (-18+/−3.4 bpm, p&lt;0.001), but effect diminished at end of HUTT. Phentolamine significantly increased upright heart rate at 5 min (20+/−3.7 bpm, p&lt;0.01) and at end of HUTT (14+/−5 bpm (p&lt;0.05) compared with placebo. With placebo, mean cerebral blood flow velocity decreased by 33+/−6% at HUTT, but phenylephrine infusion, volume loading, and phentolamine infusion all attenuated the decrease in mean middle cerebral artery velocity (despite worsening systemic hemodynamics with alpha-blockade). Excessive sympathetic activity contributes to decreased cerebral blood flow during HUTT.</td>
<td>• Volume loading, alpha-agonist infusion, and alpha-blockade all blunted decrease in mean middle cerebral artery velocity (despite worsening systemic hemodynamics with alpha-blockade). Excessive sympathetic activity contributes to decreased cerebral blood flow during HUTT.</td>
</tr>
<tr>
<td>Jankovic JJ, et al. 1993 7687093 (295)</td>
<td>Study type: Analitcal, Randomized double-blind placebo controlled, prospective cohort,</td>
<td>Size: n=97 pts</td>
<td>Inclusion: At 18 centers between 1989 to 1990, OH (≥15 mmHg fall from supine to standing position plus symptoms) due to autonomic failure. (n=18, Shy Drager; n=22 Parkinson disease; n=27 DM)</td>
<td>Intervention: Midodrine 2.5 mg, 5 mg, or 10 mg 3x daily, for 4 wk Comparator: Placebo for 4 wk 1&lt;sup&gt;st&lt;/sup&gt; endpoint: Midodrine increased standing SBP by 22 mmHg vs. 3 mmHg for placebo (p&lt;0.001). Midodrine increased standing DBP by 15 mmHg vs. 3 mmHg for placebo (p&lt;0.001). Supine SBP increased 13 mmHg vs. -2mmHg for placebo (p&lt;0.001). Symptom improvement was significant with 10 mg for blurred vision, syncope, and energy level (p&lt;0.01). Improvement with energy level occurred with midodrine 2.5 and 5 mg doses.</td>
<td>• Scalp tingling (13.5%), supine HTN (8%) Midodrine significantly improves standing SBP and symptoms of OH.</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion</td>
<td>Exclusion</td>
<td>Intervention</td>
<td>Comparator</td>
</tr>
<tr>
<td>-------</td>
<td>-----</td>
<td>-----------</td>
<td>-----------</td>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>Jordan J, et al. 1998 9727818 (297)</td>
<td>To assess various medication effect in severe OH from autonomic failure</td>
<td>Severe OH due to multiple system atrophy or PAF</td>
<td>Secondary causes of autonomic failure, contraindications to pressor agents (CAD, CHF)</td>
<td>Seated BP effect of <strong>Intervention:</strong> Phenylpropanolamine 12.5 mg (25 mg in pts not responsive to 12.5 mg), <strong>Comparator 1:</strong> yohimbine 5.4 mg, <strong>Comparator 2:</strong> indomethacin 50 mg, <strong>Comparator 3:</strong> Ibuprofen 600 mg, <strong>Comparator 4:</strong> Caffeine 250 mg, <strong>Comparator 5:</strong> Methylphenidate 5 mg, <strong>Comparator 6:</strong> Midodrine 5 mg</td>
<td></td>
</tr>
<tr>
<td>Kaufmann H, et al. 1988 2452997 (298)</td>
<td>To assess the effect of midodrine OH in autonomic failure</td>
<td>Several OH with multiple system atrophy, or idiopathic OH.</td>
<td></td>
<td>Midodrine titrated from 2.5 mg 4x daily to total daily dose of 0.5 mg/kg (25-40 mg/d) for 7 days, <strong>Comparator:</strong> Placebo</td>
<td>Midodrine increased standing BP significantly in 3 of 7 pts (p&lt;0.05) and these pts reported improved orthostatic symptoms. In 4 pts, fludrocortisone, midodrine, and the combination did not increase standing BP or symptoms, and in these pts the decrease paralleled decrease in body weight.</td>
</tr>
<tr>
<td>Low PA, et al. 1997 9091692 (299)</td>
<td>Assess midodrine in neurogenic OH</td>
<td>≥18 y of age or older, symptomatic neurogenic OH (due to a structural lesion of adrenergic pathways, central or peripheral), ≥15 mmHg SBP postural change, postmenopausal</td>
<td></td>
<td>Midodrine 10 mg 3x daily, <strong>Comparator:</strong> Placebo</td>
<td>Primary: improvement in standing SBP: mean increased SBP of 21.8 mmHg, p&lt;0.001. Midodrine effect was independent of fludrocortisone (mean dose 0.35+/−0.33 mg) and independent of wearing compression garments. Symptoms of lightheadedness improved over entire study, and reached significance at second wk of</td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
Study type: Analytical, randomized controlled, prospective case-control  
Size: n=20 pts | Inclusion: SCI (n=10) and age and sex matched able bodied individuals (n=10)  
Exclusion: Smokers, history of CV disease | Intervention: Midodrine 10 mg  
Comparator: Baseline  
Then tilt table testing on 2 separate days | 1° endpoint: Tilt table (Progressively tilted from supine to 30, 45, and 60 degrees) and symptoms. Stage and time at which participant withdrew or was withdrawn from tilt were recorded.  
• Steady state and dynamic cerebral blood flow response to tilt is similar in SCI and AB; midodrine improved orthostatic tolerance in SCI by 59% (p=0.003) as calculated by the formula orthostatic tolerance index = final tilt degree x time the last stage was tolerated.  
• Only assessment of MCA and PCA, without measurement of carotid, vertebral, or upstream arteries. No study of time of SCI until assessment by tilt, |  
Ramirez CE, et al. 2014 [25185131](301) | Aim: To assess whether atomoxetine would be superior to midodrine in improving upright BP and OH  
Study type: Analytical, randomized, single-blind placebo controlled, prospective crossover  
Size: Not mentioned | Inclusion: Pts with severe autonomic failure (PAF, multiple systems atrophy, Parkinson disease) with OH defined as SBP ≥20 mmHg or DBP ≥10 mmHg within 3 min of standing or 60 degree HUTT  
Exclusion: autonomic failure secondary to DM, | Intervention: Atomoxetine 18 mg  
Comparator 1: Midodrine 5–10 mg  
Comparator 2: Placebo, with SBP, DBP, and heart rate assessed Q5 mins for 60 m | Primary: Post-treatment upright SBP at 1 min.  
Secondary: Post-treatment seated SBP and DBP, upright DBP and heart rate, and OH Questionnaire and Q1 symptom scores. Atomoxetine improved upright SBP to a great extent than midodrine (means difference =7.5 mmHg, p=0.03) and upright DBP (means difference =4.1mmHg, p=0.05). Atomoxetine improve OH related symptoms (p=0.02) but not midodrine |  
| Size: n=171 pts (multiple system atrophy, n=40 pts; PAF, n=37 pts, diabetic neuropathy, n=37 pts, Parkinsonism, n=19 pts) | women or on contraception at 25 centers  
Exclusion: Pregnant or lactating women, preexisting sustained supine HTN of ≥ 180/110 mmHg, concomitant administration of sympathomimetic agents, adrenoreceptor alpha-agonist or antagonists, or vasoactive drugs, or significant systemic illness  
Medication, p=0.02. Global symptom relief score improved significantly. |
<table>
<thead>
<tr>
<th>Study</th>
<th>Size: n=65 pts</th>
<th>amyloidosis, or paraneoplastic syndrome</th>
<th>Aim: To assess pyridostigmine alone or in combination with midodrine in neurogenic OH</th>
<th>Study type: Analytical, randomized, double-blind, placebo controlled, prospective crossover</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright RA, et al. 1998</td>
<td>9674789 (303)</td>
<td>105</td>
<td>Inclusion: Adults &gt;18 y of age with neurogenic OH (multiple system atrophy, n=17; PAF, n=15; autoimmune autonomic neuropathy, n=9; diabetic autonomic neuropathy, n=11; or unspecified neurogenic OH, n=6). OH defined as SBP drop ≥ 30 mmHg or mean BP drop ≥ 20 mmHg within 3 min of standing.</td>
<td>Exclusion: Pregnant, lactating, evidence of failure of other organ systems or of systemic illness that could affect autonomic function, CHF, significant CAD, significant arrhythmia, renal disease, severe anemia, hypothyroidism, and cerebrovascular accidents, concomitant therapy with anticholinergic, adrenergic antagonists, vasoactive agents</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size: n=58 pts</th>
<th>Intervention: Pyridostigmine 60 mg</th>
<th>Comparator 1: Pyridostigmine 60 mg + midodrine 2.5 mg</th>
<th>Comparator 2: Pyridostigmine 60 mg + midodrine 5 mg</th>
<th>Comparator 3: Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singel W, et al. 2006</td>
<td>16476804 (302)</td>
<td>Primary: Standing DBP at 1 h post drug: pyridostigmine increased it from 49+/−14 to 56+/−17 mmHg (p=0.02). Pyridostigmine with midodrine 5 mg significantly increase standing DBP compared to pyridostigmine + midodrine 2.5 mg (p=0.03) and placebo (p=0.002) and almost significantly compared to pyridostigmine alone (p=0.51)</td>
<td>Secondary: Influence on SBP and supine BP: no significant change, in SBP (p=0.36) or DBP (p=0.85); relation of symptoms to change in BP: significant association between change in symptom score at 1 h to change in standing BP, p&lt;0.001</td>
<td>• Pyridostigmine alone and in combination with midodrine with resultant improvement in symptoms without significantly affecting supine HTN.</td>
</tr>
</tbody>
</table>

Intervention 1: Midodrine 2.5 mg

Intervention 2: Midodrine 10 mg

Intervention 3: Midodrine 20 mg

Comparator: Placebo

1° endpoint: Midodrine 2.5 mg did not significantly increase standing SBP at any time point.
- Midodrine 10 mg increased standing SBP significant 1 h post ingestion with a mean increase of 34 mmHg, p<0.05.
- Midodrine 20 mg increased standing SBP significantly at 1 to 4 h post ingestion with a

Excessive HTN with 20 mg dose. Supine SBP >200 mmHg occurred in 17% of pts on 10 mg, and in 41% of pts taking 20 mg.

Midodrine at doses of 10 mg and 20 mg improves SBP with
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Secondary endpoints</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biaggioni I, et al. 2015 25350981 (304)</td>
<td>To evaluate whether droxidopa is beneficial in treatment of neurogenic OH</td>
<td>18 y of age, symptomatic OH assoc with Parkinson disease, multiple system atrophy, PAF, dopamine beta-OHase deficiency, or non-diabetic autonomic neuropathy, with SBP decrease ≥ 20 mmHg or DBP decrease ≥ 10 mmHg within 3 mins standing</td>
<td>Droxidopa 100 mg TID and adjusted upward; mean dose at randomization was 389.6 +/- 180.9 mg 3x daily, then randomized to continue droxidopa</td>
<td>After upward adjustment of droxidopa adjustment then withdraw to placebo for 14 days</td>
<td>Self Rated OH Questionnaire [6-item OHSA and 4-item OHDAS]: Primary: pts change on OHSA item 1: dizziness/lightheadedness</td>
<td>During open label 58.6% reported ≥1AE, most commonly headache (11%); dizziness (8.3%); fatigue (5.5%); During double blind treatment, falls (2%), headache (4%), URI (4%), and dizziness (4%)</td>
</tr>
</tbody>
</table>

| Freeman R, et al. 1999 10599797 | To assess DL-DOPS in neurogenic OH | Autonomic failure pts with severe, symptomatic OH (n=6) | 3-4-DL-threodihydroxyphenylserine (DL-DOPS) 1000 mg | 1<sup>st</sup> endpoint: DL-DOPS increased supine SBP (p<0.001), tilted SBP (p<0.05), supine DBP (p<0.01) and tilted DBP (p<0.01) with | The norepi precursor DL-DOPS decreases BP fall with 60 degree tilt orthostatic challenge. | • During open label 58.6% reported ≥1AE, most commonly headache (11%); dizziness (8.3%); fatigue (5.5%); During double blind treatment, falls (2%), headache (4%), URI (4%), and dizziness (4%) |

<p>| | | | | Unanticipated carryover effect of persistence of symptomatic improvement during withdrawal phase even in the placebo group. Secondary endpoints favor use of droxidopa in symptomatic neurogenic OH. | | |</p>
<table>
<thead>
<tr>
<th>(305)</th>
<th><strong>Study type:</strong> Analytical, Randomized double-blind, placebo controlled crossover, prospective cohort, <strong>Size:</strong> n=10 pts</th>
<th>Multiple system atrophy; n=4, PAF</th>
<th><strong>Comparator:</strong> Placebo then 60 degree tilt table</th>
<th>Peak SBP occurring 300 m after medication ingestion. Plasma norepi increased in supine and tilt after DL-DOPS ingestion (p&lt;0.0001). There was no significant effect on heart rate, forearm vascular resistance with DL-DOPS vs. placebo. Trend toward improvement in symptoms and quality of life of orthostatic intolerance seen with DL-DOPS (p&lt;0.06)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hauser RA, et al. 2014 24326693 (306)</td>
<td><strong>Aim:</strong> To assess droxidopa effect in neurogenic OH in Parkinson disease,</td>
<td><strong>Inclusion:</strong> 51 pts with Parkinson disease enrolled in clinicaltrials.gov NCT01176240, droxidopa for neurogenic OH in Parkinson disease interim analysis; <strong>Exclusion:</strong> N/A</td>
<td><strong>Intervention:</strong> Droxidopa dosage optimization for ≤ 2 wk followed by 8 wk of maintenance therapy (100-600 mg 3x daily), mean study-drug dosage was 433 mg</td>
<td><strong>Primary:</strong> Change in OH questionnaire composite score from baseline to wk 8</td>
</tr>
<tr>
<td>Kaufmann H, et al. 2003 12885750 (307)</td>
<td><strong>Aim:</strong> To assess L-DOPS effect on BP and orthostatic tolerance in severe neurogenic OH</td>
<td><strong>Inclusion:</strong> Severe symptomatic OH (n=11 with multiple system atrophy, n=8 with PAF</td>
<td><strong>Intervention:</strong> L-threo-3,4-dihydroxyphenylserine (L-DOPS) with dose based on dose ranging study</td>
<td><strong>1° endpoint:</strong> L-DOPS significantly increased mean BP in supine (101+/-4 to 141 +/-5 mmHg) and standing (60 +/-4 to 100 +/-6 mmHg, p&lt;0.001) • At 3 m of standing, 94% of pts were able to stand compared to 84% with placebo, p&lt;0.001. • L-DOPS showed increase in plasma NE</td>
</tr>
<tr>
<td>Study Title</td>
<td>Study Type</td>
<td>Size</td>
<td>Inclusion</td>
<td>Exclusion</td>
</tr>
<tr>
<td>-------------</td>
<td>------------</td>
<td>------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>Kaufmann H, et al. 2014</strong>&lt;br&gt;24944260 (308)</td>
<td>Analytical, Randomized placebo controlled, prospective cohort trial of droxidopa responders</td>
<td>n=162 pts</td>
<td>Symptomatic neurogenic OH due to Parkinson disease, multiple system atrophy, PAF, or non-diabetic autonomic neuropathy</td>
<td>95 titration failures (50 had treatment failure, 12 AEs, 6 withdrew consent, 4 protocol violations, 23 other failures, 6 randomized in error)</td>
</tr>
<tr>
<td><strong>Figueroa JJ, et al. 2015</strong>&lt;br&gt;25448247 (309)</td>
<td>Analytical, Randomized controlled, prospective crossover cohort</td>
<td>n=13 pts</td>
<td>Moderately severe neurogenic OH, diagnosis of Parkinson disease, diabetic neuropathy, multiple system atrophy, autonomic failure, laboratory evidence of moderately severe adrenergic failure as measure by Valsalva-induced hypotension</td>
<td>Pregnancy, lactation, motor impairment affecting hand coordination, dementia, severe systemic illness, inability to tolerate</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion</td>
<td>Intervention</td>
<td>Comparator</td>
</tr>
<tr>
<td>-------</td>
<td>-----</td>
<td>-----------</td>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>Platts SH, et al. 2009 19456003 (310)</td>
<td>To assess ability of 2 compression garments to prevent hypovolemia-related OI</td>
<td>n=19 healthy volunteers, 32–54 y of age, and passing a modified Air Force Class III physical; and n=16 hypovolemic control pts</td>
<td>To mimic plasma volume loss due to spaceflight pts given furosemide 0.5 mg/kg, consumed low-salt diet for 36 H</td>
<td>Russian Kentavr – non-inflatable elastic shorts and gaiters, n=10 then did 15 m 80 degree HUT T</td>
</tr>
<tr>
<td>Podoleanu C, et al. 2006, 17010806 (311)</td>
<td>To assess lower limb compression bandage effect on OH in elderly persons</td>
<td>Pts with symptoms signs of OI (asymptomatic after standing in initial 3 m, but cannot tolerate afterward due to increasing hypotensive symptoms, progressive decrease in BP pattern during diagnostic tilt testing</td>
<td>Leg compression bandages at 40 –60 mmHg for 10 m and then of the abdomen too (20 – 30 mmHg) for 10 m</td>
<td>Sham compression, then measured effect on 60 degree modified Italian HUT T</td>
</tr>
<tr>
<td>Protheroe CL, et al. 2011 22194814</td>
<td>To assess effect of graded calf compression stockings on orthostatic tolerance</td>
<td>Healthy volunteers</td>
<td>HUTT and LBNP (-20 mmHg, -40 mmHg, and -60 mmHg for 10 min each) on 3 occasions with different types of stocking:</td>
<td>CV or</td>
</tr>
</tbody>
</table>
| (312) | **Study type:** Analytical, randomized double-blind placebo-controlled crossover, prospective cohort  
**Size:** n=15 pts | Neurological disease  
**Intervention:** Calf-length graded compression stocking,  
**Comparator 1:** Standard calf-length socks not designed to provide compression (calf placebo),  
**Comparator 1:** Ankle-length socks (ankle-placebo)  
**Aim:** To reduce OH in respiratory impedance  
**Effect on isometric handgrip:** - | Calf circumference may predict individuals who improve with compression stockings more than others.  
- Testing was performed in healthy volunteers, and not pts with OI. |
| --- | --- | --- | --- |
| Clarke DA, et al.  
2010  
20350727  
(313) | **Aim:** Effect on isometric handgrip on initial OH in young persons  
**Study type:** Analytical, Randomized controlled, prospective cohort,  
**Size:** n=14 pts | Inclusion: Young pts median age: 17 y of age range 15-22 y of age with initial OH (defined as transient decrease in SBP >40 mmHg or a decrease in DBP >20 mmHg within 15 s of standing) with symptoms  
Exclusion: Systemic disease, vasovagal fainting, chronic OI  
**Intervention:** Isometric contraction of nondominant arm for 1 m then standing for 5 m while maintaining isometric handgrip  
**Comparator:** Standing alone  
**1st endpoint:** With standing alone compared to baseline, MAP decreased by 42 +/- 10% (p<0.01), heart rate increased by 62 +/- 18% (p<0.01), cardiac output decreased by 33 +/- 17% (p<0.05), and TPR was unchanged at 17 +/- 21% (p=0.65).  
On standing with isometric handgrip, MAP decreased by 31 +/-9% (p<0.01), heart rate increased by 33 +/-17% (p<0.01), cardiac output decreased by 2 +/-14% (p<0.05), and TPR decreased by 30 +/-15% (p<0.01).  
- Maximum force isometric handgrip before and during standing can blunt the decrease in MAP and cardiac output in younger pts with initial OH. No formal evaluation of symptoms performed. Less than maximal force handgrip not performed. |
| Krediet CT, et al. 2006  
16714361  
(314) | **Aim:** Assess leg crossing to increase orthostatic tolerance,  
**Study type:** Analytical, Randomized placebo controlled crossover, cross-sectional cohort  
**Size:** n=9 pts | Inclusion: Healthy pts  
Exclusion: No medications except oral contraceptive. No alcohol, tobacco, and caffeine use.  
**Intervention:** Orthostatic tolerance challenged at same time  
**Comparator 1:** With leg crossing  
**Comparator 2:** Without leg crossing  
**1st endpoint:** All pts sustained greater orthostatic challenge with leg crossing (34 +/-2 min), than during control (26 +/-2 min) or with placebo (23 +/-3 min, p<0.001). Heart rate increase was lower (+13 bpm) with leg crossing during HUTT compared to control (+18 bpm, p<0.05)  
- Leg crossing increased orthostatic tolerance in healthy pts |
| Thijs RD, et al. 2007  
17679677  
(315) | **Aim:** To evaluate respiratory impedance to reduce OH in autonomic failure  
**Study type:** Analytical, randomized controlled, prospective crossover  
**Size:** n=9 pts | Inclusion: Pts with autonomic failure (PAF, n=4; multiple system atrophy, n=3, amyloidosis, n=1, anti-Hu neuropathy, n=1, Parkinson disease, n=1) and symptomatic OH. Healthy pts as control  
**Intervention:** Inspiratory obstruction through narrowing of inspiratory tube of 2 way nonrebreathing valve (IO)  
**Comparator 1:** NS  
**Comparator 2:** Muscle tensing of pursed lips during inspiration increased MAP  
**1st endpoint:** IO increased MAP by 8 mmHg (-1 to 13 mmHg), mean cerebral blood flow velocity (mCBFV) by 8% (2 to 23%).  
Muscle tensing increased MAP by 9 mmHg (1 to 10 mmHg), mCBFV by 9% (-7 to 18%).  
- Muscle tensing and inspiratory impedance and muscle tensing had similar effects in increasing MAP and mean cerebral blood flow velocity, but no difference in symptom improvement was noted. |
<table>
<thead>
<tr>
<th>Size: n=20 pts</th>
<th>(n=10)</th>
<th>Exclusion: Cardiac disease or used antihypertensive medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion:</td>
<td>Cardiac disease or used antihypertensive medications</td>
<td></td>
</tr>
<tr>
<td>Comparator 3:</td>
<td>Breathing through pursed lips during inspiration</td>
<td></td>
</tr>
<tr>
<td>Comparator 4:</td>
<td>Inspiratory sniffing</td>
<td></td>
</tr>
<tr>
<td>Comparator 3: legs without leg crossing</td>
<td>by 1 mmHg (-7 to 8 mmHg), mCBFV by 2% (-11 to 9%).</td>
<td></td>
</tr>
<tr>
<td>No significant difference in symptom scores was noted between maneuvers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tutaj M, et al. 2006 16096819 (316)

**Aim:** Assess effect of countermaneuvers in familial dysautonomia and active standing

**Study type:** Analytical, randomized controlled, prospective crossover

**Size:** n=17 pts

**Inclusion:** Familial dysautonomia with IKBKAP gene mutation

**Exclusion:** Pts unable to comply with discontinuation of fludrocortisone or midodrine for 18 h.

**Intervention:** Leg crossing, Comparator 1: Squatting, Comparator 2: Bending forward with abdominal compression.

**Medication affecting CV system** (fludrocortisone, midodrine) held for 18 h prior to procedures

1^ endpoint: 7 of 17 pts able to perform all 4 countermaneuvers. 16 of 17 pts able to perform at least 2 countermaneuvers.

SBP increase during bending forward (+23 mmHg, p=0.0005), squatting (+49 mmHg, p=0.002), leg crossing (+8.3 mmHg, p=0.01), abdominal compression (+27 mmHg), p=0.001).

DBP increase during bending forward (+12 mmHg, p=0.0005), squatting (+38 mmHg, p=0.004), leg crossing (+11.6 mmHg, p=0.02) but no change during abdominal compression, (+2.0 mmHg, p=0.30).

Pyridostigmine alone and in combination with midodrine with resultant improvement in symptoms without significantly affecting supine HTN.

- Squatting was most effective countermaneuver in increasing BP but only 7 of 17 pts with familial dysautonomia were able to perform it adequately. Other countermaneuvers increase BP to lesser degree, with leg crossing likely least effective

<table>
<thead>
<tr>
<th>Size: n=58 pts</th>
<th>Inclusion: Adults &gt;18 y of age with neurogenic OH (multiple system atrophy, n=17; PAF, n=15; autoimmune autonomic neuropathy, n=9; diabetic autonomic neuropathy, n=11; or unspecified neurogenic OH, n=6).  OH defined as SBP drop ≥ 30 mmHg or mean BP drop ≥ 20 mmHg within 3 m of standing.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion:</td>
<td>Pregnant, lactating, evidence of failure of other organ systems or of systemic illness that</td>
</tr>
<tr>
<td>Intervention:</td>
<td>Pyridostigmine 60 mg, Comparator 1: pyridostigmine 60 mg + midodrine 2.5 mg, Comparator 2: pyridostigmine 60 mg + midodrine 5 mg, Comparator 3: Placebo</td>
</tr>
</tbody>
</table>
| Primary: | Standing DBP at 1 h post drug: pyridostigmine increased it from 49+/−14 to 56+/−17 mmHg (p=0.02). Pyridostigmine with midodrine 5 mg significantly increase standing DBP compared to pyridostigmine + midodrine 2.5 mg (p=0.03) and placebo (p=0.002) and almost significantly compared to pyridostigmine alone (p=0.51)

Secondary: Influence on SBP and supine BP: no significant change, in SBP (p=0.36) or DBP (p=0.85); relation of symptoms to change in BP: significant association between change in symptom score at 1 h to change in standing BP, p<0.001.

**Squatting was most effective countermaneuver in increasing BP but only 7 of 17 pts with familial dysautonomia were able to perform it adequately. Other countermaneuvers increase BP to lesser degree, with leg crossing likely least effective**
could affect autonomic function, CHF, significant CAD, significant arrhythmia, renal disease, severe anemia, hypothyroidism, and cerebrovascular accidents, concomitant therapy with anticholinergic, adrenergic antagonists, vasoactive agents

**Data Supplement 34. Nonrandomized Trials, Observational Studies, and/or Registries of Neurogenic Orthostatic Hypotension – (Section 6.1)**

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Jordan J, et al. 1999 10073520 (317) | **Study type:** Analytical, observational, prospective case control,  
**Size:** n=30 pts | **Inclusion criteria:** Severe OH due to autonomic failure (PAF, n=10; multiple system atrophy, n=9); healthy controls, n=11  
**Exclusion criteria:** None | **1° endpoint:** 480 mL tap water  
**Results:** In both autonomic failure and healthy controls, water ingestion raised SBP by 11 mmHg (p<0.001). No significant change in plasma volume was seen in healthy controls and 5 pts with autonomic failure. Norepi levels increased in controls with water ingestion. | • Water ingestion increased BP in autonomic failure and healthy controls, possibly through sympathetic activation |
| Jordan J, et al. 2000 10662747 (318) | **Study type:** Analytical, observational, prospective case control,  
**Size:** n=66 pts | **Inclusion criteria:** primary autonomic failure with “disabling” OH. MSA, n=28; PAF, n=19. Healthy controls, n=19  
**Exclusion criteria:** Secondary causes of autonomic failure (DM, amyloidosis) | **1° endpoint:** 480 mL tap water  
Vasoactive medications and fludrocortisone discontinued ≥5 half-lives before testing  
**Results:** With water drinking, BP increased 33+/−5/16+/−3 mmHg (p<0.001) in MSA, and increased 37+/−7/14+/−3 mmHg in PAF (p<0.001). There was no difference between drinking cold vs. warm water. Drinking 480 mL had a greater pressor response than 240 mL water. Healthy controls also noted an increase in SBP of 11+/−2.4 mmHg (p<0.001). Healthy controls undergoing ganglionic blockade did not have pressor effect with water. Enhanced pressor effect present with yohimbine plus water. | • Water ingestion has a pressor response in autonomic failure, with BP increase also seen in healthy pts. The peak elevation in BP was 30 to 35 mins after ingestion. This effect is largely sympathetically driven. |
| Shannon JR, et al. 2002 Protocol 1:  
**Study type:** Analytical,  
**Inclusion criteria:** 18 consecutive pts with primary autonomic failure | **1° endpoint:** Protocol 1:  
**Rapid water ingestion of 480 mL at room temperature** |
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Results</th>
<th>Improves orthostatic tolerance in pts with autonomic failure as well as post-prandial hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>11904109</td>
<td>observational, prospective cohort</td>
<td>(multiple system atrophy n=9, and PAF n=9) with disabling OH, and n=9 pts with idiopathic orthostatic intolerance with 6 mo of symptoms,</td>
<td>None</td>
<td><strong>Intervention:</strong> 480 mL tapwater at room temperature in &lt;5 min then active standing</td>
<td>no tapwater</td>
<td>Protocol 1: Seated BP increased from 117/67 mmHg before water drinking to 150/78 mmHg with water drinking (P&lt;0.01). After 1 min of standing, BP increased from 83/53 mmHg before water drinking to 114/86 mmHg with water drinking (p&lt;0.01). Maximal tolerated standing time increased from 5+/-3 min before water drinking to 11+/-10 min after drinking (p=0.06). Protocol 2: Baseline BP was 138/77 mmHg, and with eating BP reached an average nadir of 95/57 mmHg. With water ingestion, BP increased to average peak 174/86 mmHg, and average nadir of 116/65 mmHg</td>
<td></td>
</tr>
<tr>
<td>15548493</td>
<td>(320) Analytical, observational, prospective cohort</td>
<td>n=27 pts</td>
<td>n=27 pts</td>
<td><strong>Intervention:</strong> eat a meal then 480 mL tapwater at room temperature then active standing</td>
<td>no tapwater</td>
<td>Protocol 2: Baseline BP was 138/77 mmHg, and with eating BP reached an average nadir of 95/57 mmHg. With water ingestion, BP increased to average peak 174/86 mmHg, and average nadir of 116/65 mmHg</td>
<td></td>
</tr>
<tr>
<td>Young TM, et al. 2004</td>
<td>Analytical, observational, prospective cohort</td>
<td>chronic autonomic failure (7 pts with multiple system atrophy [MSA] which is preganglionic, and 7 pts with PAF which is postganglionic</td>
<td>None</td>
<td><strong>1st endpoint:</strong> 480 mL of distilled water at room temperature within 5 min then remained seated for 15 mins before standing for 5 min (Stand 1) then seated for 15 min then standing for 5 min again (Stand 2)</td>
<td>no tapwater</td>
<td>Results: Water ingestion raised SBP and DBP and lowered heart rate at 3 min and 5 min of Stand 1 compared to before water, all p&lt;0.01. Water ingestion raised SBP and DBP and lowered heart rate at 3 min of Stand 2 compared to before water, all p&lt;0.01, but at 5 min, only SBP and DBP had significance, p&lt;0.01.</td>
<td>Water ingestion increased standing BP and reduced symptoms due to OH. Increase in standing BP appeared related to increase in baseline BP after water ingestion. Pressor effect occurred sooner in PAF (within 5 mins) compared to MSA (13 mins)</td>
</tr>
<tr>
<td>Humm AM, et al. 2008</td>
<td>Analytical, randomized controlled crossover,</td>
<td>PAF with sympathetic and parasympathetic dysfunction with severe OH.</td>
<td></td>
<td><strong>1st endpoint:</strong> 480 mL distilled room temperature water, then supine cycle ergometer followed by active standing</td>
<td>no tapwater</td>
<td></td>
<td>N/A</td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
prospective cohort

**Size:** n=8 pts

**Exclusion:** None

**Results:** Without water ingestion, with exercise there was SBP fall (42.1+/−24.4 mmHg), DBP fall (25.9+/−10 mmHg). With water ingestion, with exercise, SBP fall was still present (49.8+/−18.9 mmHg), DBP fall (26.0+/−9.1 mmHg) but BP remained higher after water intake although not quite significant (p=0.09). Without water ingestion, 3 of 8 pts completed 5 min standing protocol, whereas with water ingestion, 7 of 8 pts completed protocol.

### Data Supplement 35. Nonrandomized Trials, Observational Studies, and/or Registries of Neurogenic Orthostatic Hypotension – (Section 6.1)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axelrod FB, et al. 1995 8690848 (322)</td>
<td><strong>Aim:</strong> To assess midodrine effect in treating OH in familial dysautonomia, <strong>Study type:</strong> Analytical, observational, open label, prospective cohort <strong>Size:</strong> n=9 pts</td>
<td>Inclusion: Familial dysautonomia, OH Exclusion: None 5 pts were on fludrocortisone which was continued</td>
<td>Intervention: Midodrine 2.5 3x daily titrated up Comparator: No midodrine</td>
<td>Results: Average dose: 3.6 mg TID All 9 pts had dizziness at baseline, and with midodrine 7 had improvement or resolution of dizziness. Mean increase in standing BP was not significant.</td>
<td>No placebo control, but most pts noted symptomatic improvement in this small open label study</td>
</tr>
<tr>
<td>Fouad-Tarazi FM, et al. 1995 7503082 (323)</td>
<td><strong>Aim:</strong> To assess efficacy of midodrine with ephedrine, <strong>Study type:</strong> Analytical, Randomized double-blind, placebo controlled crossover, prospective cohort <strong>Size:</strong> n=8 pts</td>
<td>Inclusion: autonomic insufficiency (idiopathic OH, n=7, multiple system atrophy, n=1), unable to tolerate other treatments because of physical disability, gastric irritation, fluid retention, or resistant hypokalemia Exclusion: recent history of persistent supine hypertension &gt;180/100 mmHg unrelated to</td>
<td>Intervention: Midodrine (titrated from 2.5 to 10 mg 3x daily) Comparator: ephedrine (titrated from 6 to 24 mg 3x daily) to where supine SBP between 140-180 mmHg, and supine DBP &lt;100 mmHg and standing SBP≥ 80 mmHg</td>
<td>Results: Mean midodrine dose 8.4 mg 3x daily. Mean ephedrine dose 22.3 mg 3x daily. Midodrine and ephedrine both increased supine BP vs. placebo (p&lt;0.01 for both) not significantly different from each other. Ephedrine (vs. placebo) did not increase standing BP but did heart rate (p&lt;0.05). Midodrine increased standing SBP and DBP vs. placebo (p&lt;0.001) and vs. ephedrine (p&lt;0.001). Only midodrine produced a significant reduction in postural symptoms as</td>
<td>Midodrine: supine HTN (n=1), scalp tingling (n=1) Midodrine was able to significantly improve tolerance to standing with greater maintenance of SBP with standing compared to ephedrine and placebo</td>
</tr>
<tr>
<td>Study</td>
<td>Authors</td>
<td>Year</td>
<td>Journal</td>
<td>Aim</td>
<td>Inclusion</td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
<td>------</td>
<td>---------</td>
<td>-----</td>
<td>-----------</td>
</tr>
<tr>
<td>Denq JC, et al. 1997</td>
<td>9430805 (324)</td>
<td></td>
<td></td>
<td>Aim: Whether compression of different capacitance beds can improve symptomatic neurogenic OH</td>
<td>Pts with neurogenic OH (multiple system atrophy, PAF, or autonomic neuropathy)</td>
</tr>
<tr>
<td>Mathias CJ, et al. 2001</td>
<td>11710796 (325)</td>
<td></td>
<td></td>
<td>Aim: Effect of L-DOPS in management of neurogenic OH</td>
<td>18–75 y of age with autonomic failure and symptoms (dizziness, syncope) and OH (drop in SBP &gt;=20 mmHg)</td>
</tr>
<tr>
<td>Henry R, et al. 1999</td>
<td>10406369</td>
<td></td>
<td></td>
<td>Aim: Effect of compression hosiery in elderly persons with OH</td>
<td>elderly pts with reproducible, symptomatic OH (&gt;20 mmHg)</td>
</tr>
<tr>
<td>Study type: Analytical, observational, open label, prospective cohort</td>
<td>Exclusion: None</td>
<td>Comparator: baseline without compression hose then 90 degree HUTT</td>
<td>Comparator: baseline without compression hose then 90 degree HUTT</td>
<td>Comparator: baseline without compression hose then 90 degree HUTT</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Size: n=10 pts</td>
<td>n=10 pts</td>
<td>n=10 pts</td>
<td>n=10 pts</td>
<td>n=10 pts</td>
<td></td>
</tr>
<tr>
<td>Study type: Analytical, observational, prospective cohort</td>
<td>Study type: Analytical, observational, prospective cohort</td>
<td>Study type: Analytical, observational, prospective cohort</td>
<td>Study type: Analytical, observational, prospective cohort</td>
<td>Study type: Analytical, observational, prospective cohort</td>
<td></td>
</tr>
<tr>
<td>Comparator: baseline without compression hose then 90 degree HUTT</td>
<td>Intervention 1: Some pts received antihypotensive medications (L-threo-3,4-dihydroxyphenylserine [L-DOPS], n=5), Intervention 3: midodrine, n=3</td>
<td>Results: Delta SBP was significantly less after hemodialysis with the abdominal band (-19.4 mm Hg) vs. without the abdominal band (-36.2 mm Hg, p&lt;0.002). Supine SBP elevation was not seen with the abdominal band (149 vs. 153 mm Hg). Delta HR after hemodialysis was significantly greater with the band.</td>
<td>Results: Delta SBP was significantly less after hemodialysis with the abdominal band (-19.4 mm Hg) vs. without the abdominal band (-36.2 mm Hg, p&lt;0.002). Supine SBP elevation was not seen with the abdominal band (149 vs. 153 mm Hg). Delta HR after hemodialysis was significantly greater with the band.</td>
<td>Results: Delta SBP was significantly less after hemodialysis with the abdominal band (-19.4 mm Hg) vs. without the abdominal band (-36.2 mm Hg, p&lt;0.002). Supine SBP elevation was not seen with the abdominal band (149 vs. 153 mm Hg). Delta HR after hemodialysis was significantly greater with the band.</td>
<td></td>
</tr>
<tr>
<td>Interventions: Inflatable abdominal band was able to reduce post dialysis OH, in pts already receiving antihypotensive medications</td>
<td>Inflatable abdominal band was able to reduce post dialysis OH, in pts already receiving antihypotensive medications</td>
<td>Inflatable abdominal band was able to reduce post dialysis OH, in pts already receiving antihypotensive medications</td>
<td>Inflatable abdominal band was able to reduce post dialysis OH, in pts already receiving antihypotensive medications</td>
<td>Inflatable abdominal band was able to reduce post dialysis OH, in pts already receiving antihypotensive medications</td>
<td></td>
</tr>
<tr>
<td>Aim: Effect of leg muscle pumping and tensing on orthostatic pressure</td>
<td>Inclusion: normotensive pts (n=6); hypoadrenergic OH (OH, n=7) of which PAF comprised n=4.</td>
<td>Intervention: leg crossing</td>
<td>Comparator: no leg crossing</td>
<td>Comparator: no leg crossing</td>
<td></td>
</tr>
<tr>
<td>Comparator: no leg crossing</td>
<td>Results: Leg crossing resulted in increase in BP (13+/-2 mmHg vs. 9+/-7 mmHg), and cardiac output (49+/-13% vs. 38+/-15%) in normal pts vs. pts respectively. Pts with PAF and non-PAF noted increase in BP and cardiac output.</td>
<td>Results: Leg crossing resulted in increase in BP (13+/-2 mmHg vs. 9+/-7 mmHg), and cardiac output (49+/-13% vs. 38+/-15%) in normal pts vs. pts respectively. Pts with PAF and non-PAF noted increase in BP and cardiac output.</td>
<td>Results: Leg crossing resulted in increase in BP (13+/-2 mmHg vs. 9+/-7 mmHg), and cardiac output (49+/-13% vs. 38+/-15%) in normal pts vs. pts respectively. Pts with PAF and non-PAF noted increase in BP and cardiac output.</td>
<td>Results: Leg crossing resulted in increase in BP (13+/-2 mmHg vs. 9+/-7 mmHg), and cardiac output (49+/-13% vs. 38+/-15%) in normal pts vs. pts respectively. Pts with PAF and non-PAF noted increase in BP and cardiac output.</td>
<td></td>
</tr>
<tr>
<td>Aim: Whether physical maneuvers can improve orthostatic tolerance in autonomic failure</td>
<td>Inclusion: autonomic dysfunction (hypoadrenergic) with OH, n=7; healthy pts, n=6</td>
<td>Comparator: Standing upright until presyncopal, followed by Intervention 1: leg-crossing and then standing upright</td>
<td>Comparator: Standing upright until presyncopal, followed by Intervention 1: leg-crossing and then standing upright</td>
<td>Comparator: Standing upright until presyncopal, followed by Intervention 1: leg-crossing and then standing upright</td>
<td></td>
</tr>
<tr>
<td>Comparator: Standing upright until presyncopal, followed by Intervention 1: leg-crossing and then standing upright</td>
<td>Results: In autonomic dysfunction group, 5 of 7 pts had orthostatic dizziness within 10 min of standing. (BP 139/75 mg supine decreasing to 75/50 mmHg upright, MAP 58 mmHg). Leg crossing improved SBP to 95/60 mmHg with MAP 72 mmHg. With recurrence of orthostatic intolerance and improved BP, with squatting having larger effect.</td>
<td>Results: In autonomic dysfunction group, 5 of 7 pts had orthostatic dizziness within 10 min of standing. (BP 139/75 mg supine decreasing to 75/50 mmHg upright, MAP 58 mmHg). Leg crossing improved SBP to 95/60 mmHg with MAP 72 mmHg. With recurrence of orthostatic intolerance and improved BP, with squatting having larger effect.</td>
<td>Results: In autonomic dysfunction group, 5 of 7 pts had orthostatic dizziness within 10 min of standing. (BP 139/75 mg supine decreasing to 75/50 mmHg upright, MAP 58 mmHg). Leg crossing improved SBP to 95/60 mmHg with MAP 72 mmHg. With recurrence of orthostatic intolerance and improved BP, with squatting having larger effect.</td>
<td>Results: In autonomic dysfunction group, 5 of 7 pts had orthostatic dizziness within 10 min of standing. (BP 139/75 mg supine decreasing to 75/50 mmHg upright, MAP 58 mmHg). Leg crossing improved SBP to 95/60 mmHg with MAP 72 mmHg. With recurrence of orthostatic intolerance and improved BP, with squatting having larger effect.</td>
<td></td>
</tr>
</tbody>
</table>
Aim: To assess acetylcholinesterase inhibition in orthostatic intolerance during HUT

**Study type:** Analytical, observational open-label, prospective cohort,

**Size:** n=18 pts

**Inclusion:** at least 18 y of age old with orthostatic intolerance

**Exclusion:** Pregnancy or lactating, failure of other organ systems or of systemic illness that could affect study results, autonomic function or pts ability to cooperate (CHF, significant CAD, significant arrhythmia, renal disease, severe anemia, hypothyroidism, and cerebrovascular accidents), therapy with anticholinergic, adrenergic antagonists, vasoactive agents, or medications that could interfere with autonomic function unless discontinued for 5 half-lives before study

**Intervention:** Pyridostigmine 60 mg

**Comparator:** No pyridostigmine

**Primary:** Heart rate: 1 h after pyridostigmine, heart rate was significantly lower in both supine (73.0 vs. 78.9 bpm) and upright position (110.6 vs. 123.7 bpm, p<0.001)

**Secondary:** Other CV parameters: no significant difference in SBP, DBP, MAP, SV, cardiac index; Influence on baroreflex sensitivity (BRS): significantly higher after pyridostigmine (p<0.005); Influence on plasma catecholamines: plasma norepi significantly higher 1 h after pyridostigmine for supine (p=0.03) and upright (p=0.005) positions.

Heart rate blunting and increased plasma catecholamine levels were associated with significant amelioration of orthostatic symptoms (p=0.01)

Acetylcholinesterase inhibition may enhance sympathetic ganglionic transmission and improves orthostatic intolerance

---

### Data Supplement 36. RCTs Involving Dehydration and Drugs – (Section 6.2)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anley C, et al.</td>
<td>Aim: To assess which</td>
<td>Inclusion: All</td>
<td>Intervention: OT, oral fluid and</td>
<td>1° endpoint: Time to discharge from the</td>
<td>• With no difference in time to</td>
</tr>
<tr>
<td>Year</td>
<td>Study</td>
<td>Aim</td>
<td>Study type</td>
<td>Size</td>
<td>Inclusion</td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>-----</td>
<td>------------</td>
<td>------</td>
<td>-----------</td>
</tr>
<tr>
<td>2011</td>
<td>20584756 (293)</td>
<td>treatment protocol for exercise-associated postural hypotension results in earlier discharge</td>
<td>Analytical, randomized, prospective cohort</td>
<td>n=28 pts</td>
<td>Children with moderate dehydration (having at least 4 standard published criteria) at single center</td>
</tr>
<tr>
<td>2002</td>
<td>12444837 (331)</td>
<td>To compare oral rehydration therapy with IV therapy for moderate dehydration in children</td>
<td>Analytical, randomized, prospective cohort</td>
<td>n=34 pts</td>
<td>Children with moderate dehydration (having at least 4 standard published criteria) at single center</td>
</tr>
<tr>
<td>2006</td>
<td>17146319 (332)</td>
<td>To determine effects of rapid (&lt;30 min) IV vs oral rehydration immediately after dehydration during subsequent exercise in non heat acclimated men</td>
<td>N/A</td>
<td>Each subject performed 3 trials: 1) Dehydration phase, pts walked or ran for 75 min at 50% VO2 max with airflow directed to enhance evaporative sweat loss</td>
<td></td>
</tr>
<tr>
<td>Study type: Analytical, randomized, prospective cohort</td>
<td>Inclusion: Healthy males</td>
<td>Results: IV rehydration resulted in more rapid plasma volume restoration (p&lt;0.05)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size: n=8 pts</td>
<td>Exclusion: N/A</td>
<td>However, there was no significant improvement in exercise duration (IV: 72.6+/−28.9 min; oral: 70.6+/−8.2 min) during the heat tolerance testing with IV vs. oral rehydration.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rehydration phase</strong></td>
<td></td>
<td>Sensation of thirst was significantly lower in oral rehydration than IV fluid (p&lt;0.05)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rehydration treatments were randomly assigned to receive amount of fluid lost during dehydration:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intervention 1:</strong> IV rehydration (0.45% saline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intervention 2:</strong> Oral rehydration (0.45% saline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intervention 3:</strong> No fluid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Then:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3) heat-tolerance test:</strong> immediately after 30 min rehydration period, pts performed a 75 min heat tolerance test in 37°C chamber</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Maughan RJ, et al. 1995**
*8549573 (333)*

<table>
<thead>
<tr>
<th>Aim: To study the effect of sodium content of drinks on rehydration after exercise</th>
<th>Inclusion: Healthy males</th>
<th>1^st endpoint: Effect of sodium content of drinks on rehydration after exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type: Analytical, randomized, prospective cohort</td>
<td>Exclusion: N/A</td>
<td>Results: Net fluid balance at end of trial: Sodium content 2 mmol/L: −689 mL Sodium content 26 mmol/L: −359 mL Sodium content 52 mmol/L: 2 mL Sodium content 100 mmol/L: 98 mL</td>
</tr>
<tr>
<td>Size: n=6 pts</td>
<td></td>
<td>• Plasma volume was higher with sodium contents of 52 and 100 mmol/L compared to 2 mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cumulative urine output was higher on sodium content 2 mmol/L than with 52 mmol or 100 mmol/L.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rehydration and retained volume is greater with ingestion of fluid with increasing sodium concentration</td>
</tr>
<tr>
<td></td>
<td>Pts were dehydrated by intermittent cycle exercise in warm and humid environment then ingested 1.5 times body mass loss of:</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Intervention 1:</strong> Na content 2 mmol/L (108 mosmol/kg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Intervention 2:</strong> Na content 26 mmol/L (158 mosmol/kg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Intervention 3:</strong> Na content 52 mmol/L (206 mosmol/kg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Intervention 4:</strong> Na content 100 mmol/L (300 mosmol/kg)</td>
<td></td>
</tr>
</tbody>
</table>

**Merson SJ, et al. 2008**
*18463891 (334)*

<table>
<thead>
<tr>
<th>Aim: To investigate differing sodium chloride concentrations affect rehydration</th>
<th>Inclusion: Healthy men without Hx of CV or renal disease</th>
<th>1^st endpoint: Sodium chloride concentration effect on rehydration after exercise and subsequent exercise capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type: Analytical, randomized, prospective</td>
<td>Exclusion: N/A</td>
<td>Results: Pts retained more of test drink as the sodium concentration of the drink increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Increased sodium content of the test drink improved hydration compared to lower sodium and no sodium test drinks. Higher sodium drinks did not affect repeat exercise performance.</td>
</tr>
<tr>
<td></td>
<td>Exercise via cycle ergometer with measured VO2 max then drinking 150% of fluid lost as sweat:</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Intervention 1:</strong> NaCl 0 mmol</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Intervention 2:</strong> NaCl 30 mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Intervention 3:</strong> 40 mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Intervention 4:</strong> 50 mmol/L</td>
<td></td>
</tr>
</tbody>
</table>
cohort

**Size:** n= 8 pts

Then exercised again to 95% of VO\(_2\) peak or exhaustion

(As measured by corresponding decreasing urine output). 
- Significantly more fluid was retained on 40 and 50 mmol/L NaCl compared to 0 mmol/L (p<0.01).
- Greater net negative fluid balance was seen 4 h after finishing drinking with lower sodium concentration test drink.
- There was no effect of the sodium content of the drink on time to exhaustion on repeat exercise (p>0.8)

**El-Sayed H, et al. 1996**

**Aim:** To evaluate salt supplementation in syncope with OI

**Study type:** Analytical, Randomized placebo controlled, prospective cohort

**Size:** n=20 pts

**RDBPCT:**

<table>
<thead>
<tr>
<th>Intervention:</th>
<th>Comparator:</th>
</tr>
</thead>
<tbody>
<tr>
<td>sodium chloride 10 mmol</td>
<td>Placebo 12x daily then 60 degree HUTT with LBNP up to -40 mmHg</td>
</tr>
</tbody>
</table>

1° endpoint: Effect of salt administration on plasma volume and orthostatic tolerance in pts with posturally related syncope

Results:
RDBPCT: 8 of 10 pts taking salt, vs. 3 of 10 taking placebo showed significant increases in plasma and blood volumes (p<0.05); all pts with increased plasma and blood volumes showed improved tolerance to orthostatic stress (time to presyncope)

Open label: 7 of 11 taking salt had increased plasma and blood volumes, and these pts showed improved symptoms of orthostatic tolerance

- Pts with salt supplementation (increasing plasma volume by >90 mL) had significant increase in orthostatic tolerance. Pts with signs of high salt intake at baseline (by 24 h urinary sodium excretion) did not benefit from additional salt loading

**Summary/Conclusion**

Pts with signs of high salt intake at baseline (by 24 h urinary sodium excretion) did not benefit from additional salt loading

**Greenleaf JE, et al. 1998**

**Aim:** To evaluate various carbohydrate electrolyte fluid formulations for consumption by astronauts to restore plasma

**Study Type/Design:** Analytical, observational, open label, prospective cohort

**Size:** n=11 pts

**Inclusion:** Recurrent syncope without etiology

**Exclusion:** N/A

**RDBPCT:**

<table>
<thead>
<tr>
<th>Intervention:</th>
<th>Comparator:</th>
</tr>
</thead>
<tbody>
<tr>
<td>slow sodium 10 mmol 12x daily (pts told it was a &quot;mineral dietary supplement&quot;)</td>
<td>Placebo 12x daily then 60 degree HUTT with LBNP up to -40 mmHg</td>
</tr>
</tbody>
</table>

Pls dehydrated for 24 h with moderate dehydration confirmed by plasma osmolality (298-305 mOsm/kg) then drank 1 of 6 fluid formulations (12 mL/kg: 898-927 mL):

- Intervention 1: water

Sodium content appears to be more important than total osmotic content for inducing hypervolemia.
Study type: Analytical, observational, prospective cohort

Size: n=7 pts

Exclusion: N/A

Intervention 2: 19.6 mEq/L Na
Intervention 3: 157 mEq/L Na
Intervention 4: 19.6 mEq/L Na + glucose
Intervention 5: Performance® ~20 mEq Na
Intervention 6: Power Surge® ~20 mEq Na

1° endpoint: Plasma volume and total body water

Results:
At rest, drinking formulations with higher sodium had greater increases in plasma volume. 157 Na resulted in 7.6% increase in plasma volume. Lower sodium content beverages but with higher total osmolality did not hydrate as well.

At rest, drinking 157 Na (the largest Na content), induced the greatest hypervolemia: 7.6%, p<0.05. water ingestion did not increase plasma volume.

With exercise, high sodium intake beverages were no more effective than low sodium beverages for plasma volume stabilization. However, water was the least effective with an initial loss (17%) of plasma volume within the first 9 min of exercise.

Shirreffs SM, et al. 1996 8897383 (336)

Aim: To study the interaction between volume and composition of fluids ingested for rehydration effectiveness

Study type: Analytical, observational, prospective cohort

Size: n=12 pts

Inclusion: Healthy men

Exclusion: N/A

Each subject exercised to induce sweat loss of 2% of body mass then drank beverages with different sodium concentration and volumes:

Sodium concentration:
Intervention 1: low sodium (23 mmol/L)
Or
Intervention 2: high sodium (61 mmol/L)

Both drinks also contained small amounts of potassium and glucose (90 mmol/L).

Volume:
Intervention A: 50% of body mass loss
Intervention B: 100% of body mass loss
Intervention C: 150% of body mass loss
Intervention D: 200% of body mass loss

• Drinking a large volume beverage may be inadequate to rehydrate if the sodium concentration is insufficient, and drinking a high-sodium concentration beverage may be inadequate if a large enough volume is not consumed.
Repeat tests were separated 1 wk apart

1° endpoint: Rehydration effectiveness as measured by urine volume output and whole body net fluid balance

Results:
Total urine output with low sodium beverage: A=135 mL, B= 493 mL, C=867 mL, D, 1361 mL.

- Total urine output with high sodium beverage: A=144 mL, B=260 mL, C=602 mL, D=1001 mL
- Pts rehydrating with low sodium beverage were in a more negative state of fluid balance with Intervention A (-909 mL) than Intervention C (-128 mL) or D (-135 mL)
- Pts rehydrating with high sodium beverage were in a more negative state of fluid balance with Intervention A (-958 mL) than Intervention D (+427 mL).

<table>
<thead>
<tr>
<th>Jeukendrup AE, et al. 2009</th>
<th>Aim: To study the effects of increasing carbohydrate and sodium content on fluid delivery</th>
<th>Inclusion: Healthy males</th>
<th>Each subject undertook 4 trials each &gt;7 days apart</th>
</tr>
</thead>
<tbody>
<tr>
<td>19232115 (337)</td>
<td>Study type: Analytical, observational, prospective case control,</td>
<td>Exclusion: N/A</td>
<td>Carbohydrate group (CHO, n=10 pts)</td>
</tr>
<tr>
<td></td>
<td>Size: n=20 pts</td>
<td></td>
<td>Intervention 1: G0: water + 20 mmol/L sodium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention 2: G3: 3% glucose + 20 mmol/L sodium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention 3: G6: 6% glucose + 20 mmol/L sodium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention 4: G9: 9% glucose + 20 mmol/L sodium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sodium group (Na, n=10 pts)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention 1: Na0: 6% glucose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention 2: Na20: 6% glucose + 20 mmol/L sodium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention 3: Na40: 6% glucose + 40 mmol/L sodium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention 4: Na60: 6% glucose + 60 mmol/L sodium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1° endpoint: Fluid delivery surrogately measured by plasma deuterium enrichment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Results:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Glucose group: trend for time to plateau with increasing carbohydrate concentration (GO:34 min, G3: 35 min, G6:43 min, G9:51 min)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Plasma deuterium enrichment was significantly greater with 3% glucose (p&lt;0.001) than no carbohydrate, 6% glucose, or 9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Increasing the glucose content above 3% did not further increase fluid delivery. Sodium content did not significantly affect fluid delivery, although there was a trend for reaching plateau time more quickly with higher sodium content.</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Study type</td>
<td>Size</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>-----------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Beckett NS, et al. 1999 10618673 (338)</td>
<td>To assess OH prevalence and associated factors in elderly hypertensive pts</td>
<td>Analytical, observational, cross-sectional study</td>
<td>n=1,241 pts</td>
</tr>
<tr>
<td>Blake AJ, et al. 1988, 3266440 (339)</td>
<td>To assess falls and their associated causes</td>
<td>Descriptive cross sectional survey</td>
<td>n=356 pts</td>
</tr>
<tr>
<td>Burke V, et al. 1992 1484937 (340)</td>
<td>To assess relation of drug treatment to postural fall in BP in elderly</td>
<td>Descriptive, cross-sectional survey</td>
<td>n=843 pts</td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
<table>
<thead>
<tr>
<th><strong>Craig GM, et al. 1994</strong>&lt;br&gt;7971628 (341)</th>
<th><strong>Aim:</strong> Presentation of OH in elderly&lt;br&gt;<strong>Study type:</strong> Descriptive retrospective chart review&lt;br&gt;<strong>Size:</strong> n=50 pts</th>
<th><strong>Inclusion:</strong> Elderly pts with OH (defined as ≥ 20 mmHg fall in SBP)&lt;br&gt;<strong>Exclusion:</strong> N/A</th>
<th><strong>1° endpoint:</strong> Factors associated with orthostatic fall in SBP ≥ 20 mmHg&lt;br&gt;<strong>Results:</strong> Presenting features of OH: Falls 64%, poor mobility 44%, unsteadiness 38%, confusion 22%.&lt;br&gt;<strong>Medication usage in OH pts:</strong> • Diuretic 56%, benzodiazepine 26%, anti-depressant 24%, anti-parkinsonian therapy 22%, phenothiazine 18%, BB 12%, hydralazine 10%, calcium antagonist 8%, nitrates 6%.&lt;br&gt;● Medication was primarily responsible for OH in 66%, and implicated in 80% of cases.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fotherby MD, et al. 1994</strong>&lt;br&gt;7870633 (342)</td>
<td><strong>Aim:</strong> Assess prevalence of OH in elderly HTN pts whether anti-HTN therapy was continued or not,&lt;br&gt;<strong>Study type:</strong> Analytical, observational, prospective cohort&lt;br&gt;<strong>Size:</strong> n=47 pts</td>
<td><strong>Inclusion:</strong> Pts ≥ 65 y of age, BP &lt;175/100 mmHg on pharmacological treatment &gt;1.&lt;br&gt;<strong>Exclusion:</strong> MI or stroke within preceding 6 mo, having angina or known major illness, diabetes, Parkinson disease, or on medication other than anti-hypertensives known to affect BP&lt;br&gt;• Following treatment withdrawal, pts whose SBP was ≥175 mmHg and/or whose DBP &gt;100 mmHg on 2 occasions were withdrawn from the study and deemed unsuitable for anti-HTN withdrawal</td>
<td><strong>1° endpoint:</strong> Prevalence of OH&lt;br&gt;<strong>Intervention:</strong> Anti-HTN medication withdrawal, BP measured at 1, 3, 6, 9, and 12 mo of anti-HTN therapy withdrawal&lt;br&gt;<strong>Comparator:</strong> Continuing on anti-HTN had BP measure at 6 and 12 mo.&lt;br&gt;<strong>Results:</strong> For pts stopping anti-HTN medication, the number of OH fell from 11 (23%) on anti-HTN treatment to 4 (11%, p&lt;0.05) off treatment.&lt;br&gt;• The pts continuing anti-HTN medication showed no significant change in prevalence of OH, 5 (38%) at baseline, and 4 (31%) at 12 mo.&lt;br&gt;• Pts with OH on treatment (vs. those with OH on treatment) were older (79 y of age vs. 74 y of age, p=0.05) and had higher pre-withdrawal SBP (164+/−21 vs. 147 +/−17 mmHg, p=0.02)&lt;br&gt;● Withdrawal of anti-HTN therapy can decrease OH occurrence. Those with OH on anti-HTN treatment tended to be older and had higher prewithdrawal SBP&lt;br&gt;● 13 of the 47 pts did not meet criteria for anti-hypertensive withdrawal&lt;br&gt;● OH defined as mean SBP fall ≥ 20 mmHg on standing from supine</td>
</tr>
<tr>
<td><strong>Jansen RW, et al. 1996</strong>&lt;br&gt;8636581 (343)</td>
<td><strong>Aim:</strong> To assess post-prandial hypotension and relation to chronic use of CV medications&lt;br&gt;<strong>Study type:</strong> Analytical, observational, prospective</td>
<td><strong>Inclusion:</strong> Nursing home residents, sinus rhythm, be able to stand from supine position within 30 s and remain standing for 10 min&lt;br&gt;<strong>Comparator:</strong> Standing test, then&lt;br&gt;<strong>Intervention:</strong> repeat standing test after eating meal. Same protocol repeated in 3 to 14 days.&lt;br&gt;<strong>1° endpoint:</strong> BP and heart rate before and after postural change;</td>
<td><strong>● Post-prandial responses in BP and heart rate are similar, and CV medication administration did not affect post-meal findings. However, the CV medication did affect BP after standing suggesting this</strong></td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Size</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>1st endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jodaitis L, et al. 2015</td>
<td>Association of OH with use of drugs with psychotropic, CV, or diuretic effect</td>
<td>n=285 pts</td>
<td>Older (pts $\geq$75 y of age) in pts screened for OH (defined as reduction of $\geq$20 mmHg in SBP or $\geq$10 mmHg in DBP within 3 min of standing)</td>
<td>Presence of pacemaker, insulin-dependent DM</td>
<td>Prevalence of OH</td>
<td>Mean age was 85 +/- 5 y of age in pts with OH, and 84 +/- 4 y of age without OH. Prevalence of OH was 41% (30% for SBP, 23% for DBP). Pts with OH vs. without OH were more likely to have falls (62% vs. 40%, p&lt;0.001) and syncope (29% vs. 4%, p&lt;0.001). There was no difference in proportions of pts receiving drugs or drug potentially associated with falls and/or OH.</td>
</tr>
<tr>
<td>Kamaruzzaman S, et al. 2010</td>
<td>Association of OH and medication use in British Women's Heart and Healthy Study</td>
<td>n=3,775 pts</td>
<td>British Women's Heart and Healthy Study cohort, OH (defined as SBP $\geq$ 20 mmHg and/or diastolic BP $\geq$ 10 mmHg).</td>
<td>N/A</td>
<td>Prevalence of OH</td>
<td>Higher prevalence of OH in women with HTN than without HTN (79% vs. 64%, p&lt;0.001). No association of OH to coronary heart disease, diabetes, COPD, or cancer. Prevalence of OH was 28% (95% CI: 26.6–29.4) among women 60-80 y of age. Among BP lowering medication, only BB had higher odds of OH (OR: 1.26, 95% CI: 1.09–1.47, p&lt;0.01). Women on multiple antihypertensive drugs ($\geq$ 3 vs. 0) had increased odds of OH (OR: 1.99, 95% CI: 1.30–3.05, p=0.003). OH was associated with all-cause mortality (OR: 1.10, 95% CI:1.07–1.14, p&lt;0.001)</td>
</tr>
<tr>
<td>McLachlan CY, et al. 2014</td>
<td>To assess frequency, nature, and causality of ADE resulting in acute admissions</td>
<td>n=22 pts</td>
<td>All admissions at single center in New Zealand between 10/1/2011</td>
<td>Presence of pacemaker, insulin-dependent DM</td>
<td>Prevalence of ADE</td>
<td>ADE comprises a significant amount of admissions at this single center, with the syncope being the postprandial hypotension associated with all causes of mortality (OR: 1.47, p&lt;0.01). Women only had increased odds of OH and death associated with OH.</td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
<table>
<thead>
<tr>
<th>Study type: Analytical, observational, prospective cohort</th>
<th>Size: n=96 pts</th>
<th>Study type: Analytical, observational, prospective cohort</th>
<th>Size: n=911 pts</th>
<th>Study type: Analytical, observational, prospective cohort</th>
<th>Size: n=80 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study type:</strong> Analytical, observational, prospective cohort</td>
<td>Size: n=96 pts</td>
<td><strong>Inclusion:</strong> Nursing home residents ≥ 60 y of age, life expectancy &gt;3 mo, able to stand at least 1 min</td>
<td><strong>Exclusion:</strong> N/A</td>
<td><strong>Inclusion:</strong> Pt’s ≥ 65 y of age, mild or moderate ischemic stroke, admitted to hospital ≤24 h of stroke onset, living at home, could be on antihypertensive medication (”treated group”, n=40) or not (”untreated group”, n=40)</td>
<td><strong>Exclusion:</strong> Hemorrhagic stroke, comorbidity affecting BP regulation (DM or Parkinson disease), know postural hypotension, MI in previous 3 mo, severe HF (NYHA III or IV), AF, urea &gt;10 mmol/L, hemoglobin &lt;10 g/dL, antibiotic requirement, serious illness,</td>
</tr>
<tr>
<td>Study type: Analytical, observational, prospective cohort</td>
<td>Size: n=911 pts</td>
<td><strong>1st endpoint:</strong> supine BP, 1-min standing BP, 3-min standing BP, and heart rate</td>
<td><strong>Results:</strong> After multivariate analysis, significantly associated (p&lt;0.05) with OH were: elevated supine BP before breakfast, lightheadedness with standing, male gender, Parkinson disease medications, lower body mass index. Diuretic, antianginal, antiarrhythmics, and ACE-inhibitors were not associated with OH.</td>
<td><strong>Exclusion:</strong> N/A</td>
<td><strong>1st endpoint:</strong> BP and heart rate measurements while supine, sitting, and standing within 3 d of stroke onset (”day 1”), and again 4 to 7 days (”wk 1”) after stroke onset</td>
</tr>
</tbody>
</table>

Of 336 admissions, 96 (28.6%) were related to ADE. 65 (19.3%) were caused by ADE, and 31 (9.2%) were contributed to by an ADE.  
- Most common adverse effects were postural hypotension and/or vasovagal syncope (29%)  
- Most common implicated medications were vasodilators (23%), psychotropic medications (18%), and diuretics (16%), chronotropic medications [amiodarone, BB, diltiazem, digoxin] (11%)  

Ooi WL, et al. 1997 9109468 (347)  
Panayiotou B, et al. 2002 11824858 (348)  

Antihypertensive medication use was not associated with OH, but lower body mass index and Parkinson disease medications were.

In pts with mild to moderate ischemic stroke, antihypertensive therapy is not associated with OH. Presence of cardiac dysfunction was associated with OH.
Poon IO, et al. 2005 15811171 (349)

**Aim:** To describe prevalence of symptomatic and asymptomatic OH in elderly veterans and relation to medications

**Study type:** Retrospective chart review,

**Size:** n=342 pts

**Inclusion:** Pts ≥75 y of age, with documented sitting and standing BP readings, who attended geriatric clinic in electronic medical record database (MEDVAMC) between 6/2002 and 6/2003

**Exclusion:** Pts unable to stand, no assessment of sitting and standing BP, autonomic dysfunction, Parkinson disease.

**1st endpoint:** Prevalence of OH, medication prevalence

**Results:**

- 189 (55%) pts had OH. Prevalence of OH in pts who had no causative medication was 35%. Prevalence OH in pts on 1, 2, or ≥3 causative medications was 58%, 60%, and 65% respectively, with a significant relationship x²=15.18, p=0.002)

- Associated with highest prevalence of OH was hydrochlorothiazide (65%), lisinopril (60%), furosemide (56%), and terazosin (54%) for cardiac medications. Other medications associated with OH included paroxetine (86%), trazodone (58%), olanzapine (57%), and quetiapine (56%)

- With increasing number of causative medications, the prevalence of OH increased. The highest association among cardiac medications included HCTZ and lisinopril. The effect of work-up bias is not accounted for, as there are many pts on these medications without orthostatic symptoms or BP measurements.

- OH defined as SBP reduction ≥20 mmHg or DBP ≥10 mmHg within 3 mins of standing +/- symptoms

- Potentially causative medications of OH were those reported with >1% incidence of OH

Raiha I, et al. 1995 7726701 (350)

**Aim:** To evaluate predisposing factors to postural hypotension in elderly

**Study type:** Analytical, observational, prospective cohort

**Size:** n=347 pts

**Inclusion:** Baseline and 10 y follow-up survey of elderly (pts >65 y of age) in Turku, Finland in 347 pts.

**Exclusion:** Living in an institution

**1st endpoint:** Prevalence of postural hypotension, 10 y mortality

**Results:**

- Prevalence of postural hypotension was 28%. Predisposing factors for postural hypotension: elevated supine BP (p<0.001).
- Chronic CV diseases, body mass index, medication, and abnormal ECG were not associated with postural hypotension

- Only supine HTN was associated with postural hypotension, but there was not effect on mortality. No medication (nitrates, diuretics, BB, orther antihypertensives) was associated with postural hypotension.

- Postural hypotension was defined as ≥ 20 mmHg after 3 mins of standing.

---

**Data Supplement 38. Nonrandomized Trials, Observational Studies, and/or Registries of Pseudosyncope – (Section 8)**

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
<table>
<thead>
<tr>
<th>Study Type</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>1st Endpoint</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Practice guideline consensus (European Society of Cardiology)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Frequent attacks, often many times a day, eyes closed, prolonged episodes, often many mins in duration, no apparent trigger for attack, prone to being ‘suggestible’ which favors triggering attacks in clinic/laboratory</td>
<td>Summarizes the key clinically useful markers to aid recognition of PPS/PNES</td>
</tr>
<tr>
<td>Tilt-test induction of PPS/PNES examined retrospectively to assess clinical features</td>
<td>Diagnosis of PPS/PNES by Tilt-test and video EEG</td>
<td>N/A</td>
<td>Pseudosyncope</td>
<td>PPS/PNES can be diagnosed and differentiated from vasovagal syncope by use of a tilt-test.</td>
<td>Provides a quantitative assessment of clinical features distinguishing PPS/PNES from vasovagal syncope</td>
</tr>
<tr>
<td>Retrospective observational study of PNES pts diagnosed by inpatient or outpatient EEG or video-EEG</td>
<td>Diagnosed PPS/PNES</td>
<td>N/A</td>
<td>New onset of medically unexplained symptoms (MUS) in pts diagnosed with PPS/PNES.</td>
<td>Many PPS/PNES pts exhibit other medically unexplained symptoms, but in most cases the medically unexplained symptoms were present prior to diagnosis of PPS/PNES and only infrequently became manifest for the first time later during the approx. 1 y follow-up.</td>
<td></td>
</tr>
<tr>
<td>Single center prospective syncope evaluation</td>
<td>Presentation of TLOC or apparent TLOC</td>
<td>N/A</td>
<td>Frequency of PPS/PNES in a TLOC population</td>
<td>A stepwise evaluation of apparent TLOC cases in an ambulatory clinic may yield a diagnosis in 2/3. More than 50% of cases are either vasovagal syncope or PPS/PNES.</td>
<td></td>
</tr>
</tbody>
</table>
| Elliot JO, et al. 2014 | **Study type:** Observational Quantitative assessment in PNES alone or PNES with epilepsy  
**Study size:** PNES alone 84, PNES + epilepsy 281; No Controls  
**Inclusion criteria:** Retrospective study of pts admitted to an epilepsy monitoring unit over a 6 y period  
**Exclusion criteria:** N/A  
**1° endpoint:** Predictors of video-EEG confirmed PPS/PNES in an epilepsy monitoring unit  
**Results:**  
• 5 Biologic predictors of PNES alone  
• 1 Psychological predictor  
• 2 Social predictors |
| --- | --- |
| Mayor, et al. 2012 | **Study type:** Prospective observational  
**Size:** n=44 previously diagnosed cases  
**Inclusion criteria:** Prior diagnosis of PPS/PNES in which pts completed self-reporting symptom questionnaires or otherwise reported symptom frequency during follow-up  
**Exclusion criteria:** N/A  
**1° endpoint:** Symptom recurrence after being told the nature of the diagnosis  
**Results:** Median self-reported symptom frequency dropped from 10 to 7.5/mo over 6 mo. 7 of 44 became symptom free, and 10/44 had >50% reduction of event frequency. Nevertheless, baseline levels of life-style impairment did not improve.  
• Apart from identifying the diagnosis of PPS/PNES, further efforts are needed to diminish adverse life-style impact of this condition. |
| Mayor, et al. 2010 | **Study type:** Prospective observational of psychodynamic psychotherapy (no controls)  
**Size:** n=66 pts of whom 47 were followed full study duration  
**Inclusion criteria:** Diagnosed PPS/PNES  
**Exclusion criteria:** N/A  
**1° endpoint:** PPS/PNES event frequency  
**Results:** With follow-up of 12–61 mo (mean 50 mo), 25% were symptom free and 40% achieved event reduction >50%. Health care utilization declined significantly (p=0.039)  
• Psychodynamic interpersonal therapy may be associated with reduction of symptom frequency and healthcare utilization. |
| Reuber M, et al. 2007 | **Study type:** Uncontrolled observational assessment of tailored psychotherapy in pts with functional neurologic impairment  
**Size:** n=91 enrollees; 63 completed treatment and 34 completed final questionnaires  
**Inclusion criteria:** Functional neurological symptoms but NOT just PPS/PNES  
**Exclusion criteria:** N/A  
**1° endpoint:** Therapeutic impact of individualized psychotherapy using validated questionnaires  
**Results:** Questionnaires throughout approx. 6 mo follow-up revealed that multiple patient-centered psychiatric instruments improved by at least 1 SD in 50% of pts  
• Individualized psychotherapy may be beneficial but one-size does not fit all. |
### Data Supplement 39. RCTs for Pseudosyncope – (Section 8)

<table>
<thead>
<tr>
<th>Study Acronym;</th>
<th>Study Type;</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein LH, et al. 2010 20548043 (360)</td>
<td>Study type: RCT; Size: n=36 pts randomized to standard therapy vs. CBT psychotherapy</td>
<td>Inclusion criteria: Diagnosis of PPS/PNES</td>
<td>Intervention: CBT in addition to standard therapy</td>
<td>1° endpoint: Symptom recurrence frequency</td>
<td>• CBT tended to improve short-term outcomes but larger controlled studies are needed.</td>
</tr>
<tr>
<td>LaFrance Jr WC, et al. 2010 20739647 (358)</td>
<td>Study type: Prospective double-blind RCT of sertraline in PPS/PNES; Size: 38 enrollees; n=26 completed study</td>
<td>Inclusion criteria: Diagnosed PPS/PNES</td>
<td>Comparator: Standard therapy alone</td>
<td>Results: Sertraline was associated with 48% symptom reduction vs. 8% with placebo. However, intention-to-treat not reported and baseline differences resulted in no significant difference</td>
<td>• Sertraline initially appeared to be more effective than placebo with reduction of symptom frequency from baseline. However, after adjustment for baseline differences the effect was deemed nonsignificant.</td>
</tr>
<tr>
<td>Santos, et al. 2014 25650860 (359)</td>
<td>Study type: Observational effects of psychoanalytic therapy; no controls; Size: n=37 pts</td>
<td>Inclusion criteria: PNES diagnosed by video-EEG</td>
<td>Comparator: Individual psychoanalytic therapy proved beneficial in this uncontrolled study</td>
<td>1° endpoint: Symptom recurrence frequency during follow-up</td>
<td>• Individual psychoanalytic therapy proved beneficial in this uncontrolled study</td>
</tr>
<tr>
<td>Study Acronym; Author; Year Published</td>
<td>Aim of Study; Study Type*; Study Size (N)</td>
<td>Patient Population</td>
<td>Study Intervention (# patients) / Study Comparator (# patients)</td>
<td>Endpoint Results (Include Absolute Event Rates, P value; OR or RR; and 95% CI)</td>
<td>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>------------------------------------------</td>
<td>--------------------</td>
<td>---------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Zhang Q, et al. 2009 19183119 (361)</td>
<td><strong>Aim</strong>: Aimed to measure the diagnostic value of a protocol on the management of children and adolescents with syncope. <strong>Study type</strong>: Multi center, prospective consecutive pts &lt;18 y of age with syncope. <strong>Size</strong>: n=474 consecutive pts presenting with syncope. (20 mo period)</td>
<td><strong>Inclusion criteria</strong>: &lt;18 y of age with syncope as defined as TLOC and postural tone caused by cerebral hypoperfusion <strong>Exclusion criteria</strong>: Pts with symptoms compatible with seizures, vertigo, or shock were excluded.</td>
<td><strong>Intervention</strong>: 1° Step: H&amp;P, and ECG 2° Step: Echo, Holter, CT, Psych evaluation. 2° Step diagnostic maneuvers were only performed if 1° step did not yield a definitive diagnosis. HUTT was only used if unexplained syncope. <strong>Comparator</strong>: None</td>
<td>1° endpoint: Initial diagnostic work-up (H&amp;P &amp; ECG) gave a definitive diagnosis in 59 (12.4%). 2° Step diagnostic work-up required in 326 (87%). 1) n=382 HUTT identified VVS in 203, POTS in 87. No final diagnosis in 89 pts (TILT YIELD): 76% 2) n=10 had a neurological event (additional testing is unnecessary unless challenged by H&amp;P).</td>
<td>• HUTT can help with the diagnosis. An extensive neurological work-up is not indicated unless the H&amp;P is suspicious for a neuro condition (i.e. vertigo seizure) <strong>Summary</strong>: HUTT can help make the diagnosis of VVS. An extensive neurological work-up should be reserved for pts whose H&amp;P is concerning for a neuro condition.</td>
</tr>
<tr>
<td>Miyake, et al. 2015 26277987 (362)</td>
<td><strong>Aim</strong>: Aimed to evaluate the incidence of cardiac disorders among children with mid-exertional syncope. <strong>Study type</strong>: Single center, retrospective evaluation of children who presented for cardiac evaluation with exertional syncope (1999-2012) <strong>Size</strong>: n=60 pts</td>
<td><strong>Inclusion criteria</strong>: ≤18 y of age with mid-exertional syncope an EKG and ECHO and at least one of the following: TTT, EST, EPS <strong>Exclusion criteria</strong>: Pts with known structural heart defects or known arrhythmia disorders</td>
<td><strong>Intervention</strong>: None, Clinical Evaluation Only <strong>Comparator</strong>: None</td>
<td>1° endpoint: 28 Non cardiac Diagnosis 32 Cardiac Diagnosis LQT (n=10) CPVT (n=6) SVT (n=5) VT (n=2) VF (n=2) HCM (n=2) LVNC (n=1) • No difference in symptoms between cardiac and noncardiac pts preceding syncope or following syncopal event.</td>
<td>• Reported symptoms before and after a mid-exertional syncopal event may not distinguish between a benign noncardiac condition and a cardiac condition. <strong>Summary</strong>: Mid-exertional syncope in children carries a high-risk of being diagnosed with a cardiac condition.</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>PubMed ID</td>
<td>Aim</td>
<td>Study type</td>
<td>Inclusion criteria</td>
</tr>
<tr>
<td>---------</td>
<td>------</td>
<td>-----------</td>
<td>-----</td>
<td>------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Zhang, et al.</td>
<td>2013</td>
<td>22417947 (363)</td>
<td><strong>Aim:</strong> Value of Hx taking in identifying children with cardiac syncope</td>
<td><strong>Study type:</strong> Multicenter prospective consecutive series of pts in the Pediatric Syncope Unit</td>
<td>≤18 y of age with suspected syncope admitted to the Pediatric Syncope Unit of 5 hospitals in China</td>
</tr>
<tr>
<td>Qingyou, et al.</td>
<td>2004</td>
<td>14727100 (364)</td>
<td><strong>Aim:</strong> To determine usefulness in children with unexplained syncope.</td>
<td><strong>Study type:</strong> Single center prospective study of pts with unexplained syncope.</td>
<td>≤18 y of age with unexplained syncope.</td>
</tr>
<tr>
<td>Udani, et al.</td>
<td>2004</td>
<td>15269465 (365)</td>
<td><strong>Aim:</strong> Aimed to measure the diagnostic value of a HUTT</td>
<td><strong>Study type:</strong> Single center, prospective consecutive pts &lt;18 y of age with syncope.</td>
<td>&lt;18 y of age with strong clinical suspicion of neurocardiogenic syncope</td>
</tr>
<tr>
<td>Fouad, et al.</td>
<td>1993</td>
<td>7681189 (366)</td>
<td><strong>Aim:</strong> Measure the diagnostic value of a HUTT in pts with syncope compared to healthy controls w/o syncope</td>
<td><strong>Study type:</strong> Single center, retrospective study of syncopal pts and prospective</td>
<td>&lt;18 y of age with strong clinical suspicion of neurocardiogenic syncope</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Intervention</td>
<td>Comparator</td>
<td>1st endpoint</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>-------------------------------------------</td>
<td>------------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lerman-Sagie, et al.</td>
<td>Measure the diagnostic value of a HUTT in pts with syncope compared to healthy controls w/o syncope</td>
<td>&lt;18 y of age with strong clinical suspicion of neurocardiogenic syncope.</td>
<td>HUTT following Hx and clinical examination</td>
<td>Healthy controls</td>
<td>Syncope on tilt test</td>
</tr>
<tr>
<td></td>
<td>Study type: Single center, prospective study</td>
<td>Exclusion criteria: Healthy controls without syncope.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Size: n=44 syncope pts (16±3 y vs. 18 healthy controls (16±2 y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al Dhahri, et al.</td>
<td>Measure the usefulness of ILR in children with unexplained syncope.</td>
<td>Pts with unexplained syncope undergoing ILR after conventional diagnostic testing failed to provide a definitive diagnosis.</td>
<td>ILR implantation</td>
<td>None</td>
<td>Identification of a substrate on ILR interrogation to explain causal syncope.</td>
</tr>
<tr>
<td></td>
<td>Study type: Retrospective study of pts with unexplained syncope after initial evaluation identified cause of syncope.</td>
<td>Exclusion criteria: None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Size: n=15 syncope pts (10–18 y of age vs. n=10 healthy controls (11–18 y of age)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Size: n=42 pts (25 males) with a median age of 11.5 y of age (1.4–19.0 y of age) underwent ILR implantation. There were 14 pts (33%) with normal ECGs and echocardiograms. In these pts, the ILR device was implanted at a median age of 12.4 y of age (2.7–17.5 y of age).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 6/15 (43%) of symptomatic pts ha a positive tilt
- 0/10 (0%) normal volunteers had a positive tilt

Summary: HUTT offers a simple, noninvasive, high-yielding diagnostic tool for the evaluation of syncope in children.
| Babikar, et al. 2007 17764457 (369) | **Aim:** Measure the usefulness of ILR in children  
**Study type:** Retrospective single center  
**Size:** n=23 pts (11.4± 4.3 y of age) underwent ILR. 11 pts with syncope and 3 with pre-syncope underwent ILR.  
**Inclusion criteria:** Pediatric pts undergoing ILR  
**Exclusion criteria:** None  
**Intervention:** ILR implantation  
**Comparator:** None  
**1° endpoint:** Identification of a substrate on ILR interrogation to explain causal syncope.  
14 pts (61%) underwent ILR for recurrent syncope or pre-syncope. ILR uncovered:  
- Polymorphic VT (n=1)  
- SVT (n=1)  
- Type II AV block (n=1)  
1 pts would infection and 1 pts relocated for discomfort  
**Summary:** ILR facilitated diagnosis in majority of pts with syncope or pre-syncope with a relatively low complication rate. |
| Rossano, et al. 2003 12949317 (370) | **Aim:** Measure the usefulness of ILR in children  
**Study type:** Retrospective multi-center center  
**Size:** n=21 pts (12.3± 5.3 y of age) underwent ILR. Of these, 16 underwent ILR for unexplained syncope.  
**Inclusion criteria:** Pediatric pts undergoing ILR where conventional testing failed to produce a diagnosis.  
**Exclusion criteria:** None  
**Intervention:** ILR implantation  
**Comparator:** None  
**1° endpoint:** Identification of a substrate on ILR interrogation to explain causal syncope.  
Of the 16 pts, 6 (40%) were identified as having an arrhythmia to explain syncope.  
- Junctional bradycardia (1)  
- SVT (2)  
- TdP (1)  
- Asystole (1)  
- VT (1)  
No complications of ILR  
**Summary:** ILR facilitated diagnosis in majority of pts with syncope or pre-syncope with zero complication rates. |
| Ergul, et al. 2015 25348219 (371) | **Aim:** Measure the usefulness of ILR in children  
**Study type:** Retrospective single-center center  
**Size:** n=12 pts (9.4± 4.3 y of age) underwent ILR. All had a structurally normal heart with exception 1 pts having TOF. Of the 12 pts 6 had exertional syncope.  
Average monitoring period: 20 mo  
**Inclusion criteria:** Pediatric pts with unexplained syncope undergoing ILR. All pts had a normal ECG and event recorder and 10/12 had a normal EST.  
**Exclusion criteria:** None  
**Intervention:** ILR implantation  
**Comparator:** None  
**1° endpoint:** Identification of a substrate on ILR interrogation to explain causal syncope.  
6 pts, (50%) were identified as having pre-syncope:  
- PMVT (3)  
- CPVT (1)  
- Asystole (1)  
- NST (1)  
No complications of ILR  
Of the 6 pts with exertional syncope, 4 were identified as having a malignant arrhythmia.  
**Summary:** ILR is useful in establishing symptom rhythm correlation in the majority of pts with unexplained syncope. ILR should strongly be considered in pts with unexplained exertional syncope. |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>1st endpoint</th>
<th>Summary</th>
</tr>
</thead>
</table>
| Vlahos, et al. 2008 17899242 (372) | **Aim:** Understand the relationship of family Hx in diagnosing syncope  
**Study type:** Retrospective single center, case-control  
**Size:** n=76 pts (11.8±2.9 y of age) with syncope and n=29 control non syncope pts (11.3±2.9 y of age) | **Inclusion criteria:** Syncope diagnosis  
**Exclusion criteria:** None | **Intervention:** None  
**Comparator:** None | **1st endpoint:** Comparison family Hx of syncope between 2 groups | Of the 76 pts with diagnosis of syncope, 68 had a positive family history of syncope (89%) compared to 1/29 (3.5%)  
**Summary:** Family Hx of vasovagal symptoms should be meticulously sought and is of value in the diagnosis of neurocardiogenic syncope in pediatric pts. |
| Alehan, et al. 1996 8833492 (373) | **Aim:** Assess sensitivity and specificity of TTT  
**Study type:** Prospective single center, case-control  
**Size:** n=20 pts (12.0±2.5) with unexplained syncope and 10 healthy controls | **Inclusion criteria:** Syncope diagnosis  
**Exclusion criteria:** No identifiable cause of syncope following ECG, ECHO, EEG, Hx & physical exam | **Intervention:** HUTT 25 mins  
**Comparator:** 10 healthy age-matched controls | **1st endpoint:** Tilt results  
1) During TTT, symptoms were elicited in 15 (75%) of the pts with unexplained syncope but in only one (10%) of the control group (p<0.001).  
2) Sensitivity 75%  
3) Specificity 90%  
4) 40% of positive tilt responders had a family Hx  
**Summary:** The head-up tilt test is a noninvasive, sensitive, specific diagnostic tool for evaluating children with unexplained syncope. |
| Thilenius, et al. 1991 2000273 (374) | **Aim:** Assess sensitivity and specificity of TTT  
**Study type:** Prospective single center  
**Size:** n=35 pts (8-19) with unexplained syncope | **Inclusion criteria:** Syncope diagnosis  
**Exclusion criteria:** No identifiable cause of syncope following ECG, ECHO, EEG, H&P | **Intervention:** HUTT  
**Comparator:** None | **1st endpoint:** Tilt results  
1) During TTT, symptoms were elicited in 26 (75%) of the pts with unexplained syncope.  
**Summary:** The head-up tilt test is a noninvasive, sensitive, specific diagnostic tool for evaluating children with unexplained syncope. |
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Aim: Effectiveness of salt and fludrocortisone in prevention of VVS in children</th>
<th>Inclusion criteria: &gt;1 syncope or presyncope; +HUTT; &lt;18 y of age; no prior therapy for syncope</th>
<th>Intervention: Florinef 0.1mg/day and salt 1g/d</th>
<th>1st endpoint: Syncope or pre-syncope recurrence</th>
<th>Summary: Symptoms were more frequent in the placebo group.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salim, et al. 2005 15708690 (238)</td>
<td><strong>Aim</strong>: Effectiveness of salt and fludrocortisone in prevention of VVS in children</td>
<td><strong>Inclusion criteria</strong>: &gt;1 syncope or presyncope; +HUTT; &lt;18 y of age; no prior therapy for syncope</td>
<td><strong>Intervention</strong>: Florinef 0.1mg/day and salt 1g/d</td>
<td><strong>1st endpoint</strong>: Syncope or pre-syncope recurrence</td>
<td>• Follow up 176+117d; recurrence 36% in controls and 55% active arm (p&lt;0.04).</td>
</tr>
<tr>
<td></td>
<td><strong>Study type</strong>: Randomized (pediatric)</td>
<td></td>
<td><strong>Comparator</strong>: Placebo</td>
<td></td>
<td><strong>Summary</strong>: Symptoms were more frequent in the placebo group.</td>
</tr>
<tr>
<td></td>
<td><strong>Size</strong>: n=32; flurinelf 0.1mg/day and salt 1g/d n=18; control n=14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Inclusion criteria</strong>: No structural heart disease</td>
<td></td>
<td><strong>Comparator</strong>: Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Exclusion criteria</strong>: No structural heart disease</td>
<td></td>
<td><strong>Intervention</strong>: Florinef 0.1mg/day and salt 1g/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Study type</strong>: Randomized (pediatric)</td>
<td><strong>Exclusion criteria</strong>: No structural heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Size</strong>: n=32; flurinelf 0.1mg/day and salt 1g/d n=18; control n=14</td>
<td></td>
<td><strong>Intervention</strong>: Florinef 0.1mg/day and salt 1g/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Massin MM, et al. 2004 15289772 (375)</td>
<td><strong>Aim</strong>: Analyzed the etiology of consecutive cases of syncope presenting to a pediatric emergency room.</td>
<td><strong>Inclusion criteria</strong>: Primary complaint of syncope (witnessed and unwitnessed) upon presentation to the emergency department.</td>
<td><strong>Intervention</strong>: None</td>
<td><strong>1st endpoint</strong>: Clinical diagnosis</td>
<td>Of the 226 pts presenting with syncope, neurocardiogenic accounted for 80% of the diagnosis. Neurologic disorders were identified in 9%. A prodrome was a significant (p&lt;.05) factor in diagnosing neurocardiogenic syncope (present in 88% of cases); however a prodrome was also observed in 52% of those with a neurologic disorder. Clinical Hx with particular attention to the events is the most critical piece of information required. <strong>Limitation</strong>: ECG were not obtained in 58% of the pts and as such the utility of an ECG cannot be measured in this study.</td>
</tr>
<tr>
<td></td>
<td><strong>Study type</strong>: Prospective cohort study</td>
<td><strong>Exclusion criteria</strong>: None</td>
<td><strong>Comparator</strong>: None</td>
<td><strong>Safety endpoint</strong>: None</td>
<td><strong>Summary</strong>: Symptoms were more frequent in the placebo group.</td>
</tr>
<tr>
<td></td>
<td><strong>Size</strong>: n=252 presentations of syncope in 226 pts (mean age 10.8 ± 3.6 y of age)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Inclusion criteria</strong>: Primary complaint of syncope (witnessed and unwitnessed) upon presentation to the emergency department.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Exclusion criteria</strong>: None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Intervention</strong>: None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Comparator</strong>: None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>1st endpoint</strong>: Clinical diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen L, et al. 2011 21629199 (376)</td>
<td><strong>Aim</strong>: Analyze the spectrum of underlying diseases in children presenting with syncope.</td>
<td><strong>Inclusion criteria</strong>: Presentation with syncope</td>
<td><strong>Intervention</strong>: All pts underwent H&amp;P, orthostatic vital sign measurements and an ECG.</td>
<td><strong>1st endpoint</strong>: Clinical diagnosis</td>
<td>Vasovagal syncope was diagnosed in 32% of pts. POTS was diagnosed in 32% of pts. Cardiogenic syncope accounted for 1.5% of the cases. Approximately 31.5% of the cases of syncope were undiagnosed.</td>
</tr>
<tr>
<td></td>
<td><strong>Study type</strong>: Multicenter retrospective chart review</td>
<td><strong>Exclusion criteria</strong>: None</td>
<td><strong>Comparator</strong>: None</td>
<td><strong>Safety endpoint</strong>: None</td>
<td><strong>Summary</strong>: Symptoms were more frequent in the placebo group.</td>
</tr>
<tr>
<td></td>
<td><strong>Size</strong>: n=888 children (median age 12.0 ± 3.0 y of age)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Inclusion criteria</strong>: Presentation with syncope</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Exclusion criteria</strong>: None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Intervention</strong>: All pts underwent H&amp;P, orthostatic vital sign measurements and an ECG.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Comparator</strong>: None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>1st endpoint</strong>: Clinical diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Safety endpoint</strong>: None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>1st endpoint</th>
<th>Safety endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colman N, et al. 2009</td>
<td>To determine whether Hx taking can be used as a tool in identifying pts presenting with syncope who are more likely to have LQT syndrome.</td>
<td>All LQT pts confirmed genotype positive.</td>
<td>Clinical assessment with detailed Hx and detailed family Hx.</td>
<td>Clinical comparison</td>
<td>None</td>
<td>72% of pts with LQTS had a family Hx of syncope and 66% had a family Hx of sudden death. This is in contradistinction to pts presenting to the ED with syncope without LQT where the family Hx of syncope was 9% and sudden death 10% (p&lt;0.001). Syncope while supine and syncope with exercise were significantly more common in the LQTS cohort compared to the ED cohort.</td>
</tr>
<tr>
<td></td>
<td>Study type: Retrospective study comparing 2 populations. The control cohort was evaluated as part of a Dutch Fainting Assessment Trial</td>
<td>Exclusion criteria: &gt;40 y of age.</td>
<td>Comparator: LQT pts compared to a consecutive heterogeneous group of patients with syncope presenting to the emergency department</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Size: n=32 LQTS pts, n=113 pts in ED with syncope, and n=69 known vasovagal syncope pts.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tretter JT, et al. 2013.</td>
<td>To identify characteristics that distinguishes VVS from cardiac syncope.</td>
<td>All pts (newborn to 18 y of age) presenting to the outpatient faculty with diagnosis of syncope)</td>
<td>Syncope at follow-up and comparison between 2 groups of etiology</td>
<td>None</td>
<td>Any one of the following 4 parts of a cardiac screen: (1) abnormal cardiac physical exam ± (2) abnormal findings on ECG ± (3) concerning family Hx ± (4) exertional syncope has 100% specificity and 60% specificity.</td>
</tr>
<tr>
<td></td>
<td>Study type: Retrospective review of pts presenting a vasovagal syncope vs. cardiac syncope.</td>
<td>Exclusion criteria: None</td>
<td>Comparator: Vasovagal Symptoms vs. Cardiac Syncope Symptoms (identified from the ICD database and the cardiac stress lab database)</td>
<td></td>
<td>None</td>
<td>1. There was no difference between the 2 groups with respect to chest pain or palpitations. 2. Preceding symptoms of lightheadedness, dizziness, visual and hearing changes were significantly less common in the cardiac group (41% vs. 84%). 3. ECG established the diagnosis 47% of time compared to 0% in vasovagal cohort. 4. 11/17 (65%) with cardiac syncope had episodes of syncope surrounding exertion.</td>
</tr>
</tbody>
</table>
| | Size: n=89 pts 4–18 y of age presenting to cardiology outpatient. Compared to 17 pediatric pts over the same era that were diagnosed with cardiac syncope. | | | Safety endpoint: None | | |"
<table>
<thead>
<tr>
<th>Study Title</th>
<th>Authors</th>
<th>Year</th>
<th>PubMed ID</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>1st endpoint</th>
<th>Safety endpoint</th>
<th>Results</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritter S, et al. 2000.</td>
<td>10799622, (379)</td>
<td>Understand the clinical symptoms in pts with syncope.</td>
<td>Syncope diagnosis</td>
<td>Pts with previously known cardiac disease (cardiomyopathies, arrhythmias, or CHD)</td>
<td>None</td>
<td>Use of H&amp;P, and ECG in identifying pts with cardiac syncope.</td>
<td>None</td>
<td>None</td>
<td>Of the 21 pts with cardiac related syncope, a (1) personal Hx of exercise induced syncope; (2) positive family Hx, (2) abnormal ECG, and 4) normal echo.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MacCormick JM, et al. 2011</td>
<td>21616715 (380)</td>
<td>Understand the signs and symptoms before the cardiac syncope and before the patient was diagnosed with a channelopathy.</td>
<td>Syncope diagnosis amongst consecutive gene positive probands</td>
<td>Pts with syncope and LQT that was not genetically confirmed.</td>
<td>None</td>
<td>Clinical presentation of syncope.</td>
<td>None</td>
<td>None</td>
<td>20 pts with syncope (median age 13.9 y of age) with 17 describing symptoms prior to syncope (lightheadedness and dizziness in 47%). Similarly drowsiness and weakness post-syncope were noted in 84% of cases.</td>
<td>Young pts with cardiac syncope frequently have symptoms similar to neurocardiogenic syncope. The presence of symptoms before and after fainting may not completely distinguish between benign neurocardiogenic and cardiac syncope.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grubb BP, et al. 1992</td>
<td>1382276 (381)</td>
<td>Understand the utility of HUTT testing in the evaluation of recurrent syncope of unknown etiology in children and adolescents.</td>
<td>A minimum of 3 episodes of syncope in the preceding 6 mo with the cause of syncope unknown by H&amp;P, ECG, echocardiogram, and exercise stress test.</td>
<td>None</td>
<td>Clinical outcomes following HUTT results.</td>
<td>None</td>
<td>None</td>
<td>During the baseline HUTT 6 pts (20%) had a positive HUTT and 15 additional pts (50%) during an isoproterenol infusion (total 70%) had a positive HUTT. A variety of treatments were used including BB, Florinef, and transdermal scopolamine. No further syncope occurred. This study was not designed to look at one particular treatment arm over another but assess the utility of the HUTT itself.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numan M, et al. 2015.</td>
<td>25087055 (382)</td>
<td>To report experience with pts with cardiac asystole during HUTT</td>
<td>Cardiac asystole (defined as absence of ventricular activity of &gt;3 s)</td>
<td>None</td>
<td>Clinical recurrent syncope</td>
<td>None</td>
<td>None</td>
<td>25 pts with cardiac asystole (mean pause 9.2± 5.8 s) were managed with education, symptom awareness, and one of the following Florinef, BB, alpha agonists and all</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
<table>
<thead>
<tr>
<th>Study type: Retrospective study, no placebo group.</th>
<th>Study type: Retrospective observational study</th>
<th>Study type: Retrospective review of data from the International Long QT Registry.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size: Retrospective analysis of 537 pts (age 6-22 y of age) and follow-up of 25 pts with cardiac asystole. Follow-up 19 ± 10 mo</td>
<td>Size: 150 pts (8–18 y of age) between 2007–2011. Group I HUTT positive (N=97) and Group II HUTT negative (n=53 pts) and follow to see if clinical VVS reoccurs. Average age of 1st syncope (12.3±3.1 y)</td>
<td>Size: n=1,648 pts &lt;20 y of age with LQT (genotype or genotype and phenotype)</td>
</tr>
<tr>
<td>Exclusion criteria: None</td>
<td>Inclusion criteria: 8–18 y of age with clinical VVS.</td>
<td>Inclusion criteria: QTc ≥450 msec, or a known pathogenic QT mutation, and syncope.</td>
</tr>
<tr>
<td>Comparator: None</td>
<td>Intervention: VVS pts follow after HUTT.</td>
<td>Intervention: Registry follow-up</td>
</tr>
<tr>
<td>Safety endpoint: None</td>
<td>Comparator: Compare Recurrent syncope group (n=40) and Non-recurrent syncope group (n=110). Average Follow up: 3.8±4.7 y</td>
<td>Comparator: Different LQT genotypes and BB utilization with recurrent syncope.</td>
</tr>
<tr>
<td>Summary: This study did not compare medical management vs. pacemaker therapy.</td>
<td>Summary: Recurrent syncope predictors: age at initial syncope, positive family Hx of syncope, and number of previous syncopal episodes were predictive of recurrent syncope. Positive HUTT did not predict recurrence of VVS.</td>
<td>Summary: A QTc ≥ 500 ms was a significant predictor of a first syncopal event (HR: 2.16). LQT1 male pts had the highest rate of first syncope and LQT2 females had the highest rate of first and subsequent syncopal events. BB treatment for LQT1 &amp; LQT2 pts significantly (&gt;70%) reduced subsequent syncopal events.</td>
</tr>
<tr>
<td>Study Type</td>
<td>Aim</td>
<td>Inclusion Criteria</td>
</tr>
<tr>
<td>------------</td>
<td>-----</td>
<td>--------------------</td>
</tr>
<tr>
<td>Single center, prospective study</td>
<td>Assessment of oral fluid therapy in children with vasodepressor syncope on clinical recurrence.</td>
<td>Clinical diagnosis of VVS and positive TTT</td>
</tr>
<tr>
<td>Single center, randomized; placebo-controlled. 6 mo-f/u</td>
<td>Whether oral rehydration salts is effective in treatment of children with VVS</td>
<td>At least 2 episodes of syncope in prior 6 mo. Positive HUTT with clinical diagnosis of VVS. (Children 7-17)</td>
</tr>
<tr>
<td>Single center, prospective study</td>
<td>Whether alpha-adrenergic agonist prevents syncope</td>
<td>Recurrent syncope and a positive HUTT</td>
</tr>
<tr>
<td>Single center, randomized control trial between 2003-2004. Not</td>
<td>Efficacy of midodrine in preventing VVS in children.</td>
<td>At least 3 episodes of syncope in prior 12 mo and “positive” tilt with clinical diagnosis of VVS.</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Study type</td>
</tr>
<tr>
<td>-------</td>
<td>-----</td>
<td>------------</td>
</tr>
<tr>
<td>Zhang Q, et al. 2008. 18376348 (387)</td>
<td>Efficacy of BB in conjunction with conventional treatment in reducing VVS in children.</td>
<td>Single center, prospective randomized. (2001-2003)</td>
</tr>
<tr>
<td>Scott WA, et al. 1995 7639169 (388)</td>
<td>Comparison of Atenolol vs. Florinef in treatment of neurally mediated syncope</td>
<td>Prospective randomized</td>
</tr>
<tr>
<td>Balaji S, et al. 1994. 7906701</td>
<td>Outcomes of children with neurocardiogenic syncope.</td>
<td>Single center</td>
</tr>
<tr>
<td>Exclusion criteria: Other disease ruled-out by ECG, EEG, and head imaging.</td>
<td>Comparator: Orthostatic (autonomic abnormal) response compared to orthostatic negative response</td>
<td>Safety endpoint: No</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

**Aim:** To determine whether reflex bradycardic seizures can be prevented by cardiac pacing

**Study type:** Randomized double blind study

**Size:** n=12 pts (median 2.8 y of age, mean 4 y). Duration of documented asystole (10-40 s)

**Inclusion criteria:** Children >2y of age, clinical Hx reflex anoxic seizures, documented asystole >4 s, reflex anoxic seizures at least 1/wk

**Exclusion criteria:** None

**Intervention:** Pacing strategy DDD, VVI, or ODO. Parent and patient blinded to PM strategy. 4 mo randomization to a different pacing protocol.

**Comparator:** None

**1st endpoint:** Clinical recurrent syncope

**Safety endpoint:** None

Results: Children paced either VVI or DDD significant reduction in number of syncopal events compared to a “sensing only” mode. 6 pts no further syncope when paced DDD/VVI compared to sensing only. 3 pts no further syncope regardless paced or not paced. 2 pts continued to have episodes of syncope when paced.

**Summary:** First blinded study demonstrating efficacy of pacing in severe neurally mediated syncope secondary to pallid breath holding spells. No control group of pts without a pacemaker. Cannot exclude placebo effect from pacemaker alone (though pts <3 y of age)

**Recommend hysteresis and rate drop features be applied**
**Kelly AM, et al. 2001 1153339 (391)**

**Aim:** Determine resolution of significant bradycardia related pallid-breathholding spells with permanent pacemaker (PM) implantation

**Study type:** Retrospective review

**Size:** n=10 pts (median PM implant at 14.5 mo)

**Inclusion criteria:** Pallid breath-holding spells requiring PM implantation.

**Exclusion criteria:** None

**Intervention:** Pacemaker Implantation

**Comparator:** None

**1st endpoint:** Clinical Outcome

**Safety endpoint:** None

10 pts (mean asystolic pauses 11.9 s). 5 pts had complete resolution of syncope (spells), 2 only had minor color changes without loss of consciousness, and 3 continued to have minor brief spells.

---

**Data Supplement 41. Nonrandomized Trials, Observational Studies, and/or Registries of Adult Congenital Heart Disease – (Section 10.2)**

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khairy P, et al. 2004 15051640 (392)</td>
<td><strong>Study type:</strong> Retrospective Cohort Multicenter (6) <strong>Size:</strong> n=252 pts</td>
<td><strong>Inclusion criteria:</strong> Programmed ventricular stimulation between 1985 and 2002 <strong>Exclusion criteria:</strong> Unrepaired TOF, pulmonary atresia, AV canal</td>
<td><strong>1st endpoint:</strong> Composite of sustained VT or SCD</td>
<td>• Programmed ventricular stimulation is of diagnostic and prognostic value in risk stratifying pts with repaired TOF.</td>
</tr>
<tr>
<td></td>
<td><strong>Results:</strong> Age at EPS ≥18 y, palpitations, prior palliative surgery, Modified Lown ≥2, cardiothoracic ratio ≥0.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Khairy P, et al. 2004 19808416 (393) | **Study type:** Multicenter cohort study **Size:** n=37 pts | **Inclusion criteria:** TGA atrial baffle with ICD **Exclusion criteria:** N/A | **1st endpoint:** Risk factors for shocks | • High rates of appropriate shocks are noted in secondary but not primary prevention. Supraventricular arrhythmias may be implicated in the etiology of ventricular tachyarrhythmias; BB seem protective, and inducible VT does not seem to predict future events. |
| | | | **Results:** Annual rates of appropriate shocks were 0.5% and 6.0% in primary and secondary prevention, respectively (p=0.0366) | |
### Data Supplement 42. Nonrandomized Trials, Observational Studies, and/or Registries of Geriatrics – (Section 10.3)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion</th>
<th>Comment(s)</th>
</tr>
</thead>
</table>
| Paling D, et al. 2011 22067373 (394) | **Aim:** To assess for CCS mediated falls in older adults (comparing those ≥80 y of age vs. 61–79 y pf age)  
**Study type:** Prospective Observational  
**Size:** n=101 pts with unexplained falls  
**Inclusion criteria:** Unexplained Falls  
**Exclusion criteria:** Pts with clear cardiac or neurological etiology of their syncope were treated as appropriate and excluded from this analysis. | **1° endpoint:** Combination of TT/CSM provided diagnosis in 62% of pts, and was significantly more likely to be positive in pts ≥80 y of age (68% vs. 50%, p=.001)  
**Safety endpoint (if relevant):** N/A | Summary:  
Diagnosis using TT/CSM in 62% pts; diagnostic sensitivity was relatively higher in those ≥80 yrs. |  |
| Cooke J, et al. 2011 21382922 (395) | **Aim:** To assess type of syncope wth age  
**Study type:** Retrospective, observational  
**Size:** n=3,002 pts  
**Inclusion criteria:** All consecutive pts referred to a tertiary referral syncope unit over a decade were included.  
**Exclusion criteria:** N/A | **1° endpoint:** Type of Syncope in relation to age.  
**1° Safety endpoint (if relevant):** N/A | Summary:  
OH was the most commonly observed abnormality (test positivity of 60.3%). Neurocardiogenic syncope demonstrated a bimodal age distribution. Of 194 pts with carotid sinus hypersensitivity, the median age (IQR) was 77 (68–82) y of age. Those with vasovagal syncope (n=80) had a median (IQR) y of age of 30 (19–44). There were 57 pts with isolated postural orthostatic tachycardia syndrome. Of the total pts, 75% were female. They had a median (IQR) y age of 23 (17–29). |  |
| Duncan GW, et al. 2010 20444805 (396) | **Aim:** To clarify prevalence and character of VVS in OA  
**Study type:** Prospective, observational  
**Size:** n=1,060 pts  
**Inclusion:** Pts presenting to syncope clinic. Comparisons of those <60 to those ≥60  
**Exclusion criteria:** <18 y of age  
**1° endpoint:** Diagnosis  
**1° Safety endpoint (if relevant):** N/A | Summary:  
Older pts even more likely than young to have VVS. The clinical presentation differed significantly between older vs. younger pts. Older pts were less likely to give a typical Hx. |  |
| Anpalaham M, et al. 2012 22284256 (397) | **Aim:** To explore the relationship between falls and NMS  
**Age:** 76.8±5.7 y  
**Study type:** Propective Observational  
**Inclusion criteria:** Study of consecutive admissions for falls aged ≥65 y  
**Exclusion criteria:** those with an identifiable medical cause for the fall or a Hx of loss of | **1° endpoint:** 5/21 of those with nonaccidental falls had NMS  
**1° Safety endpoint (if relevant):** N/A | Summary:  
Syncope underestimated in older adults as many have NMS with associated amnesia often confounding assessment |  |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion</th>
<th>1° endpoint</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richardson DA, et al. 1997</td>
<td>to assess for CSS-mediated syncope in pts with falls</td>
<td>Unexplained fallers age ≥50 y</td>
<td>diagnosis of CSS with cardiac inhibition</td>
<td>65/279 had cardioinhibitory carotid hypersensitivity, raising question of pacing.</td>
</tr>
<tr>
<td>Study type: Prospective, observational</td>
<td>Exclusion criteria: (1) presented with a single simple accidental fall (simple slip or trip); (2) presented with a readily or subsequently diagnosed medical cause; (3) were cognitively impaired (4) unable to speak English or illiterate; (5) lived outside a 15 mile radius of the RVI; (6) were immobile; or (7) were registered blind. Exclusions to CSM were: (1) MI within 3 mo; (2) stroke within 3 mo; (3) history of ventricular dysrhythmia; or (4) presence of carotid bruit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size: n=200 pts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GIS Ungar A, et al. 2006</td>
<td>Older adults (≥65 referred to ER) (mean age 79±7), 160 ≥75</td>
<td>65 and older with transient LOC</td>
<td>Diagnosis</td>
<td>Definite diagnosis in 40.1%, suspected in 57.9%</td>
</tr>
<tr>
<td>Study type: Observational</td>
<td>Exclusion criteria: Presyncope or cognitive impairment</td>
<td>1° Safety endpoint (if relevant): N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size: n=231 pts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>1° endpoint</td>
<td>Summary</td>
</tr>
<tr>
<td>-------</td>
<td>-----</td>
<td>--------------------</td>
<td>-------------</td>
<td>---------</td>
</tr>
<tr>
<td>GIS</td>
<td>To study 2 y f/u of guideline algorithm on outcomes in older adults (age ≥60, mean 78.7±6.8)</td>
<td>Pts assessed using GIS diagnostic algorithm Pts referred to clinic for syncope/falls or dizziness</td>
<td>Recurrent syncope and mortality</td>
<td>Total mortality 17.5% and syncope 32.5%; Higher death in pts with cardiac syncope Increased recurrence and mortality with age Recurrence corresponded to age and disability</td>
</tr>
<tr>
<td>O'Mahony, et al. 1998</td>
<td>Diagnostic sensitivity of algorithm in pts 61–91 y of age</td>
<td>Pts with unexplained syncope, falls, or dizziness were referred for assessment</td>
<td>Diagnostic sensitivity and specificity</td>
<td>High aggregate sensitivity of clinical thought process. Utility of TT esp in context of syncopal amnesia.</td>
</tr>
<tr>
<td>Aging Clin Exp Res Ungar, et al. 2015</td>
<td>To assess w/u of protocol in pts with dementia</td>
<td>Pts ≥65 with dementia (83±6 yo) with falls or syncope. (52% falls, 45% syncope and 3% overlap); 60% did not remember episode</td>
<td>Diagnosis</td>
<td>Pts with dementia and high comorbidity, still with successful w/ workup</td>
</tr>
</tbody>
</table>
### Data Supplement 43. Nonrandomized Trials, Observational Studies, and/or Registries of Syncope in Athletes – (Section 10.5)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Maron BJ, et al. 2015 19221222 (402) | **Study type**: National registry  
**Size**: n=1,866 athletes | **Inclusion criteria**: Athletes who died suddenly or survived cardiac arrest; 19 y of age (+/- 6 y of age)  
**Exclusion criteria**: N/A | **1st endpoint**: SCD or cardiac arrest  
**Results**: Most common CV cause were HCM (36%) and congenital coronary artery anomalies (17%) | • SCD in young US athletes was higher than previously estimated, but low nonetheless (<100 per y) |
| Maron BJ, et al. 2007 17652294 (403) | **Study type**: Multicenter registry  
**Size**: n= 506 pts | **Inclusion criteria**: ICDs implanted between 1986 and 2003  
**Exclusion criteria**: N/A | **1st endpoint**: ICD intervention terminating VT or VF  
**Results**: ICD intervention terminated VT or VF in 103 pts (20%) | • ICD interventions effective in pts with HCM |
| Corrado, et al. 2006 17018804 (404) | **Study type**: Longitudinal cohort  
**Size**: Population based, per 100,000 person years | **Inclusion criteria**: Athletic and non athletic population 12–35 y of age in Veneto, Italy between 1974–2004  
**Exclusion criteria**: N/A | **1st endpoint**: Incidence of CV death and cause specific CV death in screened athletes and unscreened non athletes  
**Results**: 55 SCD in screened athletes (1.9 deaths/100,000 person-years) and 265 sudden deaths in unscreened non athletes (0.79 deaths/100,000 person-years). Incidence of SCD in athletes decreased by 89%. The incidence of SCD in unscreened nonathletic pts did not change significantly. | • Incidence of SCD declined after implementation of pre participation screening program for young athletes |
| James CA, et al. 2013 23871885 (405) | **Study type**: Longitudinal cohort  
**Size**: n=87 pts | **Inclusion criteria**: Pts with desmosomal mutations  
**Exclusion criteria**: N/A | **1st endpoint**: VT/VF, HF, and ARVC/D  
**Results**: Compared to those who did not exercise, pts in the second (OR: 6.64 p= 0.013) third (OR: 16.7, p=0.001) and top (OR: 25.3, p<0.001) quartiles were increasingly likely to meet Task Force Criteria for ARVC/D. Survival from first VT/VF event was lowest among those in top quatile before (p=0.036) and after (p=0.005) exercise. For pts in top quartile, a reduction in exercise decreased VT/VF risk (p=0.04) | • Endurance and frequent exercise increased the risk of VT/VF, HF and ARVC/D in pts with desmosomal mutations. |
References


© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
Zaidi A, Clough P, Cooper P, et al. Misdiagnosis of epilepsy: many seizure

Song PS, Kim JS, Park J, et al. Seizure

Grubb BP, Gerard G, Roush K, et al. Differentiation of convulsive syncope and epilepsy with head


© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.


© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.


© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.


## Author Relationships With Industry and Other Entities (Comprehensive)—2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope (March 2015)

<table>
<thead>
<tr>
<th>Committee Member</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Win-Kuang Shen <em>(Chair)</em></td>
<td>Mayo Clinic Arizona—Professor of Medicine; Mayo Clinic College of Medicine—Chair, Department of Cardiovascular Diseases</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
| Robert S. Sheldon *(Vice Chair)* | University of Calgary Department of Medicine—Professor | None | None | None | • AA Pharma—POST 4  
• Apotex Corp—POST 5, POST 6  
• Network for Centers of Excellence | • Concordia Healthcare | None |
| David G. Benditt | University of Minnesota Medical School, Cardiovascular Division—Professor of Medicine | • Medtronic*  
• St. Jude Medical* | None | None | • ZOLL | None | None |
| Mitchell I. Cohen | University of Arizona School of Medicine-Phoenix—Clinical Professor of Child Health; Phoenix Children’s Heart Center—Co-Director; Phoenix Children’s Hospital, Pediatric Cardiology—Chief | None | None | None | • Purdue Pharmaceuticals (DSMB) | None | None |
| Roy Freeman§ | Harvard Medical School—Professor of Neurology; Beth Israel Deaconess Medical Center, Center for Autonomic and Peripheral Nerve Disorders—Director | • Astellas Pharma  
• Biogen  
• Johnson & Johnson*  
• Lundbeck*  
• Pfizer*  
• Spinifex* | None | None | • Dong (DSMB) | • AstraZeneca  
• Shire | None |
| Daniel E. Forman | University of Pittsburgh—Professor of Medicine; University of Pittsburgh Medical Center—Chair, Geriatric Cardiology Section; VA Pittsburg Healthcare Systems—Director, Cardiac Rehabilitation | None | None | None | None | None | None |
| Zachary D. | University of Washington School | None | None | None | None | None | None |

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
<table>
<thead>
<tr>
<th>Committee Member</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldberger</td>
<td>of Medicine, Harborview Medical Center Division of Cardiology—Assistant Professor of Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
| Blair P. Grubb   | University of Toledo Medical Center, Medicine and Pediatrics—Professor | ● Biotronik  
● Medtronic | None | None | None | None | None | None |
| Mohamed H. Hamdan| University of Wisconsin School of Medicine, Cardiovascular Medicine—Professor and Chief of Cardiovascular Medicine | None | None | ● Clinic Notes  
● F2 Solutions | None | None | None | None |
| Andrew D. Krahn  | The University of British Columbia, Division of Cardiology—Professor of Medicine and Head of Division | ● Medtronic | None | None | None | ● Boston Scientific*  
● Medtronic* | None | None |
| Mark S. Link     | University of Texas Southwestern Medical Center, Department of Medicine, Division of Cardiology—Director, Cardiac Electrophysiology; Professor of Medicine | None | None | None | None | None | None |
| Brian Olshansky  | University of Iowa Carver College of Medicine, Cardiovascular Medicine—Emeritus Professor of Internal Medicine; Mercy Hospital North Iowa—Electrophysiologist | ● Boehringer-Ingelheim  
● Daiichi-Sankyo  
● Lundbeck  
● On-X | ● Daiichi-Sankyo  
● Lundbeck | None | ● Amarin (DSMB)  
● Sanofi-aventis (DSMB) | ● Thompson Reuters†  
● Up to Date (Editor) | None | None |
| Satish R. Raj    | University of Calgary, Cardiac Sciences—Associate Professor | ● GE Healthcare  
● Lundbeck* | None | None | ● Apotex Corp  
● CIHR*  
● CANet*  
● Medtronic  
● NIH* | ● American Autonomic Society†  
● Association of Clinical and Translational Sciences†  
● Dysautonomia International† | ● Defendant, postural tachycardia syndrome, 2015 | None |
| Roopinder        | University of Alberta, Medical | None | None | None | None | None | None | None |

© 2017 by the American College of Cardiology Foundation, American Heart Association, Inc., and Heart Rhythm Society.
<table>
<thead>
<tr>
<th>Committee Member</th>
<th>Employment</th>
<th>Consultant</th>
<th>Speakers Bureau</th>
<th>Ownership/Partnership/Principal</th>
<th>Personal Research</th>
<th>Institutional, Organizational, or Other Financial Benefit</th>
<th>Expert Witness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaur Sandhu</td>
<td>Division of Cardiology—Assistant Professor of Medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Dan Soraia</td>
<td>Mayo Clinic Arizona, Cardiovascular Diseases—Assistant Professor of medicine</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Benjamin C. Sun</td>
<td>Oregon Health &amp; Science University—Associate Professor</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>• NIH–Syncope Risk Stratification Study (PI)*</td>
<td>None</td>
<td>• Defendant, emergency medicine standard of care for evaluation of syncope, 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• NIH (DSMB)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• NIH–Identifying Hospital Practices to Reduce ED Crowding (PI)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clyde W. Yancy</td>
<td>Northwestern University Feinberg School of Medicine, Division of Cardiology—Professor of Medicine and Chief; Diversity &amp; Inclusion—Vice Dean</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>• NIH–Effectiveness of Prescription Monitoring Program in Emergency Departments (PI)*</td>
<td>• Patient Centered Outcomes Research Institute†</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• NIH–Improving Syncope Risk Stratification in Older Adults (PI)*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This table represents all relationships of committee members with industry and other entities that were reported by authors, including those not deemed to be relevant to this document, at the time this document was under development. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person’s gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Please refer to [http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy](http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy) for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

*Significant relationship.
†No financial benefit.
Dr. Roy Freeman, the official representative of the American Academy of Neurology, resigned from the writing committee in November 2016, prior to the final balloting process; recusals noted are from the initial round of balloting. We thank him for his contributions.

ACC indicates American College of Cardiology; AHA, American Heart Association; CANet, Cardiac Arrhythmia Network of Canada; CIHR, Canadian Institute of Health Research; DSMB, data safety monitoring board; ED, emergency department; HRS, Heart Rhythm Society; NIH, National Institutes of Health; PI, principal investigator, and VA, Veteran’s Affairs.