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

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

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ACC/AHA Task Force Members, see page e98

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry may apply; see Appendix 1 for detailed information. †ACC/AHA Task Force on Clinical Practice Guidelines Liaison. ‡ACC/AHA Representative. §HRS Representative. ‖ACEP and SAEM Joint Representative. ¶ACC/AHA Task Force on Performance Measures Liaison.

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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

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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[1,2] and on the basis of internal re-evaluation. Similarly, the presentation and delivery of guidelines are re-evaluated 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.[3]

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[4] and other methodology articles.[5–8]

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.[4–7] 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 and formal systematic review 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

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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)

CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — **Benefit >>> Risk**

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — **Benefit >> Risk**

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A 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) — **Benefit = Risk**
(Generally, LOE A or B use only)

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

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)

Consensus of expert opinion based on clinical experience

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.

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 inter-

vention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 1).[4–6]

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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.[9]

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 was endorsed by the American College of Emergency Physicians, the 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 physiology, pathophysiology, or mechanisms of underlying conditions associated with syncope. The nature of syncope as a symptom required that the writing committee consider numerous conditions for which it can be a symptom, and as much as possible, we have addressed the involvement of syncope only as a presenting symptom. Because of the plausible association of syncope and sudden cardiac death (SCD) in selected populations, this document discusses risk stratification and prevention of SCD when appropriate. The use of the terms *selected populations* and *selected patients* in this document is intended to direct healthcare providers to exercise clinical judgment, which is often required during the evaluation and management of patients with syncope. When a recommendation is made to refer a patient to a specialist with expertise for further evaluation, such as in the case of autonomic neurology, adult congenital heart disease (ACHD), older populations, or athletes, the writing committee

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Table 2. Relevant ACC/AHA Guidelines

Title	Organization	Publication Year (Reference)
ACC/AHA guideline policy relevant to the management of syncope		
Supraventricular tachycardia	ACC/AHA/HRS	2015[10]
Valvular heart disease	AHA/ACC	2014[11]
Device-based therapies for cardiac rhythm abnormalities	ACCF/AHA/HRS	2012[12]
Ventricular arrhythmias and sudden cardiac death	ACC/AHA/ESC	2006[13]*
Other ACC/AHA guidelines of interest		
Hypertension*	ACC/AHA	–
Stable ischemic heart disease	ACC/AHA/ACP/AATS/ PCNA/SCAI/STS	2012 and 2014[14,15]
Atrial fibrillation	AHA/ACC/HRS	2014[16]
Non–ST-elevation acute coronary syndromes	AHA/ACC	2014[17]
Assessment of cardiovascular risk	ACC/AHA	2013[18]
Heart failure	ACC/AHA	2013[19]*
Hypertrophic cardiomyopathy	ACC/AHA	2011[20]
Assessment of cardiovascular risk in asymptomatic adults	ACC/AHA	2010[21]
Adult congenital heart disease	ACC/AHA	2008[22]*
Other related references		
Scientific statement on electrocardiographic early repolarization	AHA	2016[23]
Expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope	HRS	2015[24]
Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death	ESC	2015 and 2013[25,26]
Expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease	PACES/HRS	2014[27]
Expert consensus statement on the use of implantable cardioverter-defibrillator therapy in patients who are not included or not well represented in clinical trials	HRS/ACC/AHA	2014[28]
Expert consensus statement on ventricular arrhythmias	EHRA/HRS/APHRS	2014[29]
Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes	HRS/EHRA/APHRS	2013[25]
Guidelines for the diagnosis and management of syncope	ESC	2009[30]

*Revisions to the current documents are being prepared, with publication expected in 2017.

AATS indicates American Association for Thoracic Surgeons; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACP, American College of Physicians; AHA, American Heart Association; APHRS, Asia Pacific Heart Rhythm Society; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; PACES, Pediatric and Congenital Electrophysiology Society; PCNA, Preventive Cardiovascular Nurses Association; SCAI, Society for Cardiovascular Angiography and Interventions; and STS, Society of Thoracic Surgery.

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 and affirms the ongoing validity of the related recommendations in the context of syncope, thus obviating the need to repeat existing guideline recommendations in

Table 3. Relevant Terms and Definitions*

Term	Definition/Comments and References
Syncope	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.[24,30] 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 (ie, pseudosyncope).[24,30]
Loss of consciousness	A cognitive state in which one lacks awareness of oneself and one's situation, with an inability to respond to stimuli.
Transient loss of consciousness	Self-limited loss of consciousness[30] 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.
Presyncope (near-syncope)	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.
Unexplained syncope (syncope of undetermined etiology)	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.
Orthostatic intolerance	A syndrome consisting of a constellation of symptoms that include frequent, recurrent, or persistent lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue upon standing. These symptoms can occur with or without orthostatic tachycardia, OH, or syncope.[24] Individuals with orthostatic intolerance have ≥1 of these symptoms associated with reduced ability to maintain upright posture.
Orthostatic tachycardia	A sustained increase in heart rate of ≥30 bpm within 10 min of moving from a recumbent to a quiet (nonexertional) standing position (or ≥40 bpm in individuals 12–19 y of age).[24,30,31]
Orthostatic hypotension (OH)	A drop in systolic BP of ≥20 mm Hg or diastolic BP of ≥10 mm Hg with assumption of an upright posture.[31]
Initial (immediate) OH	A transient BP decrease within 15 s after standing, with presyncope or syncope.[31,32]
Classic OH	A sustained reduction of systolic BP of ≥20 mm Hg or diastolic BP of ≥10 mm Hg within 3 min of assuming upright posture.[31]
Delayed OH	A sustained reduction of systolic BP of ≥20 mm Hg (or 30 mm Hg in patients with supine hypertension) or diastolic BP of ≥10 mm Hg that takes >3 min of upright posture to develop. The fall in BP is usually gradual until reaching the threshold.[31]
Neurogenic OH	A subtype of OH that is due to dysfunction of the autonomic nervous system and not solely due to environmental triggers (eg, dehydration or drugs).[33,34] Neurogenic OH is due to lesions involving the central or peripheral autonomic nerves.
Cardiac (cardiovascular) syncope	Syncope caused by bradycardia, tachycardia, or hypotension due to low cardiac index, blood flow obstruction, vasodilatation, or acute vascular dissection.[35,36]
Noncardiac syncope	Syncope due to noncardiac causes, which include reflex syncope, OH, volume depletion, dehydration, and blood loss.[35]
Reflex (neurally mediated) syncope	Syncope due to a reflex that causes vasodilation, bradycardia, or both.[24,30,31]
Vasovagal syncope (VVS)	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.[24] 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.
Carotid sinus syndrome	Reflex syncope associated with carotid sinus hypersensitivity.[30] Carotid sinus hypersensitivity is present when a pause ≥3 s and/or a decrease of systolic pressure ≥50 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.
Situational syncope	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.
Postural (orthostatic) tachycardia syndrome (POTS)	A clinical syndrome usually characterized by all of the following: 1) frequent symptoms that occur with standing (eg, lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue); and 2) an increase in heart rate of ≥30 bpm during a positional change from supine to standing (or ≥40 bpm in those 12–19 y of age); and 3) the absence of OH (>20 mm Hg reduction in systolic BP). Symptoms associated with POTS include those that occur with standing (eg, lightheadedness, palpitations); those not associated with particular postures (eg, bloating, nausea, diarrhea, abdominal pain); and those that are systemic (eg, fatigue, sleep disturbance, migraine headaches).[37] The standing heart rate is often >120 bpm.[31,38–42]
Psychogenic pseudosyncope	A syndrome of apparent but not true loss of consciousness that may occur in the absence of identifiable cardiac, reflex, neurological, or metabolic causes.[30]

*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.

the present guideline when applicable or when appropriate. Table 2 also contains a list of other statements that may be of interest to the reader.

2. GENERAL PRINCIPLES

2.1. Definitions: Terms and Classification

For the purpose of this guideline, definitions of syncope and relevant terms are provided in Table 3.

2.2. Epidemiology and Demographics

Syncope has many causes and clinical presentations; the incidence depends on the population being evaluated. Estimates of isolated or recurrent syncope may be inaccurate and underestimated because epidemiological data have not been collected in a consistent fashion or because a consistent definition has not been used. Interpretation of the symptoms varies among the patients, observers, and healthcare providers. The evaluation is further obscured by inaccuracy of data collection and by improper diagnosis.

Studies of syncope report prevalence rates as high as 41%, with recurrent syncope occurring in 13.5%.[43] 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%, $P<0.001$).[44] 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.[45] Predictors of recurrent syncope in older adults are aortic stenosis, impaired renal function, atrioventricular (AV) or left bundle-branch block, male sex, chronic obstructive pulmonary disorder, heart failure (HF), atrial fibrillation (AF), advancing age, and orthostatic medications,[45] with a sharp increase in incidence after 70 years of age.[35] Reflex syncope was most common (21%), followed by cardiac syncope (9%) and orthostatic hypotension (OH) (9%), with the cause of syncope unknown in 37%.[35] In patients with New York Heart Association class III–IV HF, syncope is present in 12% to 14% of patients.[46,47]

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 (ED), or 0.77% of all ED patients. Among patients >80 years of age, 58% were admitted to hospital.[48] 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.[49–55]

Older institutionalized patients have a 7% annual incidence of syncope, a 23% overall prevalence, and a 30% 2-year recurrence rate.[56] The incidence of syncope in older adults may overlap with falls, so it may be difficult to distinguish one from the other. Older adults are predisposed to falls when syncope occurs, with a 1-year fall rate of 38% among fainters versus 18.3% among nonfainters.[57]

2.3. Initial Evaluation of Patients With Syncope: Recommendations

The time interval between the index syncopal event and the initial evaluation can vary significantly according to the medical necessity for evaluation and the patient's effort in seeking evaluation. The clinical setting in which the initial evaluation takes place also varies. The patient could seek evaluation in an outpatient setting with a generalist or a specialist or in the ED at a hospital. The recommendations in the present section are intended for consideration under the general principles of what constitutes GDMT during initial evaluation, regardless of the clinical setting. These general principles for the initial evaluation are shown in Figure 1. Additional evaluation is discussed in subsequent sections according to the outcomes of initial evaluation or in the presence of specific disease conditions.

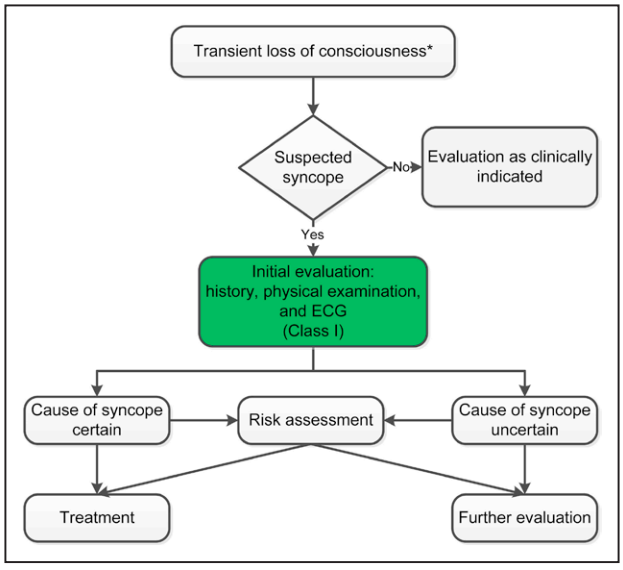

Figure 1. Syncope Initial Evaluation.
*See relevant terms and definitions in Table 3. Colors correspond to Class of Recommendation in Table 1. This figure shows the general principles for initial evaluation of all patients after an episode of syncope. ECG indicates electrocardiogram.

2.3.1. History and Physical Examination: Recommendation

Recommendation for History and Physical Examination		
COR	**LOE**	**Recommendation**
I	**B-NR**	**A detailed history and physical examination should be performed in patients with syncope.[58–66]**
See Online Data Supplement 1.		The history should aim to identify the prognosis, diagnosis, reversible or ameliorable factors, comorbidities, medication use, and patient and family needs. Cardiac syncope carries a significantly worse prognosis than does neurally mediated syncope. Prognostic factors generally separate neurally mediated from cardiac syncope and are described in Section 2.3.3. The diagnostic history focuses on the situations in which syncope occurs, prodromal symptoms that provide physiological insight, patient's self-report, bystander observations of the event and vital signs, and post-event symptoms. Video recordings are helpful when available. Time relationship to meals and physical activities and duration of the prodrome are helpful in differentiating neurally mediated syncope from cardiac syncope. Comorbidities and medication use are particularly important factors in older patients. A history of past medical conditions should be obtained, particularly with regard to the existence of preexisting cardiovascular disease.[58–66] A family history should be obtained, with particular emphasis on histories of syncope or sudden unexplained death (or drowning). Historical characteristics associated with, though not diagnostic of, cardiac and noncardiac syncope are summarized in Table 4. The physical examination should include determination of orthostatic blood pressure and heart rate changes in lying and sitting positions, on immediate standing, and after 3 minutes of upright posture.[31] Careful attention should be paid to heart rate and rhythm, as well the presence of murmurs, gallops, or rubs that would indicate the presence of structural heart disease. A basic neurological examination should be performed, looking for focal defects or other abnormalities that would suggest need for further neurological evaluation or referral.

2.3.2. Electrocardiography: Recommendation

Recommendation for Electrocardiography		
COR	**LOE**	**Recommendation**
I	**B-NR**	**In the initial evaluation of patients with syncope, a resting 12-lead electrocardiogram (ECG) is useful.[76]**
See Online Data Supplement 2.		ECG is widely available and inexpensive and can provide information about the potential and specific cause of the syncope episode (eg, bradyarrhythmia with sinus pauses or high-grade conduction block; ventricular tachyarrhythmia). It may demonstrate an underlying arrhythmogenic substrate for syncope or SCD. Subsets of patients with Wolff-Parkinson-White syndrome, Brugada syndrome, long-QT syndrome (LQTS), hypertrophic cardiomyopathy (HCM), or arrhythmogenic right ventricular cardiomyopathy (ARVC) have characteristic ECG features, which can prompt the decision to pursue further evaluation. Despite the benefit of identifying a likely cause or potential clue about the cause of syncope from the ECG, prospective studies did not conclude that ECG findings significantly affected subsequent management.[73,77–80] The prognostic value of an abnormal ECG in patients with syncope has been questioned, as well.[69,81] However, a multicenter, prospective, observational study[76] concluded that the presence of AF, intraventricular conduction disturbances, voltage criteria for left ventricular (LV) hypertrophy, and ventricular pacing were associated with increased risk of death from all causes at 1 year.

2.3.3. Risk Assessment: Recommendations

Syncope is a symptom that can be due to various causes, ranging from benign to life-threatening conditions. Risk stratification during initial evaluation is important for guiding the treatment and preventing long-term morbidity and mortality. However, risk stratification schemes for short- and long-term clinical outcomes are limited by the inclusion of all patients with syncope, without regard to the presence or absence of underlying medical conditions associated with syncope. For example, outcomes would not be expected to be similar for patients with vasovagal syncope (VVS), heart block with preserved ejection fraction, advanced cardiomyopathy and HF, acute gastric bleeding, or aortic dissection. The short-term prognosis of patients presenting with syncope is mainly related to the cause of syncope and the acute reversibility of the underlying condition; long-term prognosis is related to the effectiveness of therapy and the severity and progression of underlying diseases, especially cardiac or terminal illnesses.

Recommendations for Risk Assessment		
COR	**LOE**	**Recommendations**
I	**B-NR**	**Evaluation of the cause and assessment for the short- and long-term morbidity and mortality risk of syncope are recommended (Table 5).[68,82,83,100]**
See Online Data Supplements 3 and 4.		Syncope may be an acute result of major hemodynamic abnormalities or a manifestation of serious underlying disease. Thus, assessment of the cause of syncope and underlying comorbidities is necessary. Short-term adverse events and deaths are determined largely by the cause of syncope and the effectiveness of the treatment. In patients without a presumptive cause of syncope, risk stratification for potential short-term outcomes is necessary for immediate decision making in the acute setting. Potential predictors of increased short-term risk of death and serious outcomes are listed in Table 5. Long-term adverse events and deaths are more likely determined by the underlying medical comorbidities, many of which are cardiac. The evaluation of patients with syncope should include a full assessment of the long-term risk factors, including those listed in Table 5.[69,70,72–74,84–93,95,97]
IIb	**B-NR**	**Use of risk stratification scores may be reasonable in the management of patients with syncope.[67,68,72,73,75,87,89,100,101]**
See Online Data Supplements 3 and 4.		Investigators have reported numerous risk scores to predict adverse outcomes after syncope (examples in Table 6). This literature has important limitations, including inconsistent definitions of syncope, outcomes, outcome time frames, and predictors; inclusion of patients with serious outcomes already identified in the ED, which biases risk scores toward identifying "obvious" events; the use of composite outcomes that combine events with different pathophysiologies; small samples that limited model reliability; and limited external validation. Risk scores have not performed better than unstructured clinical judgment.[64,67–75,96,98]

Although having precise definitions for high-, intermediate-, and low-risk patient groups after an episode of syncope would be useful for managing these patients, evidence from current clinical studies renders this proposal challenging because of a large number of confounders. Risk markers from history, physical examination, laboratory investigations, study endpoints, adverse event rates, and time intervals between these events are variable from study to study. Current data are best grouped into short-term risk (associated with outcomes in the ED and up to 30 days after syncope) and long-term risk (up to 12 months of follow-up). Risk markers are summarized in Table 5.[64,67–70,72–75,82–98] The types of events, event rates, and study durations from investigations that estimated risk scores are summarized in Table 6.[64,65,76,81,87,89,92,97,99]

2.3.4. Disposition After Initial Evaluation: Recommendations

The evaluating provider must decide whether further workup can continue in an outpatient setting or whether hospital-based evaluation is required. The purpose of hospital-based evaluation is to expedite the treatment of identified serious conditions or to continue the diagnostic evaluation in the absence of a presumptive cause of syncope.[105,106]

The disposition decision is complicated by varying resources available for immediate testing, a lack of consensus on acceptable short-term risk of serious outcomes, varying availability and expertise of outpatient diagnostic clinics, and the lack of data demonstrating that hospital-based evaluation improves outcomes. In patients with a presumptive cause of reflex-mediated syncope and no other dangerous medical conditions identified, hospital-based evaluation is unlikely to provide benefit.[35] In patients with perceived higher risk, the healthcare provider may recommend a hospital-based evaluation. In this setting, a structured ED protocol can be effective as an alternative to inpatient admission.[107–110]

Decision support algorithms may reduce health service use in the evaluation of syncope (Figures 1 and 2),[105,111–113] although there are currently insufficient data to advocate the use of specific decision support algorithms for making disposition decisions.

Specialized syncope evaluation units may lead to reduced health service use and increased diagnostic rates.[114–119] However, the logistical and financial feasibility of specialized syncope units in North American settings is unknown. A wider acceptance of syncope units requires further evidence of improvement in clinical outcomes. Individual risk factors (Table 5) and risk scores (Table 6) are correlated with short- and long-term clinical outcomes, but they are not primary determinants for admission to hospital. Presence of ≥1 serious medical condition, summarized in Table 7, is the key determinant for further in-hospital management of patients after syncope.[90,98]

Recommendations for Disposition After Initial Evaluation

COR	LOE	Recommendations
I	B-NR	**Hospital evaluation and treatment are recommended for patients presenting with syncope who have a serious medical condition potentially relevant to the cause of syncope identified during initial evaluation.[105,106,120]**
See Online Data Supplements 5 and 6.		Table 7 provides examples of serious conditions associated with syncope that may require inpatient evaluation and "treatment." Arrhythmic causes may require consideration of pacemaker/implantable cardioverter-defibrillator (ICD) placement or revision and/or medication modification. Cardiac causes require treatment of the underlying condition (eg, medication management and consideration of surgical intervention for critical aortic stenosis). Finally, a large spectrum of noncardiac serious conditions may be associated with syncope and require management of the underlying problem (eg, severe anemia from a gastrointestinal bleed).
IIa	C-LD	**It is reasonable to manage patients with presumptive reflex-mediated syncope in the outpatient setting in the absence of serious medical conditions.[35]**
See Online Data Supplements 5 and 6.		Patients with presumptive VVS have a long-term risk of death similar to that of risk-matched patients without syncope.[35] Hospital-based evaluation for presumptive VVS is unlikely to improve long-term outcomes. Possible exceptions that might require hospital-based evaluation include frequent recurrent syncope with risk of injury or identified injury related to syncope.
IIa	B-R	**In intermediate-risk patients with an unclear cause of syncope, use of a structured ED observation protocol can be effective in reducing hospital admission.[107–110]**
See Online Data Supplements 5 and 6.		Two small RCTs suggest that structured ED-based protocols, consisting of time-limited observation and expedited access to cardiac testing/consultation, result in reduced health service use without adverse impact on clinical outcomes when compared with unstructured hospital admission. "Intermediate" risk factors included the following: ≥50 years of age; prior history of cardiac disease, cardiac device without evidence of dysfunction, concerning ECG findings, or family history of early SCD; and symptoms not consistent with reflex-mediated syncope. Both trials also allowed unstructured physician judgment to identify intermediate-risk patients.[107–110]
IIb	C-LD	**It may be reasonable to manage selected patients with suspected cardiac syncope in the outpatient setting in the absence of serious medical conditions.[106,121–123]**
See Online Data Supplements 5 and 6.		Hospital-based evaluation of syncope of unclear cause, in the absence of other serious identified medical conditions, has not demonstrated an improvement in patient-relevant outcomes. Several observational studies suggest modest diagnostic yield of hospital admission.[121–123] Patients evaluated for suspected cardiac syncope in outpatient settings are seldom admitted for diagnostic purposes, and it may be reasonable to extend a similar approach to EDs after initial evaluation is completed in the ED. Primary providers can consider expedited referral to specialists with expertise in syncope, as indicated by availability of resources and provider's assessment of short-term risk of serious outcomes, as an alternative to extended hospital-based evaluation.

Table 4. Historical Characteristics Associated with Increased Probability of Cardiac and Noncardiac Causes of Syncope[60,67–75]

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

SCD indicates sudden cardiac death.

Table 5. Short- and Long-Term Risk Factors*

Short-Term Risk Factors (≤30 d)	Long-Term Risk Factors (>30 d)
History: Outpatient Clinic or ED Evaluation	
Male sex[74,85,101,102]	Male sex[68,90]
Older age (>60 y)[88]	Older age[67,74,75,90]
No prodrome[68]	Absence of nausea/vomiting preceding syncopal event[93]
Palpitations preceding loss of consciousness[83]	VA[68,90]
Exertional syncope[83]	Cancer[68]
Structural heart disease[70,83,88,101,103]	Structural heart disease[68,103]
HF[74,83,85,88]	HF[90]
Cerebrovascular disease[70]	Cerebrovascular disease[68]
Family history of SCD[70]	Diabetes mellitus[104]
Trauma[68,101]	High CHADS-2 score[95]
Physical Examination or Laboratory Investigation	
Evidence of bleeding[83]	Abnormal ECG[84,90,93]
Persistent abnormal vital signs[70]	Lower GFR
Abnormal ECG[68,72,74,75,105]	
Positive troponin[75]	

*Definitions for clinical endpoints or serious outcomes vary by study. The specific endpoints for the individual studies in this table are defined in Online Data Supplements 3 and 4 and summarized in Table 6 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

The selection of a given diagnostic test, after the initial history, physical examination, and baseline ECG, is a clinical decision based on the patient's clinical presentation, risk stratification, and a clear understanding of diagnostic and prognostic value of any further testing. A broad-based use of additional testing is costly and often ineffective. This section provides recommendations for the most appropriate use of additional testing for syncope evaluation. See Figure 3 for the algorithm for additional evaluation and diagnosis for syncope.

3.1. Blood Testing: Recommendations

The availability of simple and accurate biomarkers might streamline risk stratification and diagnosis of the cause of syncope. This section reviews circulating biomarkers, which are being evaluated as markers either of hypotension or underlying disease processes. None have met with strong success.

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.[124]**
See Online Data Supplements 7 and 8.		Although broad-panel testing is common in clinical practice at the point of triage, there are no data on the utility of this approach. Data to support specific blood testing are largely descriptive data from case series and registries. Complete blood count and electrolyte panel are frequently obtained during syncope evaluation. The diagnostic yield is low when these are used routinely; however, when these blood tests are conducted in patients with a suspected related diagnosis (eg, history of peptic ulcer disease, or tarry stools associated with OH on physical examination), test results can be diagnostic and useful for guiding therapy. Thus, specific testing should stem from the assessment by history and physical examination when the nature of the syncope presentation or associated comorbidities suggests a diagnostic or more likely prognostic role for laboratory testing. Results have not been linked to clinical decision making or outcomes.[125–128]

Recommendations for Blood Testing (Continued)		
COR	**LOE**	**Recommendations**
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.**[125,127,129,130]
See Online Data Supplements 7 and 8.		Although data to support biomarker testing are in general relatively weak, there are sufficient data to suggest that natriuretic peptide is elevated in patients whose subsequent cause for syncope is determined to be cardiac. A systematic review of biomarkers found little value in contemporary troponin measurement unless acute myocardial infarction is suspected, and there is modest predictive value for high-sensitivity troponin and natriuretic peptides for major adverse cardiovascular events. The ability of troponin and natriuretic peptide measurement to influence clinical decision making or patient outcome is unknown.[129]
III: No Benefit	**B-NR**	**Routine and comprehensive laboratory testing is not useful in the evaluation of patients with syncope.**[126,131]
See Online Data Supplements 7 and 8.		There are no data on the utility of a standardized broad panel of laboratory testing in patients with syncope. Specific cardiac biomarkers may play a limited role when directed by clinical suspicion from the baseline assessment. There is little biological plausibility linking the remaining elements of broad-panel laboratory testing to the presentation or mechanism of syncope.

3.2. Cardiovascular Testing: Recommendations

Cardiovascular causes of syncope are common. The presence of significant cardiovascular diseases, often associated with the cardiovascular causes of syncope, portends a poor prognosis.[35,132] As such, cardiovascular testing can be a critical element in the evaluation and management of selected patients with syncope. It is important also to recognize that the abnormalities found during cardiovascular testing may not have a causal relationship to syncope itself. Determining the significance of such abnormalities, their causality, and whether subsequent treatment is merited requires clinical judgment and appropriate selection of cardiovascular testing.

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.**[80,99,124]
See Online Data Supplement 9.		Cardiac imaging is often used to identify a structural cardiac abnormality, and imaging with transthoracic echocardiography is widely used for this purpose because it is noninvasive and low risk. Transthoracic echocardiography can be useful when healthcare providers are concerned about the presence of valvular disease (eg, aortic stenosis), HCM, or LV dysfunction.[124,133] In a retrospective study of patients presenting with syncope and suspected cardiac disease after history, physical examination, or ECG, the echocardiogram suggested a diagnosis of cardiac syncope in 48% of the study cohort.[99] In a prospective evaluation of 650 patients referred for syncope of unknown origin, 88 patients had an abnormal history or ECG; an echocardiogram showed systolic dysfunction (LV ejection fraction ≥40%) in 24 patients[80]; and 50% of patients with LV systolic dysfunction had manifest arrhythmias, compared with 9% with minor, incidental abnormalities ($P<0.01$). Although an echocardiogram may not be able to establish the immediate cause of syncope, it provides information for a potential disease substrate related to prognosis.
IIb	**B-NR**	**Computed tomography (CT) or magnetic resonance imaging (MRI) may be useful in selected patients presenting with syncope of suspected cardiac etiology.**[134]
See Online Data Supplement 9.		Imaging modalities, including CT and MRI, are usually reserved for selected patients presenting with syncope, especially when other noninvasive means are inadequate or inconclusive. These modalities offer superior spatial resolution in delineating cardiovascular anatomy (eg, in patients with structural, infiltrative, or congenital heart disease [CHD]).[135,136] The use of CT and MRI in contemporary cardiology is increasing.[137,138] Their role in the evaluation of syncope has been investigated.[139] The use of CT or MRI increased from 21% in 2001 to 45% in 2010, as reported in a series of patients evaluated for syncope in the ED.[134] MRI is useful when there is a suspicion of ARVC or cardiac sarcoidosis.[140,141] When pulmonary embolism is suspected in patients presenting with syncope to the hospital, CT can confirm the diagnosis in selected patients.[128] CT or MRI may not provide answers about the cause of syncope. They provide information on the structural disease substrate relevant to the overall diagnosis and subsequent evaluation and follow-up in selected patients presenting with syncope.
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.**[77,99]
See Online Data Supplement 9.		Although some investigators have advocated for cardiac imaging—particularly transthoracic echocardiography—as a routine screening examination for patients with syncope who lack clear signs or symptoms of cardiovascular disease,[133] clinical evidence does not support such practice. Unexpected findings on echocardiograms to explain syncope are uncommon; a "screening" echocardiogram is of low utility.[142] In 1 evaluation of 2106 inpatients with syncope, a battery of testing, including cardiac enzymes, CT scans, echocardiography, carotid ultrasonography, and electroencephalography, contributed to the diagnosis or management in <5% of cases and helped determine the etiology of syncope <2% of the time.[77] Similarly, in another retrospective series of 128 inpatients with syncope, it was found that echocardiograms in patients with no clinical evidence of heart disease according to history, physical examination, or ECG either were normal (63%) or provided no useful additional information for arriving at a diagnosis (37%).[99] Finally, radionuclide imaging and cardiac catheterization have little role in the evaluation of syncope.

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.[132,143]**
See Online Data Supplement 10.		Exertion can result in syncope in a variety of conditions, including structural lesions, such as hypertrophic obstructive cardiomyopathy and aortic stenosis; interarterial anomalous coronary artery and pulmonary arterial hypertension; and channelopathies, such as LQTS (type 1) and catecholaminergic polymorphic ventricular tachycardia (CPVT). Subjecting a patient to a treadmill exercise test to reproduce the symptoms or evaluate the hemodynamic response to exertion (eg, hypotension) must be done with extreme caution and in an environment with proper advanced life support. In a prospective evaluation of 433 patients in which tachyarrhythmia was studied as the etiology for exertional syncope,[132] an ECG stress evaluation was felt to be the sole test useful in identifying a presumptive cause of syncope in only 2 patients. However, bradyarrhythmia may ultimately be responsible for exertional syncope as well, and may only be elicited during stress testing. In rare instances, exercise-induced ischemia[143–146] or coronary vasospasm[147] may lead to high-grade/infranodal AV block in patients with underlying coronary disease.

3.2.3. Cardiac Monitoring: Recommendations

Although cardiac monitoring is often used in the evaluation of palpitations or intermittent arrhythmias, the following recommendations and discussion are focused primarily on the use of monitoring for the evaluation of patients with syncope. The choice of monitoring system and duration should be appropriate to the likelihood that a spontaneous event will be detected and the patient may be incapacitated and unable to voluntarily trigger the recording system.

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.**
N/A		The technology of cardiac rhythm monitoring is dynamic and advancing at rapid speed. Several types of ambulatory cardiac rhythm monitoring are summarized in Table 8. Their selection and usefulness are highly dependent on patient characteristics with regard to the frequency of syncope and the likelihood of an arrhythmic cause of syncope.[148]
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 monitor[149–153]** **2. Transtelephonic monitor[150,154,155]** **3. External loop recorder[150,154–156]** **4. Patch recorder[157–159]** **5. Mobile cardiac outpatient telemetry[160,161]**
See Online Data Supplements 11 and 12.		The types of external monitoring devices are summarized in Table 8. The effectiveness of any external cardiac monitoring device for syncope evaluation is related to the duration of monitoring, continuous versus intermittent monitoring, frequency of syncope, duration of prodrome, and suddenness of incapacitation. The patient activation, before or after an event, allows for symptom rhythm correlation; however, some external loop recorders are of limited use in patients who are temporarily incapacitated around the time of syncope. External loop recorders are also limited by infrequent syncopal events. The advantage of an external loop recorder over Holter monitoring stems from a longer monitoring period, which confers a higher yield than Holter monitoring[149,153] and may offer a diagnosis after a negative Holter evaluation.[150] Although the diagnostic yield of an external loop recordermay be lower than that of an implantable cardiac monitor (ICM), the noninvasive strategy is reasonable as a first approach. One prospective, multicenter study of 392 patients (28% with syncope) reported a 4-week diagnostic yield of 24.5%, with recurrent events and previous history of supraventricular arrhythmias being strong predictors of diagnostic events.[156] The advances of new patch-based devices offer another and often less cumbersome means of identifying an arrhythmic cause for syncope.[157–159] The duration of monitoring (2 to 14 days) is often shorter than for the external loop recorder or mobile continuous outpatient telemetry. Some practices offer mobile continuous outpatient telemetry devices, which provide real-time arrhythmia monitoring and analysis. An RCT[161] of 266 patients with suspected intermittent arrhythmias demonstrated that an arrhythmia was diagnosed in 88% of mobile continuous outpatient telemetry patients versus 75% of external loop recorder patients (*P*=0.008). Importantly, therewas a similar result in the subgroup of patients presenting with syncope or presyncope, with a significantly higher diagnostic yield in the mobile continuous outpatient telemetry group (89% versus 69%; *P*=0.008).
IIa	**B-R**	**To evaluate selected ambulatory patients with syncope of suspected arrhythmic etiology, an ICM can be useful.[149,150,153,161–175]**
See Online Data Supplements 11 and 12.		Several RCTs and observational studies have demonstrated a benefit of the ICM in establishing a diagnosis in syncope of unclear etiology. In a prospective study of 60 patients with syncope of unknown origin, the diagnosis (primarily bradyarrhythmia) was made in 55% with ICM, compared with a 19% diagnostic yield with conventional testing (external loop recorder, followed by tilt-table testing and electrophysiological study [EPS]) (*P*=0.0014).[162] These findings are consistent with other studies, which generally have shown that patients who underwent the ICM approach experienced higher rates of diagnosis than those of patients who underwent the conventional approach.[164,176,177] A study on cost-effectiveness of the ICM strategy reported that the mean cost per participant was higher but the cost per diagnosis was lower in patients who received ICM than in patients who underwent conventional approaches.[162,164,178] Key confounders in cost assessment include differences in healthcare settings, heterogeneity of patient populations, pricing of devices and healthcare delivery, and changing technology.

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.**[77,182,183]
See Online Data Supplement 13.		Given that patients with syncope and structural heart disease are at high risk of death or significant arrhythmia,[184] inpatient telemetry could be a valuable diagnostic modality. However, the diagnostic yield of inpatient telemetry is low in the absence of high suspicion about an arrhythmic cause.[183] One study of 172 patients with syncope presenting to the ED and admitted to a telemetry unit revealed a diagnostic yield in 18% of patients, with 15% demonstrating bradyarrhythmias.[182] The yield was highest in older patients with HF. No deaths occurred within an average monitoring time of 4.8±2.7 days. In 1 prospective study of 2240 patients admitted to a telemetry unit, patients admitted for syncope (10%) had low rates of unexpected intensive care transfer, and most were unrelated to arrhythmic conditions.[185] Furthermore, in another prospective evaluation of 205 patients admitted to telemetry, significant arrhythmias were seen in only 12 patients with known or suspected coronary artery disease or in those with previously documented arrhythmias.[183] No arrhythmias or interventions occurred in the 7% of patients who were assigned to telemetry because of syncope. A large, prospective evaluation of 2106 patients admitted with syncope demonstrated high telemetry use (95%) but a diagnostic yield of only 5%.[77] Continuous telemetry in the hospital for patients presenting with syncope not suspected of a cardiac etiology is not cost-effective.[186,187]

Table 6. Examples of Syncope Risk Scores

Study/ Reference	Year	Sample N	Events N (%)	Outcome Definition	ED Events*	Predictors	NPV (%)†
Martin[90]	1997	252	104 (41%)	1-y death/arrhythmia	Yes	Abnormal ECG‡; >45 y of age; VA; HF	93
Sarasin[74]	2003	175	30 (17%)	Inpatient arrhythmia	Yes	Abnormal ECG‡; >65 y of age; HF	98
OESIL[67]	2003	270	31 (11%)	1-y death	N/A	Abnormal ECG‡; >65 y of age; no prodrome; cardiac history	100
SFSR[72]	2004	684	79 (12%)	7-d serious events§	Yes	Abnormal ECG‡; dyspnea; hematocrit; systolic BP <90 mm Hg; HF	99
Boston Syncope Rule[70]	2007	293	68 (23%)	30-d serious events‖	Yes	Symptoms of acute coronary syndrome; worrisome cardiac history; family history of SCD; VHD; signs of conduction disease; volume depletion; persistent abnormal vital signs; primary central nervous event	100
Del Rosso[69]	2008	260	44 (17%)	Cardiac etiology	N/A	Abnormal ECG‡/cardiac history; palpitations; exertional; supine; precipitant (a low-risk factor); autonomic prodrome (low-risk factors)	99
STePS[68]	2008	676	41 (6%)	10-d serious events¶	Yes	Abnormal ECG‡; trauma; no prodrome; male sex	–
Syncope Risk Score[75]	2009	2584	173 (7%)	30-d serious events#	No	Abnormal ECG‡; >90 y of age; male sex; positive troponin; history of arrhythmia; systolic BP >160 mm Hg; near-syncope (a low-risk factor)	97
ROSE[73]	2010	550	40 (7%)	30-d serious events#	Yes	Abnormal ECG‡; B-natriuretic peptide; hemoglobin; O_2Sat; fecal occult blood	98

*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.

AVB indicates atrioventricular block; BBB, bundle-branch block; BP, blood pressure; ECG, electrocardiogram; ED, emergency department; HF, heart failure; MI, myocardial infarction; N/A, not available; NPV, negative predictive value; O_2Sat, oxygen saturation; OESIL, Osservatorio Epidemiologico sulla Sincope nel Lazio; ROSE, Risk Stratification of Syncope in the ED; SCD, sudden cardiac death; SFSR, San Francisco Syncope Rule; STePS, Short-Term Prognosis of Syncope Study; TIA, transient ischemic attack; VA, ventricular arrhythmias; and VHD, valvular heart disease.

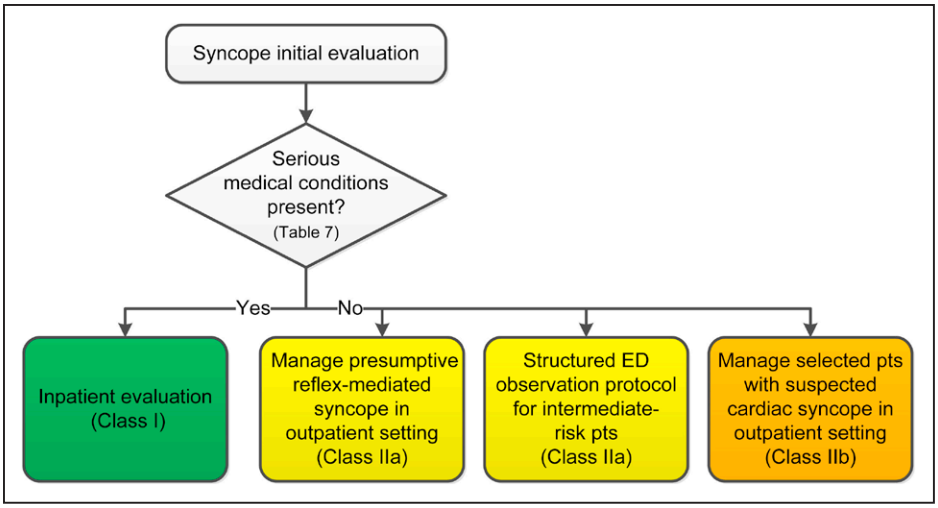

Figure 2. Patient Disposition After Initial Evaluation for Syncope.
Colors correspond to Class of Recommendation in Table 1. ED indicates emergency department; and pts, patients.

3.2.5. Electrophysiological Study: Recommendations

The EPS can identify a substrate for clinical bradyarrhythmia or tachyarrhythmia as a potential cause of syncope after a nondiagnostic initial evaluation. Despite these purported benefits, EPS has a limited role in the evaluation of syncope, especially in patients without known heart disease or with low suspicion of an arrhythmic etiology.[117,187,188] The sensitivity and specificity of EPS to assess sinus node dysfunction and AV conduction disease in patients with syncope are variable, depending on patient selection and pretest probability of a bradycardia substrate.[189–191]

Inducible ventricular tachycardia (VT) in patients with syncope, ischemic heart disease, and a prior history of myocardial infarction is predictive of spontaneous VT and prognosis. The causal relationship between the inducible VT during EPS and syncope requires clinical correlation. The lack of an inducible sustained monomorphic VT predicts lower risk of spontaneous VT and better prognosis.[192] The overall role of EPS in the evaluation of ventricular arrhythmias (VA) in patients with syncope has diminished in the past 2 decades. This is primarily due to the use of ICD as a Class I indication for the primary prevention of SCD in patients with ischemic or nonischemic cardiomyopathy and significant LV dysfunction (ejection fraction ≤35%). An EPS is no longer required in patients with syncope before consideration of ICD therapy. However, although ICDs may reduce risk of death, they may not prevent syncope. The role of EPS in patients with syncope suspected to be due to VA and acquired nonischemic heart disease is unproven.[193–198]

Recommendations for EPS

COR	LOE	Recommendations
IIa	B-NR	**EPS can be useful for evaluation of selected patients with syncope of suspected arrhythmic etiology.[91,151,199–205]**
See Online Data Supplement 14.		Diagnostic results detected during EPS occur predominantly in patients who have cardiac disease (eg, conduction system delay, coronary artery disease, cardiomyopathy, and valvular heart disease). Most of the literature evaluating EPS as a means to diagnose syncope is relatively old, and the data were obtained in referral centers where there was a high pretest probability of an arrhythmia. Eight of these small retrospective studies[91,199–205] (total n=625) found that, of the 406 patients with cardiac disease or an abnormal ECG, 41% had a positive result (of these, 21% had VT and 34% had a bradycardia).[151] Of 219 patients without evidence of heart disease, only 5% had a positive result (1% with VT and 10% with evidence of substrate for symptomatic bradycardia). Overall, the diagnostic yield of EPS was approximately 50% and 10% in patients with and without structural heart disease, respectively.
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.[205–207]**
See Online Data Supplement 14.		One prospective evaluation of 247 patients with syncope of undetermined etiology who underwent EPS found that the diagnostic yield was significantly higher in patients with an abnormal ECG than in those with a normal ECG (22% versus 3.7%) and that the diagnostic yield was low in patients with a normal ECG and without cardiac disease (2.6%).[206] In another small series of 34 patients with unexplained syncope who had normal ECGs and normal testing otherwise and who underwent EPS,[205] the results were diagnostic in only 4 patients; the results were abnormal but not diagnostic in 2 patients and were normal in the remaining 28 patients. In another evaluation of 421 patients with undiagnosed syncope who underwent noninvasive testing as a means of predicting abnormal EPS findings, a normal ECG and ambulatory monitor were associated with a lower risk of EPS abnormalities than were an abnormal ECG and ambulatory monitor (9% versus 82%).[207]

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 VVS.[208–213]**
See Online Data Supplement 15.		Tilt-table testing has been used to evaluate patients with syncope for nearly 3 decades.[208] It is an orthostatic stress test to assess the susceptibility of a vasovagal response to a postural change from a supine to an upright position. A positive response is defined as inducible presyncope or syncope associated with hypotension, with or without bradycardia (less commonly asystole). The hemodynamic response to the tilt maneuver determines whether there is a cardioinhibitory, vasodepressor, or mixed response.[214] There is general consensus that a tilt-table angle of 70 degrees for 30 to 40 minutes would provide optimal yield.[211,213,215] Adjunctive agents, such as a low dose of isoproterenol infusion or sublingual nitrates, may improve sensitivity but decrease specificity.[210,212,216,217] A positive tilt-table test suggests a tendency or predisposition to VVS induced in the laboratory. This observation during tilt-table testing cannot necessarily define a causal etiology or be entirely conclusive of a reflex mechanism for syncope in the clinical setting. Correlation of tilt-table–induced findings to patients' clinical presentation is critically important to prevent consequences of false-positive results from tilt-table testing. The utility of tilt-table testing is highest in patients with a suspected VVS when syncope is recurrent. Several factors have reduced the role of tilt-table testing in the evaluation of syncope: the overall moderate sensitivity, specificity, and reproducibility of tilt-table testing; the presence of false-positive response in controls; the increasing recognition of VVS from a structured history taking; and the availability of long-term cardiac monitoring.[24,211,213]
IIa	**B-NR**	**Tilt-table testing can be useful for patients with syncope and suspected delayed OH when initial evaluation is not diagnostic.[218,219]**
See Online Data Supplement 15.		OH with standing, or a similar fall in blood pressure within 3 minutes of upright tilt-table testing to 60 degrees,[220] is distinct from delayed OH, characterized by a sustained decrease in blood pressure occurring beyond 3 minutes of standing or upright tilt-table testing.[220,221] Delayed OH may be responsible for syncopal episodes or symptoms of orthostatic intolerance only after prolonged standing. In 1 retrospective study of 230 patients with OH, only 46% had OH within 3 minutes of head-up tilt; 15% had OH between 3 and 10 minutes; and 39% had OH only after 10 minutes of tilt-table testing.[218] In 10-year follow-up data from 165 of these patients, 54% of individuals with delayed OH progressed to classic OH.[219] The 10-year death rate in individuals with delayed OH was 29%, compared with 64% and 9% in individuals with baseline OH and controls, respectively.
IIa	**B-NR**	**Tilt-table testing is reasonable to distinguish convulsive syncope from epilepsy in selected patients.[222–225]**
See Online Data Supplement 15.		Convulsive syncope is a term that can be used to describe any form of syncope manifesting with convulsive movements (eg, myoclonus). Prolonged convulsions and marked postictal confusion are uncommon in patients with syncope associated with convulsive movements,[226] and fatigue is frequent after reflex syncope and may be confused with a postictal state.[226] Tilt-table testing has been shown to be of value in this clinical setting when a detailed history cannot clearly determine whether the convulsive movements were secondary to syncope, given the need for objective evidence to help distinguish this entity from true epileptic seizures. In a prospective study of 15 patients with recurrent unexplained seizure-like episodes who were unresponsive to antiepileptic therapy,[223] 67% had convulsive movements associated with hypotension and bradycardia during tilt-table testing. In another study of 74 patients with a questionable diagnosis of epilepsy (because of drug-refractory seizures or clinically suspected not to be true epilepsy), a cardiac diagnosis was established in 42% of patients, with >25% developing profound hypotension or bradycardia during the head-up tilt-table test, confirming the diagnosis of VVS.[225] Taken together, it can be estimated from these studies that approximately 50% of patients with either questionable or drug-refractory epilepsy have positive tilt-table tests suggestive of a vasovagal etiology.[226]
IIa	**B-NR**	**Tilt-table testing is reasonable to establish a diagnosis of pseudosyncope.[227–229]**
See Online Data Supplement 15.		Psychogenic pseudosyncope should be suspected when patients present with frequent (even daily) symptoms that mimic VVS (and, in some cases, with a history of true VVS). It is often challenging to differentiate psychogenic syncope from true syncope. However, tilt-table testing may help to elucidate the diagnosis. During tilt-table testing, the apparent unconsciousness with loss of motor control, combined with normal blood pressure and heart rate (and a normal electroencephalogram [EEG] if such a recording is obtained), rules out true syncope and most forms of epilepsy.[227–229] In 1 study of 800 patients who underwent tilt-table testing, approximately 5% were diagnosed with pseudosyncope. Compared with patients with VVS, eye closure during the event, long periods of apparent transient loss of consciousness, and increased heart rate and blood pressure are highly specific for pseudosyncope. One study of 21 patients with suspected pseudosyncope who were subjected to tilt-table testing with continuous monitoring of the ECG, EEG, and blood pressure revealed 17 patients with non-epileptiform limb shaking without significant changes on an EEG or hemodynamic changes.[227]
III: No Benefit	**B-R**	**Tilt-table testing is not recommended to predict a response to medical treatments for VVS.[230,231]**
See Online Data Supplement 15.		One of the purported advantages of tilt-table testing, in addition to suggesting a diagnosis of VVS, is the ability to assess the efficacy of pharmacological therapeutics in suppressing a vasovagal response to postural stress by evaluating the effectiveness of a therapy during repeated testing.[230,231] Several small studies suggested a possible benefit, but these data were limited by the lack of reproducibility of tilt-table testing.[232–235]

Table 7. Examples of Serious Medical Conditions That Might Warrant Consideration of Further Evaluation and Therapy in a Hospital Setting

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

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

3.3. Neurological Testing: Recommendations

3.3.1. Autonomic Evaluation: Recommendation

Syncope due to neurogenic OH is common in patients with central or peripheral autonomic nervous system damage or dysfunction. Its causes should be sought so as to provide efficient, accurate, and effective management. Some symptoms of neurogenic OH may differ from those due to dehydration, drugs, and cardiac and reflex syncope; these include persistent and often progressive generalized weakness, fatigue, visual blurring, cognitive slowing, leg buckling, and the "coat hanger" headache (a triangular headache at the base of the neck due to trapezius ischemia). These symptoms may be provoked or exacerbated by exertion, prolonged standing, meals, or increased ambient temperature. Confirmation of specific neurogenic OH conditions causing syncope often requires additional autonomic evaluation.

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.[219,236–239]**
See Online Data Supplement 16.		The care of patients with neurogenic OH is complex, especially in individuals with neurodegenerative disease. Care providers must be knowledgeable in the pathophysiology of the autonomic nervous system and the pharmacology of treatments for neurodegenerative disease.[33,240] Many symptomatic treatments for neurodegenerative disease will increase the risk of syncope due to worsening OH; selection of these treatments needs to be balanced against the increased morbidity of not treating the symptoms of the neurodegenerative disease. Such care may be provided by a neurologist, cardiologist, internist, or other physician who has sufficient training to treat these complicated patients. Syncope due to neurogenic OH is caused by either central or peripheral autonomic nervous system damage or dysfunction. Central autonomic degenerative disorders include multiple system atrophy,[241] Parkinson's disease,[242] and Lewy Body dementia.[238] Peripheral autonomic dysfunction may be due to a selective degeneration of peripheral autonomic neurons, known as pure autonomic failure,[243] or may accompany autonomic peripheral neuropathies, such as neuropathies due to diabetes amyloidosis, immune-mediated neuropathies, hereditary sensory and autonomic neuropathies, and inflammatory neuropathies. Peripheral neuropathies due to vitamin B_{12} deficiency, neurotoxic exposure, HIV and other infections, and porphyria are less common causes of neurogenic OH.[240] It can be useful to consider referring patients with the following characteristics for autonomic evaluation: Parkinsonism[241,244–246] or other central nervous system features,[247,248] peripheral neuropathies,[240] underlying diseases known to be associated with a peripheral neuropathy,[240,248] progressive autonomic dysfunction without central or peripheral nervous system features,[243,248] postprandial hypotension,[248,249] and known or suspected neuropathic postural tachycardia syndrome (POTS).[37,248,250] Autonomic evaluation may: 1) determine the underlying cause of neurogenic OH; 2) provide prognostic information; and 3) have therapeutic implications.

3.3.2. Neurological and Imaging Diagnostics: Recommendations

Many patients undergo extensive neurological investigation after an uncomplicated syncope event, despite the absence of neurological features on history or examination. A systematic review found that EEG, CT, MRI, and carotid ultrasound were ordered in 11% to 58% of patients with a presentation of syncope.[78] The evidence suggests that routine neurological testing is of very limited value in the context of syncope evaluation and management; the diagnostic yield is low, with very high cost per diagnosis.[36,77,78,251–260] The recommendations pertain to the use of these investigations in patients with syncope and not in patients in the wider category of transient loss of consciousness.

Recommendations for Neurological Diagnostics		
COR	**LOE**	**Recommendations**
IIa	**C-LD**	**Simultaneous monitoring of an EEG and hemodynamic parameters during tilt-table testing can be useful to distinguish among syncope, pseudosyncope, and epilepsy.**[229,261–263]
See Online Data Supplement 16.		Although a thoughtful and detailed history usually suffices to distinguish among convulsive syncope, epileptic convulsions, and pseudosyncope, an EEG is particularly important when a diagnosis cannot be established after a thorough initial evaluation. EEG findings are characteristic if an episode can be induced during the tilt-table testing.[261–263] Epileptiform discharges are recorded during epileptic convulsions whereas, during syncope, an EEG generally shows diffuse brainwave slowing with delta waves and a flat line pattern.[263] Pseudosyncope and psychogenic nonepileptic seizures are associated with a normal EEG.[229]
III: No Benefit	**B-NR**	**MRI and CT 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.**[78,260]
See Online Data Supplement 16.		Syncope is due to global cerebral hypoperfusion, and brain structural abnormalities are rare. Nonetheless, MRI and CT are frequently used and infrequently helpful. In 5 studies investigating patients with syncope, MRI was used in 11% of 397 patients and established a diagnosis in only 0.24%. Similarly, in 10 studies of investigation of syncope, CT was used in 57% of 2728 patients and established a diagnosis in only 1%.[77,78,256,257,260] Given the cost and impact on health service facilities, MRI and CT should not be routinely used in the assessment of syncope. Neurological imaging may be indicated if significant head injury as a result of syncope is suspected. Although there is general concern about potential radiation-mediated harm from CT, there are very limited data on the actual harm from CT for syncope evaluation.
III: No Benefit	**B-NR**	**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.**[77,78,256,257,260]
See Online Data Supplement 16.		Syncope is due to global cerebral hypoperfusion and therefore not to unilateral ischemia. A review of 5 studies of carotid artery ultrasound and Doppler use in patients with syncope found that these modalities were used in 58% of 551 patients and established a diagnosis in 0.5%.[77,78,256,257,260] Carotid artery ultrasound should not be routinely used in the assessment of syncope.
III: No Benefit	**B-NR**	**Routine recording of an EEG is not recommended in the evaluation of patients with syncope in the absence of specific neurological features suggestive of a seizure.**[36,77,254–258]
See Online Data Supplement 16.		EEGs are ordered frequently for the evaluation of syncope. A review of 7 studies of use of an EEG in patients with syncope found that it was used in 52% of 2084 patients and established a diagnosis in 0.7%.[36,77,254–258] EEGs should not be routinely used in the assessment of syncope.

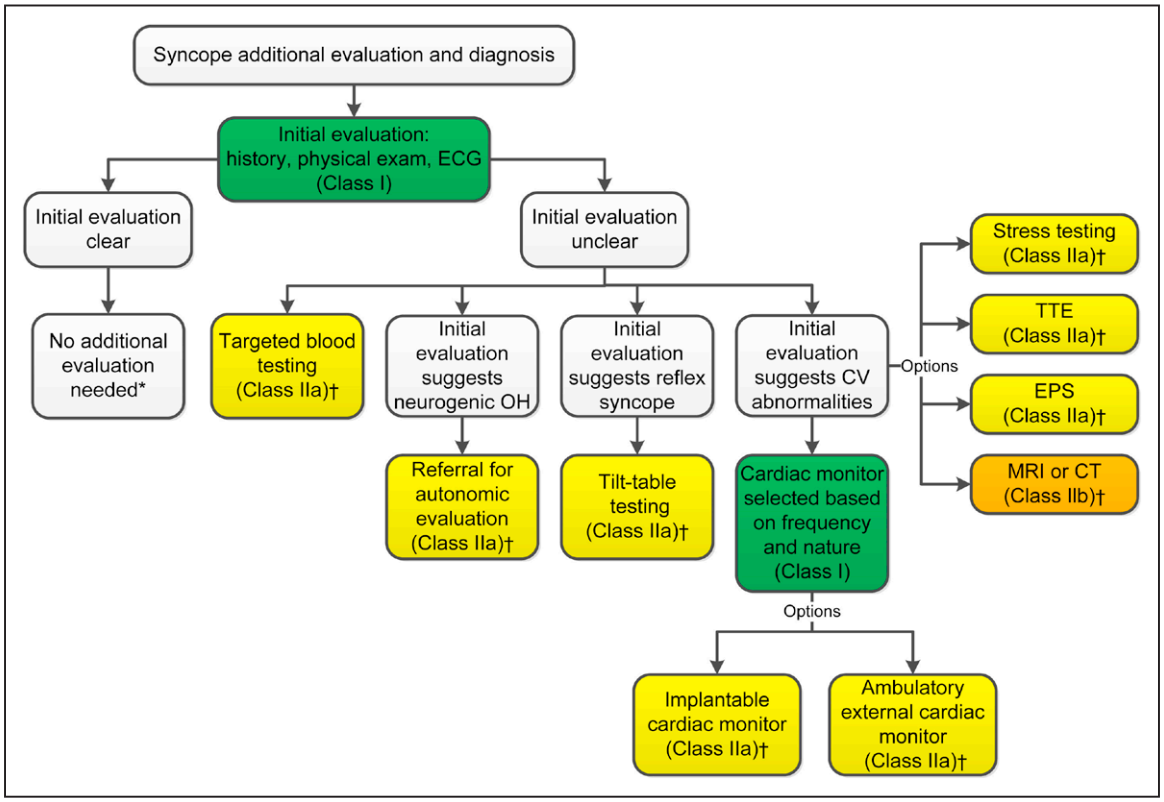

Figure 3. Additional Evaluation and Diagnosis for Syncope. Colors correspond to Class of Recommendation in Table 1. *Applies to patients after a normal initial evaluation without significant injury or cardiovascular morbidities; patients followed up by primary care physician as needed. †In selected patients (see Section 1.4). CT indicates computed tomography; CV, cardiovascular; ECG, electrocardiogram; EPS, electrophysiological study; MRI, magnetic resonance imaging; OH, orthostatic hypotension; and TTE, transthoracic echocardiography.

Table 8. Cardiac Rhythm Monitors

Types of Monitor	Device Description	Patient Selection
Holter monitor[151–153]	A portable, battery-operated device Continuous recording for 24–72 h; up to 2 wk with newer models Symptom rhythm correlation can be achieved through a patient event diary and patient-activated annotations	Symptoms frequent enough to be detected within a short period (24–72 h) of monitoring*
Patient-activated, transtelephonic monitor (event monitor)[150,154,155]	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)	Frequent, spontaneous symptoms likely to recur within 2–6 wk Limited use in patients with frank syncope associated with sudden incapacitation
External loop recorder (patient or auto triggered)†[150,154,155]	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 Newer models are equipped with a cellular phone, which transmits triggered data automatically over a wireless network to a remote monitoring system	Frequent, spontaneous symptoms related to syncope, likely to recur within 2–6 wk
External patch recorders[157–159]	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	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
Mobile cardiac outpatient telemetry[160,161]	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	Spontaneous symptoms related to syncope and rhythm correlation In high-risk patients whose rhythm requires real-time monitoring
Implantable cardiac monitor[162,167,179–181]	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	Recurrent, infrequent, unexplained syncope (or suspected atypical reflex syncope) of suspected arrhythmic cause after a nondiagnostic initial workup, with or without structural heart disease

*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.

4. MANAGEMENT OF CARDIOVASCULAR CONDITIONS

The writing committee reviewed the evidence to support recommendations in the relevant ACC/AHA guidelines 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, except for the specific cardiac conditions in Sections 4.2.4, 4.2.5, and 4.3 for which ACC/AHA guidelines are not available. The relevant guidelines are noted in Table 2.

It is pertinent to note that the principles of evaluation and management of syncope in patients with various cardiac conditions are the same as for other noncardiac conditions. A thorough history, physical examination, and baseline ECG are recommended in all patients. The determination of the immediate cause of syncope may be related, indirectly related, or unrelated to the underlying cardiac condition. Management of

patients with syncope and heart disease would include treating the immediate cause of syncope and further assessing long-term management strategies to improve prognosis. The recommendations stated in this section focus on syncope relevant to and within the context of the specific stated cardiac condition.

4.1. Arrhythmic Conditions: Recommendations

Cardiac arrhythmia is a common cause of syncope, and the prompt identification of an arrhythmic etiology has diagnostic and prognostic implications. When bradyarrhythmias and tachyarrhythmias are discovered in patients with syncope, determining their causal relationship to syncope often poses challenges for the practitioner. The baseline presence of an arrhythmia does not necessarily represent the etiology of syncope (eg, marked resting bradycardia in a young patient with syncope). Furthermore, determining the significance of atrial tachyarrhythmias and VT—which are often paroxysmal and occult on initial evaluation—poses additional challenges and may warrant a more extensive evaluation (Section 3.2). Section 4.1 broadly outlines strategies to guide the practitioner when evaluating patients with bradycardia, supraventricular arrhythmias (including AF), and VT.

4.1.1. Bradycardia: Recommendation

Recommendation for Bradycardia		
COR	**LOE**	**Recommendation**
I	**C-EO**	**In patients with syncope associated with bradycardia, GDMT is recommended.[12]**
N/A		A search and review of papers on syncope and bradycardia has been performed since the last updated guidelines were published in 2012.[12] The writing committee supports the previous recommendations pertaining to syncope in patients with sinus node dysfunction and AV conduction diseases. In adult patients presenting with syncope and chronic bifascicular block but without documented high-degree AV block, for whom other causes have been excluded, an RCT[265] showed that a dual-chamber pacemaker reduced recurrent syncope. The evidence continues to support, without change from the previous recommendation, the notion that permanent pacemaker implantation is reasonable for syncope in patients with chronic bifascicular block when other causes have been excluded. The use of adenosine triphosphate in the evaluation of syncope in older patients continues to evolve. In a small, single-blind trial of older patients (mean age 75 years) randomized to active pacing or back-up pacing with documented adenosine triphosphate–sensitive sinoatrial or AV block, there was a 75% risk reduction in syncope recurrence with dual-chamber pacing.[266] Adenosine triphosphate is not available in the United States. The writing committee has reached a consensus not to make a new recommendation on its use for syncope evaluation because of the limited data at this time.

4.1.2. Supraventricular Tachycardia: Recommendations

Recommendations for Supraventricular Tachycardia (SVT)		
COR	**LOE**	**Recommendations**
I	**C-EO**	**In patients with syncope and SVT, GDMT is recommended.[10]**
N/A		Although patients with SVT frequently manifest palpitations and lightheadedness, syncope is uncommon. Of note, older patients with paroxysmal SVT are more prone to syncope or near-syncope than are younger patients; these symptoms appear to be independent of the rate of tachycardia, which is generally slower in older adult patients than in younger patients.[267,268] Younger patients with SVT causing syncope generally have a very rapid tachycardia. Evaluation of syncope in patients with Wolff-Parkinson-White syndrome with preexcitation on ECG requires a thorough history to differentiate an arrhythmic syncope from a nonarrhythmic syncope, such as VVS, in younger patients.[269] When a patient with syncope reports antecedent palpitations and lightheadedness, VT should be more strongly suspected than SVT. EPS may be useful to distinguish a VT from an SVT responsible for syncope associated with these antecedent symptoms. It should be noted that palpitations can also precede vasovagal faints due to sinus tachycardia, so not all palpitations are necessarily due to paroxysmal SVT or VT.
I	**C-EO**	**In patients with AF, GDMT is recommended.[16]**
N/A		AF can be associated with syncope. As with other forms of SVT, syncope from a rapid ventricular response (in the absence of preexcitation) is relatively unusual. Patients with chronic AF merit control of the ventricular response or maintenance of sinus rhythm with appropriate antiarrhythmic therapy (in carefully selected patients).[16] Patients with paroxysmal AF are predisposed to an abnormal neural response during both sinus rhythm and arrhythmia, and the onset of AF may trigger VVS.[270] In patients with sinus node dysfunction, syncope could occur upon termination of AF when prolonged pauses are present.

4.1.3. Ventricular Arrhythmia: Recommendation

Recommendation for VA		
COR	**LOE**	**Recommendation**
I	C-EO	**In patients with syncope and VA, GDMT is recommended.**[12,13,220,264,271]
N/A		Patients with VA (monomorphic or polymorphic) can present with syncope, whether it is nonsustained or sustained. The mechanism of syncope from VA is multifactorial, including: rapid rate, abrupt change in rate, abnormal atrial and ventricular activation relationships, dyssynchrony of ventricular activation, changes in autonomic tone, and body position during the VA.[272] One study of 113 patients with sustained VA showed that patients who had a mean VA rate of ≥200 bpm had a 65% incidence of syncope or near-syncope, compared with only 15% among patients with a rate <200 bpm.[273] Of the patients with VA ≥200 bpm, 34% did not experience syncope or presyncope. The risk of recurrent syncope and the overall long-term prognosis of patients with VA depend on the severity of the underlying cardiac disease substrates. Indications for ICDs in patients with syncope and suspected VA are predicated on the documentation of or the risk of developing lethal VA.[12]

4.2. Structural Conditions: Recommendations

Syncope occurs not infrequently in patients with underlying heart diseases. Comprehensive guidelines exist for diagnosis and management of many of these diseases, including sections on syncope. In this section, management of syncope is discussed in patients with underlying structural heart disease. The disease-specific ACC/AHA guidelines were assessed first, and then a comprehensive review of literature published since publication of these disease-specific guidelines was performed to ensure that prior recommendations about syncope remained current. If new published data were available, they were incorporated into the present document.

4.2.1. Ischemic and Nonischemic Cardiomyopathy: Recommendation

Recommendation for Ischemic and Nonischemic Cardiomyopathy		
COR	**LOE**	**Recommendation**
I	C-EO	**In patients with syncope associated with ischemic and nonischemic cardiomyopathy, GDMT is recommended.**[12,13]
N/A		Evaluation of syncope in patients with ischemic and nonischemic cardiomyopathy encompasses diagnosis and prognosis. Treatment of syncope is based on the specific cause of syncope, whereas treatment for the underlying cardiomyopathy impacts the long-term prognosis. A review of evidence supports previously published recommendations for patients with syncope in the presence of underlying cardiomyopathy. An ICD is recommended in patients with syncope of undetermined origin with clinically relevant and significant VA induced at the time of an EPS.[28] ICD therapy is also reasonable for patients with unexplained syncope and nonischemic dilated cardiomyopathy with significant LV dysfunction.[12,13,28]

4.2.2. Valvular Heart Disease: Recommendation

Recommendation for Valvular Heart Disease		
COR	**LOE**	**Recommendation**
I	C-EO	**In patients with syncope associated with valvular heart disease, GDMT is recommended.**[11]
N/A		Patients with aortic stenosis may experience syncope during exertion. The mechanism is often hemodynamic, as opposed to arrhythmic, because of inability to augment and sustain cardiac output. In patients with valvular heart disease causing syncope, treatment is recommended by the latest guidelines.[11] Specifically, aortic valve replacement is recommended in patients with severe aortic stenosis and syncope after other causes of syncope are also considered and excluded.

4.2.3. Hypertrophic Cardiomyopathy: Recommendation

Recommendation for HCM		
COR	**LOE**	**Recommendation**
I	C-EO	**In patients with syncope associated with HCM, GDMT is recommended.**[20]
N/A		A MEDLINE search and review of papers on syncope and HCM has been performed since the last guideline was published in 2011.[20] There are no new data that would alter the 2011 recommendations. Thus, the writing committee supports the previous recommendations pertaining to syncope in patients with HCM. Although there are no randomized trials, data from registries have shown consistently that unexplained syncope is an independent predictor for SCD and appropriate ICD discharges. The present writing committee concurs that ICD implantation is reasonable in patients with HCM presenting with ≥1 recent episodes of syncope suspected to be of arrhythmic nature.

4.2.4. Arrhythmogenic Right Ventricular Cardiomyopathy: Recommendations

Recommendations for ARVC		
COR	**LOE**	**Recommendations**
I	**B-NR**	**ICD implantation is recommended in patients with ARVC who present with syncope and have a documented sustained VA.[274–278]**
See Online Data Supplement 17.		ICD indications in patients with ARVC and sustained VA are no different than guidelines-based indications for secondary prevention of SCD in other diseases.[12]
IIa	**B-NR**	**ICD implantation is reasonable in patients with ARVC who present with syncope of suspected arrhythmic etiology.[274,275,277–279]**
See Online Data Supplement 17.		Unexplained or arrhythmic-appearing syncope in patients with ARVC has consistently been associated with increased risk of SCD or appropriate therapy after ICD implantation in multiple observational studies.[274–279]

4.2.5. Cardiac Sarcoidosis: Recommendations

Recommendations for Cardiac Sarcoidosis		
COR	**LOE**	**Recommendations**
I	**B-NR**	**ICD implantation is recommended in patients with cardiac sarcoidosis presenting with syncope and documented spontaneous sustained VA.[12,280–286]**
See Online Data Supplement 18.		ICD indications in patients with cardiac sarcoidosis and sustained VA are no different than guidelines- or consensus-based indications for secondary prevention of SCD.[12,286] Macroreentry around the granulomas is the most common mechanism of VA in patients with cardiac sarcoidosis.[280,281] Other mechanisms include triggered activity and abnormal automaticity due to myocardial inflammation.[282] Unlike AV block, the results of immunosuppression in patients with VA are controversial. Some studies have shown improvement with immunosuppression,[283] whereas others have shown no benefit and even harm due to worsening VA and aneurysm formation.[284,285]
I	**C-EO**	**In patients with cardiac sarcoidosis presenting with syncope and conduction abnormalities, GDMT is recommended.[12,286–289]**
See Online Data Supplement 18.		Patients with cardiac sarcoidosis and conduction abnormalities should be treated according to the most recent guidelines for cardiac pacing.[12] Patients with cardiac sarcoidosis and conduction abnormalities have a worse prognosis than that of patients with idiopathic AV block.[286,287] Immunosuppression can result in transient reversal of AV block; however, the reversibility is unpredictable.[287–289] As such, it is recommended to proceed with pacing according to the most recent guidelines regardless of AV block reversibility.
IIa	**B-NR**	**ICD implantation is reasonable in patients with cardiac sarcoidosis and syncope of suspected arrhythmic origin, particularly with LV dysfunction or pacing indication.[290–293]**
See Online Data Supplement 18.		The presence of myocardial noncaseating granulomas and inflammation puts patients at risk of having both AV block and VA, particularly in the presence of LV dysfunction. Patients with cardiac sarcoidosis and mild-to-moderate LV dysfunction have a substantial risk of developing VA.[290–293] In a multicenter study including 235 patients with cardiac sarcoidosis who received ICD therapy for primary or secondary prevention, including patients with syncope, 36% of patients received appropriate ICD therapy. Patients who received appropriate ICD therapies were more likely to be male and to have a history of syncope, lower LV ejection fraction, ventricular pacing on baseline ECG, and a secondary prevention indication than were those who did not receive appropriate ICD therapies.[292] Therefore, given the presence of a substrate for VA in patients with cardiac sarcoidosis, ICD implantation is reasonable in patients presenting with syncope suspected to be of arrhythmic origin.
IIa	**B-NR**	**EPS is reasonable in patients with cardiac sarcoidosis and syncope of suspected arrhythmic etiology.[294]**
See Online Data Supplement 18.		In patients with cardiac sarcoidosis, programmed electrical stimulation may help identify patients at risk of having VA. According to a study of 76 patients with cardiac sarcoidosis and no cardiac symptoms, 8 (11%) had inducible sustained VA. During a median follow-up of 5 years, 6 of 8 had VA or died, versus 1 of 68 in the noninducible group.[294]

4.3. Inheritable Arrhythmic Conditions: Recommendations

The prevalence of inherited arrhythmic conditions is low, rendering the clinical significance of an abnormal test a challenge. Few syncope-specific studies exist. Most studies of patients with inherited arrhythmias are open label or not randomized and often are uncontrolled. Most of the publications included other cardiac events, such as cardiac arrest and death, either at enrollment or as an outcome. Syncope of suspected arrhythmic cause has been correlated with increased risk of SCD, cardiac arrest, or overall cardiac death. Although ICD is effective in aborting cardiac arrest and presumably reducing risk of death in the patients with inheritable rhythm disorders, its impact on syncope recurrence is unknown.[25,26,220]

4.3.1. Brugada Syndrome: Recommendations

Brugada syndrome is defined as a genetic disease characterized by an increased risk of SCD and ST elevation with type 1 morphology ≥2 mm in ≥1 lead among the right precordial leads V1 and V2, occurring either spontaneously or after intravenous administration of Class I antiarrhythmic drugs. The prevalence is higher in Asian countries than in North America or Western Europe, ranging from 0.01% to 1.00%, with a significant male predominance.[295]

Recommendations for Brugada ECG Pattern and Syncope		
COR	**LOE**	**Recommendations**
IIa	**B-NR**	**ICD implantation is reasonable in patients with Brugada ECG pattern and syncope of suspected arrhythmic etiology.[296–300]**
See Online Data Supplement 19.		Syncope is a risk factor for cardiac arrhythmic events in patients with Brugada syndrome.[296,297] ICD implantation is reasonable in these patients; however, the benefit seems to be limited to patients with suspected arrhythmic syncope.[298] Patients with syncope consistent with a reflex-mediated mechanism should not undergo the implantation of an ICD. In a meta-analysis, the relative risk of cardiac events (SCD, syncope, or ICD shock) among patients with a history of syncope or SCD was approximately 3 times higher than among patients without a prior history of syncope or SCD.[296] Data from an international registry showed that the cardiac event rate per year was 7.7% in patients with aborted SCD, 1.9% in patients with syncope, and 0.5% in asymptomatic patients.[297] In a cohort including 203 patients with Brugada, VA occurred only in patients with syncope suspected to be arrhythmic in origin, at a rate of 5.5% per year. No SCD occurred in patients with nonarrhythmic syncope or with syncope of doubtful origin.[298]
IIb	**B-NR**	**Invasive EPS may be considered in patients with Brugada ECG pattern and syncope of suspected arrhythmic etiology.[297,301,302]**
See Online Data Supplement 19.		The value of EPS in assessing the mechanism of syncope in patients with Brugada is unknown. In large registries of patients with Brugada (PRELUDE and FINGER),[297,301] inducibility of VA was higher among patients with a prior history of syncope or SCD. However, the value of EPS in predicting prognosis in patients with Brugada is essentially unknown in patients with syncope. The role of inducibility of VA in identifying high-risk patients remains controversial.[301,302] Therefore, EPS may be considered only in patients with syncope suspected to be due to an arrhythmia and is not recommended in patients with reflex syncope.
III: No Benefit	**B-NR**	**ICD implantation is not recommended in patients with Brugada ECG pattern and reflex-mediated syncope in the absence of other risk factors.[303,304]**
See Online Data Supplement 19.		In a retrospective multicenter study, appropriate ICD therapy was limited to survivors of cardiac arrest, whereas none of the other patients with syncope and/or inducible ventricular fibrillation (VF) suffered an arrhythmic event.[303,304] Given the lack of benefit of ICD therapy in patients with reflex syncope and the known rate of inappropriate shocks and ICD complications in patients who receive an ICD,[51] ICD implantation is not recommended when the syncope mechanism is believed to be reflex mediated.

4.3.2. Short-QT Syndrome: Recommendation

Short-QT syndrome is a genetic disease characterized by palpitations, syncope, and increased risk of SCD, associated with a QTc interval ≤340 ms.[25,26] It is a rare condition. Limited data are available about its prognostic significance, particularly in the absence of documented VA. Invasive EPS has shown increased vulnerability to VF induction in most patients, yet the clinical significance of this finding remains unknown.[305] Quinidine therapy might provide some protection against VA; however, there are insufficient data to make any recommendations.[305,306]

Recommendation for Short-QT Syndrome		
COR	**LOE**	**Recommendation**
IIb	**C-EO**	**ICD implantation may be considered in patients with short-QT pattern and syncope of suspected arrhythmic etiology.**
See Online Data Supplement 20.		The prevalence of short-QT syndrome is very low, ranging from 0.02% to 1.63%.[305,307–312] There is no evidence that syncope in patients with short-QT pattern is a risk factor for cardiac arrest in the absence of documented VT or VF. Therefore, ICD implantation may be limited to patients with suspected arrhythmic syncope, particularly in the presence of a family history of SCD.[306]

4.3.3. Long-QT Syndrome: Recommendations

LQTS is diagnosed in the presence of QTc ≥500 ms or LQTS risk score ≥3.5 when secondary causes have been excluded or in the presence of a pathogenic mutation in 1 of the LQTS genes. It can also be diagnosed when the QTc is 480 to 499 ms in a patient presenting with syncope.[25] There are several genetic forms of LQTS, which affect presentation and response to therapy. Given that syncope is often the result of an arrhythmic event in patients with LQTS, early recognition and treatment are needed to avoid recurrences, which could present as cardiac arrest or SCD. This is particularly true in the pediatric population, where significant overlap exists in the clinical presentation of patients with VVS and arrhythmic syncope.[313,314] Attention to the triggers and presence of palpitations preceding syncope onset have been helpful in diagnosing an arrhythmic etiology.[315]

Patients with LQTS and syncope should adhere to the lifestyle changes previously published, including avoidance of strenuous activity in LQTS1, and drugs known to prolong QT interval in all patients with LQTS.[25]

Recommendations for LQTS		
COR	**LOE**	**Recommendations**
I	**B-NR**	**Beta-blocker therapy, in the absence of contraindications, is indicated as a first-line therapy in patients with LQTS and suspected arrhythmic syncope.[316–318]**
See Online Data Supplement 21.		In the International Long QT Registry, patients who experienced ≥1 episode of syncope had a 6- to 12-fold increase in the risk of subsequent fatal/near-fatal events, independent of QTc duration. Beta-blocker therapy was associated with a significant reduction in the risk of recurrent syncope and subsequent fatal/near-fatal events. The response to beta blockers depends on the genotype, and not all beta blockers are the same.[316,319] Patients with LQTS1 appear to respond better than patients with LQTS2 and LQTS3.[316,320]
IIa	**B-NR**	**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.[317,320–324]**
See Online Data Supplement 21.		Cardiac events can occur in patients receiving beta-blocker therapy, with a prevalence ranging from 10% to 32%, depending on the genotype.[316,317] Many patients who appear to not respond to beta blockers are poorly compliant or do not tolerate the medication.[317] Therefore, ICD implantation is reasonable in patients with LQTS who continue to have syncope despite beta-blocker therapy and in those who cannot tolerate beta-blocker therapy. In a study of 459 patients with genetically confirmed LQTS who received an ICD, syncope was a predictor of appropriate therapy.[322]
IIa	**C-LD**	**Left cardiac sympathetic denervation (LCSD) 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.[325–327]**
See Online Data Supplement 21.		LCSD has been shown to be associated with a large and significant clinical benefit in patients with symptomatic LQTS who are either refractory or intolerant to beta-blocker therapy.[325,326] LCSD also reduces shocks in patients with an ICD during arrhythmia storms. Therefore, LCSD can be beneficial in patients with recurrent syncope despite beta blockade, in those who cannot tolerate beta-blocker therapy, and in those with frequent shocks from their ICD. However, LCSD alone does not completely prevent cardiac events, including SCD, during long-term follow-up.

4.3.4. Catecholaminergic Polymorphic Ventricular Tachycardia: Recommendations

CPVT is characterized by the presence of catecholamine-induced (often exertional) bidirectional VT or polymorphic VT in the setting of a structurally normal heart and normal resting ECG.[328,329] In patients with CPVT, 60% have a mutation in either the gene encoding the cardiac ryanodine receptor (*RyR2*) (autosomal dominant) or in the cardiac calsequestrin gene (*CASQ2*) (autosomal recessive).[330–333] The prevalence of the disease is estimated to be around 0.1 per 1000 patients. Patients usually present in the first or second decade of life with stress-induced syncope.[25]

Recommendations for CPVT		
COR	**LOE**	**Recommendations**
I	**C-LD**	**Exercise restriction is recommended in patients with CPVT presenting with syncope of suspected arrhythmic etiology.[328,334,335]**
See Online Data Supplements 22 and 23.		The presence of VA in patients with CPVT has been shown to correlate with increases in heart rate, highlighting the role of the sympathetic nervous system in arrhythmogenesis.[328,334] Therefore, exercise restriction, including avoidance of heavy exercise and competitive sports, is recommended in all patients with CPVT.[335]
I	**C-LD**	**Beta blockers lacking intrinsic sympathomimetic activity are recommended in patients with CPVT and stress-induced syncope.[329,334,336–339]**
See Online Data Supplements 22 and 23.		Beta blockers should be first-line therapy in patients with CPVT, as they have been shown to suppress exercise-induced arrhythmias. However, they are not always completely protective.[329,334,336] The variability in outcome with beta-blocker therapy is due to multiple factors, including dosing and compliance.[337,338] Repeat exercise testing and cardiac monitoring to document arrhythmia suppression can be reassuring.[334,339]
IIa	**C-LD**	**Flecainide is reasonable in patients with CPVT who continue to have syncope of suspected VA despite beta-blocker therapy.[319,320]**
See Online Data Supplements 22 and 23.		Despite beta-blocker therapy, breakthrough arrhythmias occur in patients with CPVT because of treatment failure, noncompliance, and subtherapeutic dosing. The addition of flecainide to conventional therapy has been shown to partly or completely suppress exercise-induced VA.[340] In patients intolerant of beta-blocker therapy, flecainide is useful as monotherapy.[341]
IIa	**B-NR**	**ICD therapy is reasonable in patients with CPVT and a history of exercise- or stress-induced syncope despite use of optimal medical therapy or LCSD.[271,342,343]**
See Online Data Supplements 22 and 23.		ICD therapy appears to reduce mortality rate in patients with CPVT and syncope or VA refractory to medical therapy. However, VT storms in patients with CPVT may not always respond to ICD shocks,[344] and shocks may precipitate early recurrence of arrhythmia because of their painful nature with resultant adrenergic state. Furthermore, the effectiveness of ICD shock therapy in CPVT depends on the mechanism of the VA, with greater success noted when shocks are delivered for VF.[345] ICD implantation should be performed in conjunction with beta-blocker therapy or LCSD when available.[342] Careful programming, including long detection intervals with high cutoff rate, is recommended to decrease the prevalence of inappropriate shocks.[342,343]
IIb	**C-LD**	**In patients with CPVT who continue to experience syncope or VA, verapamil with or without beta-blocker therapy may be considered.[346,347]**
See Online Data Supplements 22 and 23.		Verapamil alone or in combination with beta blockers helps suppress arrhythmias in patients with CPVT,[347] including delaying the onset of exercise-induced ventricular ectopy.[346,347]

Recommendations for CPVT (Continued)		
COR	LOE	Recommendations
IIb	C-LD	**LCSD may be reasonable in patients with CPVT, syncope, and symptomatic VA despite optimal medical therapy.[348–350]**
See Online Data Supplements 22 and 23.		When syncope occurs despite optimal medical therapy, LCSD may be a reasonable therapy.[348–350] In a worldwide cohort study, the percentage of patients with major cardiac events despite optimal medical therapy was reduced 68% after LCSD.[349]

4.3.5. Early Repolarization Pattern: Recommendations

Early repolarization pattern is characterized by a distinct J point and ST elevation in the lateral or inferolateral leads. The pattern is more prevalent in young athletes, particularly African Americans, with 70% of the subjects being male.[351] Early repolarization ECG pattern (>1 mm) in the inferior/lateral leads occurs in 1% to 13% of the general population and in 15% to 70% of idiopathic VF cases.[352–354] Furthermore, it has been shown in population-based studies to be associated with increased risk of cardiac death.[352,353,355–357] One study showed that the presence of a J wave increased the risk of VF from 3.4/100 000 to 11.0/100 000.[353] However, given the low incidence of VF in the general population, the absolute risk in patients with early repolarization remains low. In patients with syncope, the clinical significance of the early repolarization pattern is unknown.

Recommendations for Early Repolarization Pattern		
COR	LOE	Recommendations
IIb	C-EO	**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.**
N/A		ICD implantation may be considered in patients with early repolarization pattern and suspected cardiac syncope if they have a family history of unexplained SCD, VF, or polymorphic VT with documented early repolarization pattern in the affected family member.[358,359]
III: Harm	B-NR	**EPS should not be performed in patients with early repolarization pattern and history of syncope in the absence of other indications.[359]**
See Online Data Supplement 24.		In a multicenter study including 81 patients with early repolarization syndrome and aborted SCD who underwent EPS, VF was inducible in only 22% of cases. The VF recurrence rate was similar in patients who were inducible and in those who were noninducible.[359] Given the high prevalence of early repolarization, the possibility of inducing VF in healthy individuals, and the limited value of ventricular programmed stimulation in risk stratification, EPS is not recommended in patients with early repolarization and syncope in the absence of other cardiac indications.[352,353,360]

5. REFLEX CONDITIONS: RECOMMENDATIONS

5.1. Vasovagal Syncope: Recommendations

VVS is the most common cause of syncope and a frequent reason for ED visits.[66] The underlying pathophysiology of VVS results from a reflex causing hypotension and bradycardia, triggered by prolonged standing or exposure to emotional stress, pain, or medical procedures.[361–365] An episode of VVS is typically associated with a prodrome of diaphoresis, warmth, and pallor, with fatigue after the event. Given the benign nature of VVS and its frequent remissions, medical treatment is usually not required unless conservative measures are unsatisfactory. In some patients, effective treatment is needed, as syncopal events may result in injury and an impaired quality of life (QoL).[366–368] Despite the need and substantial efforts by investigators, there are limited evidence-based therapeutic options.[369] Preliminary data from cardiac ganglia plexi ablation in treating selected patients with VVS are encouraging but still insufficient to make recommendations at this time.[370–372] See Figure 4 for the algorithm for treatment of VVS.

Recommendations for VVS		
COR	LOE	Recommendations
I	C-EO	**Patient education on the diagnosis and prognosis of VVS is recommended.**
See Online Data Supplements 25 and 26.		In all patients with the common faint or VVS, an explanation of the diagnosis, education targeting awareness of and possible avoidance of triggers (eg, prolonged standing, warm environments, coping with dental and medical settings), and reassurance about the benign nature of the condition should be provided.
IIa	B-R	**Physical counter-pressure maneuvers can be useful in patients with VVS who have a sufficiently long prodromal period.[373–375]**
See Online Data Supplements 25 and 26.		Patients with a syncope prodrome should be instructed to assume a supine position to prevent a faint and minimize possible injury. In patients with a sufficiently long prodrome, physical counter-maneuvers (eg, leg crossing, limb and/or abdominal contraction, squatting) are a core management strategy. In a randomized, parallel, open-label trial, leg crossing with conventional therapy (ie, fluid, salt intake, counseling, and avoidance) was superior to conventional therapy in preventing syncope recurrence.[375]

Recommendations for VVS (Continued)		
COR	**LOE**	**Recommendations**
IIa	**B-R**	**Midodrine is reasonable in patients with recurrent VVS with no history of hypertension, HF, or urinary retention.[376–380]**
See Online Data Supplements 25 and 26.		Midodrine is a prodrug that is metabolized to desglymidodrine, which is a peripherally active alpha-agonist used to ameliorate the reduction in peripheral sympathetic neural outflow responsible for venous pooling and vasodepression in VVS. Studies on the efficacy of midodrine support its use. In a meta-analysis of 5 RCTs in adults and children, midodrine was associated with a 43% reduction in syncope recurrence.[318,376,378,379,381]
IIb	**B-R**	**The usefulness of orthostatic training is uncertain in patients with frequent VVS.[382–386]**
See Online Data Supplements 25 and 26.		There are 2 main methods of orthostatic training. Patients undergo repetitive tilt-table tests in a monitored setting until a negative tilt-table test occurs and then are encouraged to stand quietly against a wall for 30 to 60 minutes daily, or patients simply standing quietly against a wall at home for a prolonged period of time daily. RCTs have not shown a sustained benefit in reducing episodes of syncope recurrence with either option.[382,383,385,387]
IIb	**B-R**	**Fludrocortisone might be reasonable for patients with recurrent VVS and inadequate response to salt and fluid intake, unless contraindicated.[388,389]**
See Online Data Supplements 25 and 26.		Fludrocortisone has mineralocorticoid activity resulting in sodium and water retention and potassium excretion, which results in increased blood volume. In a pediatric population, an RCT found more recurrent symptoms in the fludrocortisone arm than in the placebo arm.[389] Serum potassium level should be monitored because of potential drug-induced hypokalemia. POST II (Prevention of Syncope Trial II) reported a marginally insignificant 31% risk reduction in adults with moderately frequent VVS, which was significant in patients after a 2-week dose stabilization period.[388]
IIb	**B-NR**	**Beta blockers might be reasonable in patients 42 years of age or older with recurrent VVS.[390–393]**
See Online Data Supplements 25 and 26.		RCTs on the efficacy and effectiveness of beta blockers for the prevention of syncope have been negative.[64,390–393] However, in a meta-analysis of a prespecified, prestratified substudy of POST I and a large observational study, an age-dependent benefit of beta blockers among patients ≥42 years of age was found, compared with those of younger age.[394,395]
IIb	**C-LD**	**Encouraging increased salt and fluid intake may be reasonable in selected patients with VVS, unless contraindicated.[396–399]**
N/A		Evidence for the effectiveness of salt and fluid intake for patients with VVS is limited. Nonetheless, in patients with recurrent VVS and no clear contraindication, such as a history of hypertension, renal disease, HF, or cardiac dysfunction, it may be reasonable to encourage ingestion of 2 to 3 L of fluid per day and a total of 6 to 9 g (100 to 150 mmol) of salt per day, or about 1 to 2 heaping teaspoonfuls. The long-term balance of risks and benefits of a strategy of increasing salt and water intake is unknown.
IIb	**C-LD**	**In selected patients with VVS, it may be reasonable to reduce or withdraw medications that cause hypotension when appropriate.[400]**
N/A		A careful examination of the patient's history for medications that may lower blood pressure (hypotensive agents) should be performed. Care should be taken to withdraw or reduce medications only where safe to do so and in conjunction with the prescribing healthcare provider.
IIb	**C-LD**	**In patients with recurrent VVS, a selective serotonin reuptake inhibitor might be considered.[393,401,402]**
See Online Data Supplements 25 and 26.		Serotonin has central neurophysiological effects on blood pressure and heart rate and acutely induces syncope during tilt-table testing.[403] Three small RCTs on selective serotonin reuptake inhibitors have been conducted on the effectiveness of fluoxetine and paroxetine in preventing syncope, with contradictory evidence of effectiveness.[393,401,402]

5.2. Pacemakers in Vasovagal Syncope: Recommendation

Pacemakers might seem to be an obvious therapy for VVS, given that bradycardia and asystole are present during some spells. Numerous observational studies and RCTs have assessed whether pacemakers are efficacious in preventing syncope.[404–409] It is becoming clear that strict patient selection on the basis of documented asystole during clinical syncope is important, and that observation combined with a tilt-table test that induces minimal or no vasodepressor response may increase the likelihood of a response to pacing. This is because a positive tilt-table test might identify patients who are likely to also have a vasodepressor response during VVS and therefore not respond as well to permanent pacing. As noted in Section 1.1, the recommendation in this section was based on a separately commissioned systematic review of the available evidence, the results of which were used to frame our decision making. Full details are provided in the ERC's systematic review report.[9]

Recommendation for Pacemakers in VVS		
COR	**LOE**	**Recommendation**
IIb	**B-R[SR]**	**Dual-chamber pacing might be reasonable in a select population of patients 40 years of age or older with recurrent VVS and prolonged spontaneous pauses.[404–408,410]**
See Online Data Supplements 27 and 28.		Among patients with a positive tilt-table test, a benefit of pacing for treatment of recurrent syncope was evident as compared with medical or no therapy in open-label trials,[52,404,406,410–412] but this result must be interpreted with caution because of the possibility of outcome ascertainment bias. In 2 RCTs, there was no statistically significant benefit seen with active pacing.[407,408] However, in a select population of patients >40 years of age with recurrent syncope and documented spontaneous pauses ≥3 seconds correlated with syncope or an asymptomatic pause ≥6 seconds, dual-chamber pacing reduced syncope recurrence. There was less benefit in patients with a positive tilt-table test that induced a vasodepressor response.[405]

SR indicates systematic review.

5.3. Carotid Sinus Syndrome: Recommendations

Carotid sinus syndrome is associated with mechanical manipulation of the carotid sinus, either spontaneously or with carotid sinus massage. It is diagnosed by the reproduction of clinical syncope during carotid sinus massage, with a cardioinhibitory response if asystole is >3 seconds or if there is AV block, or a significant vasodepressor response if there is ≥50 mm Hg drop in systolic blood pressure, or a mixed cardioinhibitory and vasodepressor response. It occurs more commonly in men >40 years of age[413,414] and is due to an abnormal reflex attributed to baroreceptor and possibly medulla dysfunction.[415,416] Carotid sinus massage should be performed sequentially over the right and left carotid artery sinus in both the supine and upright positions for 5 seconds each, with continuous beat-to-beat heart rate monitoring and blood pressure measurement.[417] Contraindications to performing carotid sinus massage include auscultation of carotid bruit and transient ischemic attack, stroke, or myocardial infarction within the prior 3 months, except if carotid Doppler excludes significant stenosis.[418]

Recommendations for Carotid Sinus Syndrome

COR	LOE	Recommendations
IIa	B-R	**Permanent cardiac pacing is reasonable in patients with carotid sinus syndrome that is cardioinhibitory or mixed.**[413,419–426]
See Online Data Supplements 29–32.		Syncope recurred in fewer patients treated with pacing than in untreated patients, with observation periods up to 5 years.[420,423] In 3 controlled, open-label trials, the relative risk reduction of syncope recurrence with pacemaker implantation was 76%.[409,427–429] There are no large RCTs.
IIb	B-R	**It may be reasonable to implant a dual-chamber pacemaker in patients with carotid sinus syndrome who require permanent pacing.**[427–430]
See Online Data Supplements 29–32.		Evidence for dual-chamber pacing versus single-chamber pacing in carotid sinus hypersensitivity is limited to a few small RCTs and limited observational data.[409,418,427–429] Although mixed, the data suggest dual-chamber pacing may prevent hemodynamic compromise and improve symptom recurrence in older adults who may have concomitant sinus node dysfunction or conduction system disease.

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.[431–437] Appropriate investigations should be undertaken to determine an underlying etiology, including causes that may be reversible.[431,433–436] Evidence for treatment is limited mainly to case reports, small case series, and small observational studies.[431,433–436] 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.[436]

6. ORTHOSTATIC HYPOTENSION: RECOMMENDATIONS

6.1. Neurogenic Orthostatic Hypotension: Recommendations

OH involves excessive pooling of blood volume in the splanchnic and leg circulations. With standing, venous

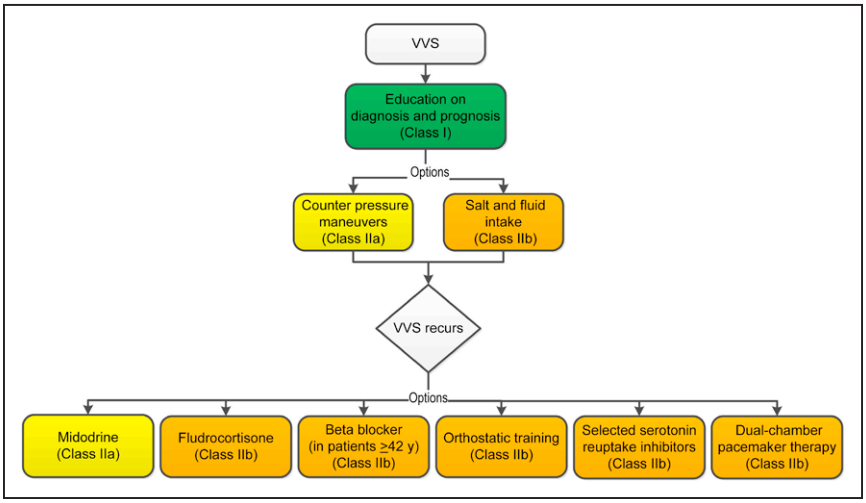

Figure 4. Vasovagal Syncope. Colors correspond to Class of Recommendation in Table 1. VVS indicates vasovagal syncope.

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return to the heart drops, with a resultant decrease in cardiac output.[31] Normally, the autonomic nervous system provides compensatory changes in vascular tone, heart rate, and cardiac contractility. In some individuals, this response may be defective or inadequate.[31] In neurogenic OH, the vasoconstrictor mechanisms of vascular tone may be inadequate because of neurodegenerative disorders, such as multiple system atrophy, pure autonomic failure, Parkinson's disease, and autonomic peripheral neuropathies, such as those due to diabetes mellitus and other systemic diseases.[31] Neurogenic OH may present clinically as classic or delayed OH. Most commonly, OH is due to dehydration or medications, such as diuretics and vasodilators. Syncope caused by OH conditions occurs in the upright position. See Figure 5 for the algorithm for treatment of OH.

Recommendations for Neurogenic OH

COR	LOE	Recommendations
I	B-R	**Acute water ingestion is recommended in patients with syncope caused by neurogenic OH for occasional, temporary relief.[438,439]**
See Online Data Supplements 33–35.		In neurogenic OH, acute water ingestion can temporarily restore orthostatic tolerance.[438–444] The pressor effect of water is most likely sympathetically driven, with the peak effect occurring 30 minutes after ingestion of ≥240 mL and additional benefit seen with ≥480 mL.[398,441,442] The presence of glucose or salt may reduce this effect by splanchnic vasodilatation or a decreased osmopressor response, respectively.[397,439] Acute water ingestion for temporary relief of OH is not intended for routine or long-term use.[24]
IIa	C-LD	**Physical counter-pressure maneuvers can be beneficial in patients with neurogenic OH with syncope.[374,445–450]**
See Online Data Supplements 33–35.		Isometric contraction, such as by leg crossing, lower body muscle tensing, and maximal force handgrip, can increase blood pressure, with the largest effect occurring with squatting versus other counter-pressure maneuvers.[374,445–450] Leg crossing increases cardiac output in patients with neurogenic hypotension.[447] Similar or larger benefit would be expected with squatting and other isometric contraction.[449] The benefit is limited to patients with sufficient prodrome and the ability to perform these maneuvers adequately and safely.[449]
IIa	C-LD	**Compression garments can be beneficial in patients with syncope and OH.[451–455]**
See Online Data Supplements 33–35.		In patients with OH, including older adult patients and those with neurogenic etiologies, compression garments can improve orthostatic symptoms and blunt associated decreases in blood pressure.[451–456] The garments should be at least thigh high and preferably include the abdomen, as shorter garments have not been proved to be beneficial.[457]
IIa	B-R	**Midodrine can be beneficial in patients with syncope due to neurogenic OH.[458–467]**
See Online Data Supplements 33–35.		Midodrine improves symptoms of OH in patients with neurogenic OH.[458–467] There is a dose-dependent effect, usually corresponding to an increase in standing blood pressure.[459,460,462,463,466,467] Its use may be limited by supine hypertension, and other common side effects include scalp tingling, piloerection, and urinary retention.[459,460,463,467]
IIa	B-R	**Droxidopa can be beneficial in patients with syncope due to neurogenic OH.[380,468–471]**
See Online Data Supplements 33–35.		Droxidopa improves symptoms of neurogenic OH due to Parkinson disease, pure autonomic failure, and multiple system atrophy.[380,468,470,471] Droxidopa might reduce falls, according to small studies.[472] Use of carbidopa in patients with Parkinson disease may decrease the effectiveness of droxidopa.[380] Use and titration of droxidopa may be limited by supine hypertension,[380,469] headache, dizziness, and nausea.[468,470–472]
IIa	C-LD	**Fludrocortisone can be beneficial in patients with syncope due to neurogenic OH.[473–476]**
See Online Data Supplements 33–35.		Fludrocortisone increases plasma volume, with a resultant improvement in symptoms of OH.[473,477,478] When taken regularly, fludrocortisone may prevent OH, at least in astronauts after space flight.[476] Supine hypertension may be a limiting factor. When supine hypertension is present, other medications should be used before fludrocortisone. Other side effects commonly seen include edema, hypokalemia, and headache, but more serious adverse reactions, such as adrenal suppression and immunosuppression, can also occur with doses >0.3 mg daily.[479,480]
IIb	C-LD	**Encouraging increased salt and fluid intake may be reasonable in selected patients with neurogenic OH.[396,398,441,443,444]**
See Online Data Supplements 33–35.		Although the data are limited for salt and fluid supplementation in patients with OH, these 2 treatments may improve blood pressure while decreasing symptoms from OH.[396,398,439–444] Salt supplementation (eg, 6 to 9 g [100 to 150 mmol; about 1 to 2 teaspoons] of salt per day) increases plasma volume, with limited benefit in patients with already high salt intake.[396] Water ingestion increases the blood pressure via a pressor effect, most likely mediated by sympathetic activation, with a peak effect approximately 30 minutes after ingestion.[398,439,441–443] This additional salt and fluid intake may not be beneficial in patients with history of hypertension, renal disease, HF, or cardiac dysfunction, and the long-term effects of these treatments, including the benefits and risks, is unknown.
IIb	C-LD	**Pyridostigmine may be beneficial in patients with syncope due to neurogenic OH who are refractory to other treatments.[466,481,482]**
See Online Data Supplements 33–35.		In patients with autonomic failure and neurogenic OH, pyridostigmine is able to improve orthostatic tolerance through increases in peripheral vascular resistance and blood pressure.[481,482] Side effects include nausea, vomiting, abdominal cramping, sweating, salivation, and urinary incontinence.[483]
IIb	C-LD	**Octreotide may be beneficial in patients with syncope and refractory recurrent postprandial or neurogenic OH.[484–487]**
See Online Data Supplements 33–35.		Splanchnic circulation pooling can contribute to OH, and this pooling can worsen in the postprandial period.[484–487] Octreotide reduces splanchnic blood flow by approximately 20%,[486] which prevents postprandial hypotension, increases blood pressure, and improves orthostatic tolerance.[484–487]

6.2. Dehydration and Drugs: Recommendations

Syncope related to medication becomes prevalent particularly in older adults, who frequently have multiple comorbidities requiring treatment and are prone to polypharmacy effects.[488–490] Cessation of offending medications is usually key for symptomatic improvement, but often feasibility of cessation of medications is limited by the necessity of the treatments.[491–493] Dehydration may manifest along a spectrum of symptoms, ranging from tachycardia to shock, depending on whether a person has compensated or uncompensated hypovolemia.[494] Orthostatic tolerance worsens with dehydration and is exacerbated by heat stress, which promotes vasodilation.[495–497] Rehydration, whether by intravenous or oral formulation, should include sodium supplementation for more rapid recovery.[21,498–501]

Recommendations for Dehydration and Drugs		
COR	**LOE**	**Recommendations**
I	C-LD	**Fluid resuscitation via oral or intravenous bolus is recommended in patients with syncope due to acute dehydration.[438,499,501–504]**
See Online Data Supplements 36 and 37.		Fluid resuscitation is recommended for syncope secondary to both dehydration and exercise-associated hypotension. The latter is likely due to peripheral vasodilation and vasovagal physiology.[438,495,504,505] Both dehydration and heat stress worsen orthostatic tolerance.[495–497] Oral fluid bolus may require less volume than intravenous fluid infusion to have a similar treatment effect because oral fluid loading has a pressor effect.[398,438,440–444,502] Beverages with increased sodium concentration (closer to normal body osmolality) rehydrate faster than beverages with lower sodium concentration or increased osmolality (eg, because of glucose content).[498–501,503,506]
IIa	B-NR	**Reducing or withdrawing medications that may cause hypotension can be beneficial in selected patients with syncope.[488–490,492,507–510]**
See Online Data Supplements 36 and 37.		Syncope is a commonly reported adverse drug reaction, often resulting in hospital admission.[488,489] The prevalence of medication-related syncope appears higher in older patients.[491,492,507,510] Several drug classes have been implicated in syncope, including diuretics, vasodilators, venodilators, negative chronotropes, and sedatives.[488–490,492,507–510] Close supervision during adjustment of medications is frequently required because of potential worsening of preexisting supine hypertension or cardiac arrhythmias.[491–493,511] Other factors to consider include frailty, HF and/or cardiac dysfunction, and the use of a large number of medications causing adverse effects because of drug-drug interactions.[488,507,511–513]
IIa	C-LD	**In selected patients with syncope due to dehydration, it is reasonable to encourage increased salt and fluid intake.[396,498–501,503]**
See Online Data Supplements 36 and 37.		In patients with dehydration, sodium supplementation improves plasma volume and improves orthostatic tolerance.[396,499,503] This additional dietary sodium may be provided as sodium tablets or sodium already dissolved in beverages.[396,498–500,503] Higher-sodium-content beverages with osmolality comparable to normal body osmolality may rehydrate faster than lower-sodium-content beverages.[498–501,503] This treatment option is not appropriate for patients with cardiac dysfunction or HF, uncontrolled hypertension, or chronic kidney disease.[19]

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.[38] 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.[38] The pathophysiology is quite varied. One condition of note is POTS, in which upright posture results in an apparently inappropriate tachycardia, usually with heart rates >120 bpm.[24]

Although syncope occurs in patients with POTS, it is relatively infrequent, and there is little evidence that the syncope is due to POTS.[24,514] Treatments that improve symptoms of POTS might decrease the occurrence of syncope, although this is unknown.[24,514–523] For further guidance on the management of POTS, we refer readers to the HRS consensus statement.[24]

8. PSEUDOSYNCOPE: RECOMMENDATIONS

Psychogenic pseudosyncope is a syndrome of apparent loss of consciousness occurring in the absence of impaired cerebral perfusion or function. Psychogenic pseudosyncope is believed to be a conversion disorder—in essence, an external somatic manifestation or response to internal psychological stresses. It is an involuntary response and should not be confused with malingering or Munchausen syndrome. Psychogenic pseudosyncope and pseudoseizures may be the same condition. The clinical distinction between the two is based on whether prominent jerky muscle movements simulating seizure activity are reported by witnesses. In the absence of associated jerky movements, the patient is likely to be referred for evaluation of syncope.[30,229,524] Psychogenic pseudosyncope does not

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result in a true loss of consciousness, but it is included in the present document because patients appear to exhibit syncope and therefore are referred for evaluation of syncope.

Several key clinical features are suggestive of the diagnosis of psychogenic pseudosyncope. None alone, however, provides a definitive diagnosis. Patients with psychogenic pseudosyncope are often young females with a higher prevalence of preexisting VVS or a history of physical and/or sexual abuse.[229,525] The apparent duration of loss of consciousness is often long (5 to 20 minutes), and episodes are frequent.[525] Some common characteristics include closed eyes, lack of pallor and diaphoresis, and usually little physical harm.[526] A normal pulse, blood pressure, or EEG during a psychogenic pseudosyncope episode can be documented.[229] Although many patients with pseudosyncope can be diagnosed with a careful history, occasionally tilt-table testing with or without transcranial Doppler and monitoring of an EEG is helpful.

Recommendations for the Treatment of Pseudosyncope

COR	LOE	Recommendations
IIb	C-LD	**In patients with suspected pseudosyncope, a candid discussion with the patient about the diagnosis may be reasonable.[30,527–529]**
See Online Data Supplements 38 and 39.		Some reports suggest that patients benefit from being informed of the suspected diagnosis in a clear but sympathetic manner that also acknowledges the involuntary nature of the attacks.[30,527,528]
IIb	C-LD	**Cognitive behavioral therapy may be beneficial in patients with pseudosyncope.[530–532]**
See Online Data Supplements 38 and 39.		Uncontrolled studies suggest that psychotherapy, particularly cognitive behavioral therapy, may be beneficial in conversion disorders.[530–532] One RCT reported that cognitive behavioral therapy provided a non–statistically significant trend toward improvement in pseudosyncope at 3 months.[530] There are no data that support significant benefit from pharmacotherapy.[529]

9. UNCOMMON CONDITIONS ASSOCIATED WITH SYNCOPE

Syncope has been reported in many uncommon diseases, according to case reports. However, specific conditions may predispose the patient to various types of syncope. Table 9 provides a list of less common conditions associated with syncope. It is not intended as a reference for differential diagnosis or a complete synopsis of all conditions associated with syncope. Furthermore, it is not necessary to fully evaluate for all these causes when the etiology remains elusive. Most of these presentations rarely cause syncope, and data are sparse. If the cause for syncope is unclear, these conditions could be included in the differential diagnosis on the basis of other clinical characteristics and/or historical features.

10. AGE, LIFESTYLE, AND SPECIAL POPULATIONS: RECOMMENDATIONS

10.1. Pediatric Syncope: Recommendations

Syncope is common in the pediatric population. By 18 years of age, it is estimated that 30% to 50% of children experience at least 1 fainting episode, and syncope accounts for 3% of all pediatric ED visits.[617–622] The incidence is higher in females and peaks between 15 to 19 years of age.[617] Neurally mediated syncope accounts for 75% of pediatric syncope, followed by psychogenic or unexplained syncope in 8% to 15% of cases.[623] Breath-holding spells are a form of syncope unique to the pediatric population. Cyanotic breath-holding spells typically occur from age 6 months to age 5 years and may be due to desaturation caused by forced expiration during crying. Pallid breath-holding spells are seen in the first 1 to 2 years of age and may be an early form of VVS. The latter episodes are associated with significant bradycardia and prolonged asystole. Pediatric cardiac syncope may result from obstruction to blood flow (HCM, aortic stenosis, pulmonary hypertension), myocardial dysfunction (myocarditis, cardiomyopathy, congenital coronary anomaly, or post–Kawasaki disease) or a primary arrhythmic etiology (LQTS, CPVT, Brugada syndrome, ARVC, or Wolff-Parkinson-White syndrome).

A detailed history with careful attention to the events leading up to the syncope and a complete physical examination can guide practitioners in differentiating the life-threatening causes of syncope (with potential for injury or SCD) from the more common and benign neurally mediated syncope. A detailed family history, with particular attention to premature SCD among first- and second-degree relatives and the manner in which those deaths occurred, is helpful. Given that many of the causes of non-CHD cardiac syncope in children who do not have a form of CHD are similar to those experienced in an adult cohort (LQTS, HCM, Wolff-Parkinson-White, Brugada, and ARVC), interventions recommended for adults with similar conditions presenting with syncope can be applied in children.

Recommendations for Pediatric Syncope		
COR	**LOE**	**Recommendations**
I	**C-LD**	**VVS evaluation, including a detailed medical history, physical examination, family history, and a 12-lead ECG, should be performed in all pediatric patients presenting with syncope.[315,618,620,624–630]**
See Online Data Supplement 40.		Although VVS is the most common cause of pediatric syncope, cardiac syncope does represent 1.5% to 6% of pediatric cases (usually defined as up to 18 years of age).[617,619,620,629,631,632] Characteristics of presenting signs and symptoms differentiating VVS from cardiac causes of syncope are generally similar to those in adults. A family history of VVS and early SCD should be sought. VVS occurs in 33% to 80% of children with syncope.[624,628] Risk factors that raise suspicion of a cardiac etiology include the absence of prodromal symptoms, presence of preceding palpitations within seconds of loss of consciousness, lack of a prolonged upright posture, syncope during exercise or in response to auditory or emotional triggers, family history of SCD, abnormal physical examination, and abnormal ECG,[626,627] although the specificity is modest.[618,627,630,633] It should be remembered that children may not be able to clearly communicate specific symptoms. Exertional syncope has been associated with LQTS and CPVT.[315,318,337,630,634] Regardless of symptoms, exertional syncope, especially mid-exertional syncope, should result in a high index of suspicion for a cardiac etiology.[633]
I	**C-LD**	**Noninvasive diagnostic testing should be performed in pediatric patients presenting with syncope and suspected CHD, cardiomyopathy, or primary rhythm disorder.[315,318,618,625,627,630,633]**
See Online Data Supplement 40.		Channelopathies are major causes of cardiac-related syncope in young people. They may be associated with a family history of SCD, and they increase the risk of SCD in these patients.[315,337,630,632,634,635] Exercise stress testing may be helpful in the diagnosis of channelopathies, such as LQTS and CPVT, which have adrenergically mediated arrhythmias. Extended monitoring is reasonable when an arrhythmia diagnosis is suspected. The types of monitoring devices, their clinical utility, and their limitations are available in Table 8. Prolonged heart rhythm monitoring can often provide a correlation between symptoms and an arrhythmia. In 5 retrospective studies of prolonged monitoring in 87 children with either syncope or presyncope, the mean diagnostic yield was 43%.[636–640] Bradyarrhythmias and high-grade AV block or asystole, as well as tachyarrhythmias, SVT, and polymorphic VT, were documented.[636–640] The diagnostic yield of an ICM is higher if the clinical indication was exertional syncope or the patient had underlying CHD.[637,639,640]
I	**C-EO**	**Education on symptom awareness of prodromes and reassurance are indicated in pediatric patients with VVS.**
See Online Data Supplement 40.		Management of children with VVS should include reassurance about the generally benign nature of this condition.[641,642] Treatment should emphasize symptom awareness and avoidance of precipitating factors that might worsen the condition, such as dehydration, standing for prolonged periods of time, hot crowded environments, and diuretic intake.
IIa	**C-LD**	**Tilt-table testing can be useful for pediatric patients with suspected VVS when the diagnosis is unclear.[624,629,643–650]**
See Online Data Supplement 40.		Tilt-table testing has a diminishing role in the diagnosis of children with unexplained syncope. The sensitivity of tilt-table testing ranges from 20% to 90%,[624,629,643,644,647,648,651,652] and the specificity ranges from 83% to 100%.[624,643,652] Pediatric patients with episodes of VVS may exhibit convulsive movements during loss of consciousness that mimic epileptic seizures. In children with syncope and convulsions on tilt-table testing, 64% exhibited cardiac asystole with pauses >3 seconds.[645] Upright tilt-table testing combined with a graded isoproterenol infusion identified 42% to 67% of patients previously thought to have a primary seizure disorder.[223,649] A combined cardiology and neurology evaluation may be warranted in this group of patients with syncope and seizure-like activity.
IIa	**B-R**	**In pediatric patients with VVS not responding to lifestyle measures, it is reasonable to prescribe midodrine.[381,620,653]**
See Online Data Supplement 40.		In a single-center prospective case series, pseudoephedrine reduced clinical symptoms in 94% of children with recurrent neurally mediated syncope.[653] In an RCT comparing patients receiving conventional therapy (health education, tilt-table training, and salt) and midodrine with patients receiving conventional therapy alone, the recurrence rate of syncope decreased from 80% to 22%.[381] In 2 prospective studies, side effects from midodrine were rare.[381,653]
IIb	**B-R**	**Encouraging increased salt and fluid intake may be reasonable in selected pediatric patients with VVS.[642]**
See Online Data Supplement 40.		In an RCT, conventional therapy and oral rehydration salts resulted in no further recurrence of syncope in 56% of patients, versus 39% in the placebo arm ($P<0.05$).[642]
IIb	**C-LD**	**The effectiveness of fludrocortisone is uncertain in pediatric patients with OH associated with syncope.[389,654,655]**
See Online Data Supplement 40.		In 2 single-center prospective case series of 0.1 mg of fludrocortisone, 83% of subjects demonstrated improvement or resolution of symptoms.[654,655] In the only pediatric RCT, children with recurrent syncope did better on placebo than on fludrocortisone.[389]
IIb	**B-NR**	**Cardiac pacing may be considered in pediatric patients with severe neurally mediated syncope secondary to pallid breath-holding spells.[656,657]**
See Online Data Supplement 40.		In 2 separate studies of 22 predominantly infants and toddlers with reflex anoxic seizures, pallid breath-holding spells, and documented prolonged asystole (pauses >4 seconds), 86% had either complete resolution or a significant reduction in the number of syncopal events with pacing.[656,657] Although the studies were not powered to address the specifics of pacing programming, either single- or dual-chamber pacing significantly reduced the number of syncopal episodes compared with a sensing-only strategy.[656,657] Single-chamber pacing with hysteresis appears as effective as dual-chamber pacing with rate drop response for the prevention of syncope and seizures. The beneficial response to pacing in these studies cannot exclude a placebo effect from pacemaker implantation itself; however, the young age of the patients with pallid breath-holding spells makes placebo effect less likely. The long-term outcome with pacing in this population has not been reported. Finally, it is important to remember that pallid breath-holding syncope does end, although some patients do present again at a later age with classic VVS. This should be balanced against the known complications of permanent cardiac pacing.
III: No Benefit	**B-R**	**Beta blockers are not beneficial in pediatric patients with VVS.[655,658]**
See Online Data Supplement 40.		In an RCT comparing metoprolol and conventional therapy, the treatment group actually had a higher recurrence rate. Side effects of beta blockers occur frequently in children.[655,659]

10.2. Adult Congenital Heart Disease: Recommendations

Recommendations for ACHD		
COR	**LOE**	**Recommendations**
IIa	**C-EO**	**For evaluation of patients with ACHD and syncope, referral to a specialist with expertise in ACHD can be beneficial.**
N/A		The care of the expanding population of ACHD survivors is complex, especially in patients with moderate-to-severe ACHD. Care providers must be knowledgeable in the anatomy and repair; be vigilant in the recognition and management of HF, arrhythmias, and pulmonary hypertension; and have a deep understanding of noncardiac comorbidities. Delivery of ACHD care in highly specialized centers has been shown to reduce mortality rate.[663] In a population-based retrospective study of 71 467 patients with ACHD from Quebec, Canada, between 1990 and 2005, care in a specialized referral center for ACHD care, compared with other care, was independently associated with reduced mortality rate, particularly in those with severe ACHD.[663]
IIa	**B-NR**	**EPS is reasonable in patients with moderate or severe ACHD and unexplained syncope.[664,665]**
See Online Data Supplement 40.		SCD is a leading cause of death in the patient with ACHD. Unexplained syncope is a concerning event. In a cohort of 252 patients with repaired tetralogy of Fallot undergoing risk stratification with programmed ventricular stimulation, induction of either monomorphic or polymorphic VT predicted future clinical VT and SCD.[664] Patients with tetralogy of Fallot and inducible monomorphic or polymorphic VT were more likely to have a history of syncope (42.9%) than were those without inducible VT (13.4%).[664] In a cohort study of ICD recipients with transposition of the great arteries after an atrial baffle procedure, 35% of patients with primary-prevention ICDs presented with syncope. In 50% of patients receiving appropriate ICD shocks, atrial tachyarrhythmias preceded or coexisted with VT.[665] It is reasonable to exclude atrial arrhythmias in patients with syncope and a CHD substrate at risk of atrial arrhythmias (eg, Mustard, Senning, Fontan, Ebstein anomaly, and tetralogy of Fallot).[665]

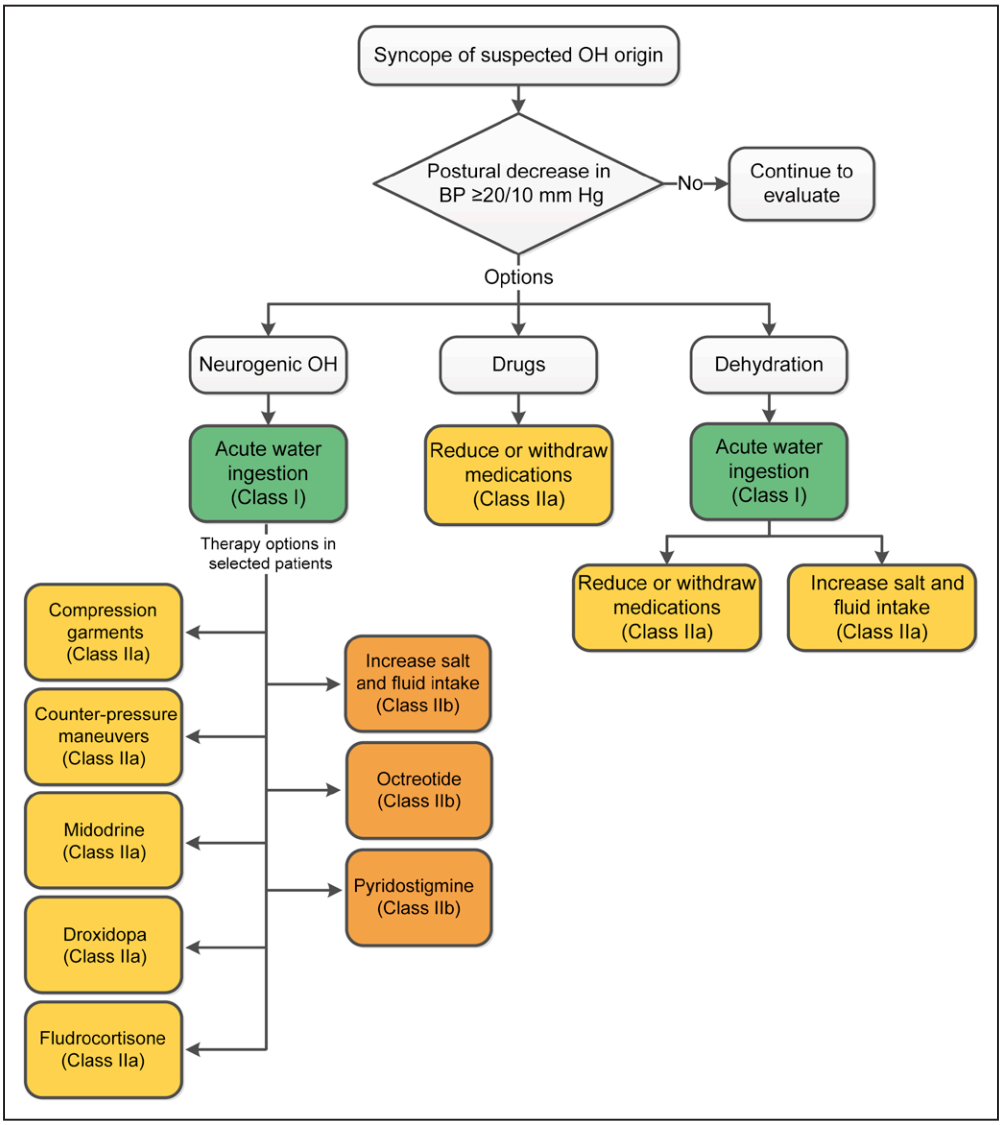

Figure 5. Orthostatic Hypotension.
Colors correspond to Class of Recommendation in Table 1. BP indicates blood pressure; and OH, orthostatic hypotension.

Patients with ACHD are at risk for syncope as a result not only of the underlying structural disease, but also as a result of a previous palliative or corrective surgery. These patients may present with syncope of both hemodynamic and either bradycardic or tachycardic origin. Care by a physician with experience in management of CHD can be beneficial. The entire spectrum of arrhythmias may be seen in adults with CHD, including bradyarrhythmias secondary to sinus or AV nodal disease, atrial arrhythmias, and VA. By age 50 years, approximately 38% of patients with ACHD will develop an atrial arrhythmia, and by age 65 years, >50% of patients with severe CHD will develop atrial arrhythmias.[660] The prevalence of VT after tetralogy of Fallot repair is 3% to 14%.[661,662]

10.3. Geriatric Patients: Recommendations

The management of syncope in older adults is particularly challenging: The incidence is high; the differential diagnosis is broad; the diagnosis is imprecise because of amnesia, falls, lack of witnesses, and polypharmacy; and secondary morbidity is high because of comorbidities, physical injury, and frailty.[35,45,666–675] The vulnerability of older adults to syncope increases because of age-associated cardiovascular and autonomic changes, decreased fluid conservation,[45,671,676–678] and an increased probability of developing multiple concurrent morbidities (with their associated pharmacological treatments) that can overwhelm homeostasis. In many instances, a syncopal event in an older adult is multifactorial, with many predisposing factors present simultaneously.

Older patients (>75 years of age) who present with syncope tend to have poor outcomes, both fatal and nonfatal.[109,679,680] Although some of the risk is attributable to the aspects of syncope described in this guideline, among older adults such risks are usually compounded by multiple morbidities and frailty, which add to age-related vulnerability to syncope,[671,681,682] and by the physical injuries associated with falls, collisions, or trauma, which more commonly result from syncope in old age.[670] Furthermore, recurrent syncope can lead to nursing home admission and a devastating loss of independence.[683] Given the multifactorial etiologies and high risks associated with syncope, a comprehensive and multidisciplinary approach is often necessary to assess for multiple morbidities, frailty, trauma, and other dimensions of health (including cognition and medications) pertinent to diagnosis and management.[77,188,684,685] A thorough history and physical examination, including orthostatic vital signs, is particularly important in older patients.[77]

Recommendations for Geriatric Patients

COR	LOE	Recommendations
IIa	C-EO	**For the assessment and management of older adults with syncope, a comprehensive approach in collaboration with an expert in geriatric care can be beneficial.**
N/A		A multidisciplinary approach helps to facilitate diagnosis of frailty and other factors that predispose to syncope and poor outcome in older adults. The goal is to make management decisions in which older patients are well informed, therapeutic choices are tailored to each patient's needs and goals of care, and decision making is successfully shared between patients and providers. Diagnostic and therapeutic approaches to syncope should incorporate considerations of age, comorbid illness, physical and cognitive functions, patient preferences, and severity of symptoms. Assessment is required of underlying cardiovascular and noncardiovascular diseases; use of medications (eg, polypharmacy, drug-drug interaction, age-related reduction in hepatic and renal clearance); the potential to reduce medications that might lower blood pressure; and circumstantial factors, such as dehydration, infection, or fever. Consideration of frailty is particularly relevant. Characteristics of frailty include weight loss, weakness, exhaustion, reduced physical activity, physical slowing, and cognitive decline, with cumulative severity and impact that typically vary between patients and even in 1 patient over time.
IIa	B-NR	**It is reasonable to consider syncope as a cause of nonaccidental falls in older adults.[666–669,686]**
See Online Data Supplement 41.		Approximately 30% of older adults who present with nonaccidental falls may have had syncope.[687] Amnesia is commonly associated with both falls and loss of consciousness, which diminishes the effectiveness of the history. Cognitive impairment is also frequently present in older adults, even in those without a formal diagnosis of dementia,[688–690] and this too can reduce the accuracy of recall of the clinical event.[666–669,673,686]

10.4. Driving and Syncope: Recommendation

The assessment of medical fitness to drive is a common issue for practitioners caring for patients with syncope. The main concern is the risk of causing injury or death to the driver or others as a result of recurrent syncope.[691] Factors to consider in assessing the risk of syncope while driving are summarized in a formula developed by the Canadian Cardiovascular Society 25 years ago[692] that estimates the risk that a driver will suddenly become incapacitated. The acceptable level of risk then becomes a societal decision.

Balancing the need to minimize risk from drivers fainting is the need for patients to drive to meet the demands of family and work. Society recognizes that

certain groups, such as younger and older adults, are allowed to drive despite their higher risk of causing harm for reasons other than syncope.[693] The societally acceptable risk of injury and death due to motor vehicle accidents has been quantified from an analysis of accident data collected in the United States, United Kingdom, and Canada.[694] In the general population, the yearly risk of serious injury and death is 0.067%, or 1 in 1500.[694] The 418 patients in POST I and POST II had a median of 3 vasovagal faints in 1 year but had no serious injuries or deaths and only 2 minor accidents in the subsequent year.[694] This provides an estimated yearly risk of serious injury and death in the VVS population of <0.0017%, less than the Risk of Harm formula predicted.[692] However, for patients with other etiologies of syncope or those in whom syncope occurred without prodrome or warning, the risk of causing harm may be higher than for patients with VVS. Public policies, laws, and regulations have not been adapted to these results, and providers caring for patients with syncope should be aware of pertinent local driving laws and restrictions. Although untreated syncope may disqualify patients from driving, effective treatment reduces the risk enough to permit driving after a period of observation has elapsed without recurrent syncope. Regulatory agencies are more likely to disqualify commercial drivers than private drivers because of the amount of driving and the impact of accidents (ie, commercial drivers typically operate vehicles heavier than private automobiles). As the risk of recurrent syncope decreases with treatment or with the natural history of a disease process, the risk of harm may become low enough for private drivers to resuming driving, but not necessarily for commercial drivers because of the higher risk of harm. The suggestions in Table 10 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.[695]

Recommendation for Driving and Syncope

COR	LOE	Recommendation
IIa	C-EO	**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.**
N/A		The writing committee encourages healthcare providers who care for patients with syncope to know pertinent driving laws and restrictions in their region (eg, states or provinces), as well as the duty of drivers or physicians to report inability of an individual to drive a motor vehicle. The Risk of Harm formula simply estimates risk and does not supersede local driving regulations.[692] In the United States, private driving is state regulated, but commercial driving requiring a US Department of Transportation commercial driver's license is federally regulated. Recommendations about commercial driving are more a legal than a medical matter, and are not within the purview of this guideline. Physicians providing care to commercial drivers should be familiar with US Department of Transportation policy.[695] Individual states may require reporting of drivers who faint. Many patients do not stop driving despite advice to do so, regardless of the duration of restriction.[696,697] Although physicians have an obligation to maintain confidentiality, if a patient's condition poses a significant risk to others, then this information should be reported as specific laws require.

10.5. Athletes: Recommendations

Syncope occurring in the athlete is predominantly of vasovagal origin, but underlying cardiac conditions may place athletes at undue risk for adverse events.[703] Syncope during exercise is associated with increased probability of cardiac causes of syncope (Table 4). A thorough history, differentiating syncope occurring during exercise from syncope occurring after exercise or at other times, with typical characteristics of dehydration or VVS, is critically important during initial evaluation. The definition of an athlete is imprecise, but *athlete* can be defined as someone who engages in routine vigorous training (eg, >150 minutes per week) and is skilled in exercises, sports, or games requiring physical strength, agility, or stamina.[704] More importantly, cardiac adaptations to high levels of exercise may lead to the "athlete's heart" and thus alter the myocardial substrate.[705] Primary or secondary prevention of syncope, morbidity, and mortality in at-risk athletes is a major consideration, but current strategies are largely inadequate.[706] The current evidence base is insufficient to support general screening with ECG or echocardiography at baseline.[706,707]

Several approved therapeutics, especially macrolide antibiotics and antihistamines/decongestants, have been associated with syncopal episodes.[708] Performance-enhancing agents, such as somatotrophic compounds and amphetamine-like stimulants, are associated with precipitous collapse. A careful history is required in the athlete with syncope to rule out exposure to any of these agents.[709] Similarly, before drugs are prescribed to highly competitive athletes, it is prudent to determine whether the drug or its metabolites are on lists of banned substances.

Recommendations for Athletes		
COR	**LOE**	**Recommendations**
I	**C-EO**	**Cardiovascular assessment by a care provider experienced in treating athletes with syncope is recommended prior to resuming competitive sports.**
N/A		A thorough history and physical examination should be completed by an experienced provider, including an assessment for OH and evidence of underlying cardiovascular disease.[709–711] Cardiovascular causes account for 75% of sport-related deaths in young athletes.[709,710] Syncope that occurs after exercise is often of benign origin and may be due to abdominal venous pooling. However, syncope during exercise is a much more compelling symptom and can be a harbinger of SCD.[712,713] Syncopal episodes first require a personal and family history to evaluate precipitating causes and benign conditions, particularly volume depletion and vasovagal activity. Concomitant illnesses, especially viral infections, should be investigated and an ECG obtained.[709,710]
IIa	**C-LD**	**Assessment by a specialist with disease-specific expertise is reasonable for athletes with syncope and high-risk markers.[706,714]**
N/A		Syncope in the competitive athlete requires an evaluation for potentially fatal causes of syncope, especially when evidence of HCM, LQTS, Wolff-Parkinson-White syndrome, ARVC, ventricular noncompaction, symptomatic mitral valve prolapse, Marfan syndrome, congenital coronary anomalies, or other at-risk conditions is present.[706,709,715,716] Any suspected cardiovascular pathology requires further evaluation, and family counseling and/or genetic testing is advised for those conditions with a known familial tendency.
IIa	**C-LD**	**Extended monitoring can be beneficial for athletes with unexplained exertional syncope after an initial cardiovascular evaluation.[717,718]**
N/A		For those with a suspected cardiovascular etiology of syncope, an evaluation includes an ECG, tilt-table testing, and imaging as clinically indicated (Figure 3).[719] Imaging may include echocardiography or MRI as required. Exercise stress testing, unless contraindicated, can be helpful. For persistent unexplained syncope, extended arrhythmia monitoring can be used, as appropriate. This is a rapidly evolving field, with no firm data on the best device and optimum monitoring period.[720]
III: Harm	**B-NR**	**Participation in competitive sports is not recommended for athletes with syncope and phenotype-positive HCM, CPVT, LQTS1, or ARVC before evaluation by a specialist.[704,721–724]**
See Online Data Supplement 42.		In the absence of vagal mechanisms, VA in patients with HCM, CPVT, LQTS1, or ARVC is catecholamine sensitive. Participation in competitive sports in that circumstance in these patients is not recommended.[704,715,716]

11. QUALITY OF LIFE AND HEALTHCARE COST OF SYNCOPE

11.1. Impact of Syncope on Quality of Life

QoL is reduced with recurrent syncope,[725–733] as demonstrated in studies that compared patients with and without syncope.[727,731] QoL associated with recurrent syncope was equivalent to severe rheumatoid arthritis and chronic low-back pain in an adult population.[728] 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.[725] In a hospital-based cohort of patients with a prior episode of syncope, 33% reported syncope-related functional impairments with daily activities, such as driving or working.[732] Those with more frequent syncope have reported poorer QoL.[726,729,730,732] There is consistent evidence that syncope is associated with worse function on multiple domains of QoL, such as perceptions of low overall physical health[725,730,734]; perception of mental health, including increased fear, somatization, depression, and anxiety[725,727,728,731,734]; and impairment in activities of daily living, such as driving, working, and attending school.

QoL impairments associated with syncope improve over time.[733] In the Fainting Assessment Study,[733] general and syncope-specific QoL improved over a 1-year period. Predictors of worse QoL over time include advanced age, recurrent syncope, neurological or psychogenic reason for syncope, and greater comorbidity at baseline.[733] Syncope-related QoL can be improved through effective diagnosis and treatment. In 1 study, use of an implantable loop recorder increased diagnostic rate, reduced syncope recurrence, and improved QoL as compared with patients who received a conventional diagnostic workup.[164] In a second study, nonpharmacological treatment of recurrent syncope was associated with reductions in recurrent syncope and improvements in QoL.[729]

11.2. Healthcare Costs Associated with Syncope

High healthcare costs are associated with the evaluation and management of syncope. Costs are defined as the resources needed to produce a set of services and are distinct from charges billed by facilities and healthcare providers.[735] Most studies have focused on facility costs and excluded professional fees and patient copays. These high costs have been estimated both in the United States and abroad. In the US Healthcare Utilization Project, total annual hospital costs exceeded $4.1 billion in 2014 dollars, with a mean cost of $9400 per admission.[736] Total costs and costs per admission for presumptive undiagnosed syncope were $1.6 billion and $7200, respectively.[736] Single-center studies from multiple countries, including Austria, the United Kingdom, Israel, and Spain, confirm similarly high costs associated with the hospital evaluation of syncope.[122,737,738]

Table 9. Conditions Uncommonly Associated with Syncope

Condition	Clinical Characteristics	Notes
Cardiovascular and Cardiopulmonary		
Cardiac tamponade	Hypotension, tachycardia, cardiogenic shock.	Often tachycardia and hypotension; may be hypotensive and bradycardic acutely.
Constrictive pericarditis[533–535]	Severe HF symptoms, including edema, exertional dyspnea, orthopnea.	May be associated with cough syncope.
LV noncompaction[536–539]	Cardiomyopathy characterized by prominent LV trabeculae and deep intertrabecular recesses, due to embryologic perturbation.	Syncope reported in 5%–9% of both adult and pediatric patients. The mechanism may be a tachyarrhythmia.
Takotsubo cardiomyopathy[540,541]	Apical ballooning and basal hypercontractility, often due to stress. Chest pain and ECG changes consistent with ischemia are commonly seen.	Syncope is uncommon and may be multifactorial.
Pulmonary embolus[128,542,543]	Hypoxemia, tachycardia; hypotension and shock leading to pulseless electrical activity cardiac arrest in severe cases.	Syncope due to bradycardia and/or hypotension. One study showed higher prevalence of pulmonary embolus in older patients with first episode of syncope after admission to the hospital. Further confirmation of this finding in the older populations is warranted.
Pulmonary arterial hypertension	Occurs more often during exertion in younger patients.	Syncope due to inability to augment or sustain cardiac output during exertion, followed by vasodilatation.
Infiltrative		
Fabry disease[544,545]	Lysosomal storage disorder with neuropathic pain, renal failure concentric LVH, and HF.	Syncope usually due to AV block.
Amyloidosis[546,547]	Systemic disease due to amyloid deposition. Light chain amyloidosis affects the kidneys, heart, and peripheral and autonomic nervous systems.	Syncope may be due to conduction system disease, arrhythmias, impaired cardiac output from restrictive cardiomyopathy, or neurological involvement. AV block is the likely cause, although VA may occur with myocardial involvement.
Hemochromatosis[548]	Systemic iron deposition causing liver disease, skin pigmentation, diabetes mellitus, arthropathy, impotence, and dilated cardiomyopathy.	Myocardial involvement more common than sick sinus syndrome and AV conduction disease.
Infectious		
Myocarditis[413,549–553]	Chest pain, arrhythmias, or profound LV systolic dysfunction. Hemodynamic collapse may occur.	VT and AV block are the likely causes of syncope; transient hemodynamic collapse is possible.
Lyme disease[554]	Lyme myocarditis with classical features of Lyme disease, including erythema migraines and neurological manifestations.	Syncope may be due to AV block, but many patients manifest VVS.[554,555]
Chagas disease[556–559]	Chagasic cardiomyopathy caused by trypanosomiasis.	Syncope and sudden death associated with ventricular tachyarrhythmias. AV block also occurs.
Neuromuscular		
Myotonic dystrophy[12,560,561]	Autosomal dominant inheritance with multiple organ systems affected. Grip myotonia, weakness, temporal wasting, alopecia, cataracts, glucose intolerance, and daytime somnolence.	Both bradyarrhythmia and tachyarrhythmias.
Friedreich ataxia[562,563]	Autosomal recessive inheritance with limb and gait ataxia, bladder dysfunction, and daytime somnolence. Diffuse interstitial fibrosis and HCM.	Syncope can be bradycardic or tachycardic. SCD is known to occur.
Kearns-Sayre Syndrome[564,565]	Mitochondrial myopathy. Chronic progressive external ophthalmoplegia; pigmentary retinopathy.	Many patients develop significant His-Purkinje disease.
Erb dystrophy[566]	Limb girdle muscular dystrophy, manifesting as scapulohymeral and/or pelvifemoral weakness and atrophy.	AV conduction disease, dilated cardiomyopathy.
Anatomic		
Lenègre-Lev disease[567–571]	Progressive fibrosis and sclerosis of cardiac conduction system, including the cardiac skeleton, including the aortic and mitral rings.	Syncope is usually due to high-grade AV block.
Cardiac tumors[572]	Triad of obstruction, embolic, and systemic signs and symptoms.	Syncope is often due to obstruction to blood flow.
Prosthetic valve thrombosis[573–575]	Ranges from asymptomatic to profound HF.	May have similar presentation to a cardiac tumor, with a high risk of embolic phenomenon and obstruction.
Anomalous coronary artery[576–579]	Common cause of exertional syncope or SCD, classically in young athletes.	Syncope can be due to Bezold Jarisch reflex, hypotension, VT, or AV block.

(*Continued*)

Table 9. Continued

Condition	Clinical Characteristics	Notes
Aortic dissection[580–582]	Aortic dissection may manifest with neurological symptoms, myocardial infarction, and HF. Syncope can occur in as many as 13% of aortic dissections.	The risk of in-hospital death, tamponade, and neurological deficits is higher in patients with syncope. Otherwise, syncope alone does not appear to increase the risk of death.
Subclavian steal[583–587]	The phenomenon of flow reversal in a vertebral artery ipsilateral to a hemodynamically significant stenosis of the subclavian artery. Severe cases resulting in vertebrobasilar ischemia may rarely result in syncope.	Syncope is generally associated with upper-extremity activity.
Coarctation of the aorta[588]	If severe, it can result in HF or aortic dissection.	Associated bicuspid aortic valve stenosis may be considered with syncope.
Rheumatoid arthritis[589]	Chronic, autoimmune inflammatory disorder with systemic manifestations.	Rarely associated with complete heart block and syncope.
Syringomyelia[590–597] Chiari malformation[598]	Arnold Chiari malformations are the most common form of syringomyelia.	Syringomyelia-induced disruption of sympathetic fibers in the thoracic spinal cord is a rare mechanism of syncope.[599]
Neck/vagal tumor[600,601]	Recurrent syncope is an uncommon complication of neck malignancy.	The mechanism may be invasion of the carotid sinus or the afferent nerve fibers of the glossopharyngeal nerve.
Endocrine		
Carcinoid syndrome[602] Pheochromocytoma[602,603] Mastocytosis[602–609] Vasoactive intestinal peptide tumor	These tumors can release vasoactive peptides and cause vasodilation, flushing, pruritus, and gastrointestinal symptoms.	Syncope is usually due to transient hypotension.
Hematologic		
Beta thalassemia major[610]	Severe anemia, multiple organ failure, and dilated cardiomyopathy due to iron overload.	Syncope may be arrhythmic.
Neurological disorders		
Seizure-induced bradycardia/ hypotension[611–614]	Generally due to temporal lobe epilepsy.	Postictal bradyarrhythmia is uncommon and likely originates from the temporal lobe or limbic system.
Migraine[615,616]	Migraine headaches are statistically associated with syncope.	Syncope may be vasovagal or due to orthostatic intolerance.

ACC indicates American College of Cardiology; AHA, American Heart Association; AV, atrioventricular; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; HF, heart failure; HRS, Heart Rhythm Society; LV, left ventricular; LVH, left ventricular hypertrophy; SCD, sudden cardiac death; VA, ventricular arrhythmias; VT, ventricular tachycardia; and VVS, vasovagal syncope.

Several investigators have estimated the costs per clinically meaningful test result. Physician reviewers determined whether the results of a diagnostic test affected clinical management at a US tertiary referral hospital after an episode of syncope.[77] The cost per informative diagnosis (as ordered in routine practice) affecting clinical management varied widely by specific diagnostic test, from postural blood pressure ($50) through telemetry ($1100) to EEG ($32 973).[77] Similar high costs per actionable diagnosis occur in children admitted for new-onset syncope. Finally, mean costs per diagnostic result were also high in an outpatient ($19 900) specialty clinic for unexplained recurrent syncope.[163]

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

Condition	Symptom-Free Waiting Time*
OH	1 month
VVS, no syncope in prior year[698]	No restriction
VVS, 1–6 syncope per year[694]	1 month
VVS, >6 syncope per year[694,698]	Not fit to drive until symptoms resolved
Situational syncope other than cough syncope	1 month
Cough syncope, untreated	Not fit to drive
Cough syncope, treated with cough suppression	1 month
Carotid sinus syncope, untreated[698]	Not fit to drive
Carotid sinus syncope, treated with permanent pacemaker[698]	1 week
Syncope due to nonreflex bradycardia, untreated[698]	Not fit to drive
Syncope due to nonreflex bradycardia, treated with permanent pacemaker[12,698]	1 week
Syncope due to SVT, untreated[698]	Not fit to drive
Syncope due to SVT, pharmacologically suppressed[698]	1 month
Syncope due to SVT, treated with ablation[698]	1 week
Syncope with LVEF <35% and a presumed arrhythmic etiology without an ICD[699,700]	Not fit to drive
Syncope with LVEF <35% and presumed arrhythmic etiology with an ICD[701,702]	3 months
Syncope presumed due to VT/VF, structural heart disease, and LVEF ≥35%, untreated	Not fit to drive
Syncope presumed due to VT/VF, structural heart disease, and LVEF ≥35%, treated with an ICD and guideline-directed drug therapy[701,702]	3 months
Syncope presumed due to VT with a genetic cause, untreated	Not fit to drive
Syncope presumed due to VT with a genetic cause, treated with an ICD or guideline-directed drug therapy	3 months
Syncope presumed due to a nonstructural heart disease VT, such as RVOT or LVOT, untreated	Not fit to drive
Syncope presumed due to a nonstructural heart disease VT, such as RVOT or LVOT, treated successfully with ablation or suppressed pharmacologically[698]	3 months
Syncope of undetermined etiology	1 month

*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

At a patient's presentation, several key questions follow: What is the likely cause of syncope? Does the patient have significant underlying heart disease and/or comorbid medical illnesses? If the cause of syncope is determined, is there an effective therapy to prevent recurrent syncope, prevent syncope-related nonfatal outcomes (injury, diminished healthcare–related QoL, lost workdays), or improve survival? What are the predictors of short- and long-term clinical outcomes? What are the key outcomes relevant to patients with syncope, including recurrent syncope? When the cause of syncope is unknown, what is the standard of care for this group of patients?

- 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 QoL, 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

Because of the concerns that patients presenting with syncope are at higher risk for an impending catastrophic event, overuse and inappropriate use of testing and hospital admission are common. Answers to the following question will improve the effectiveness of patient evaluation: How should the initial evaluation and subsequent follow-up vary by risk (low, intermediate, or high) to assess clinical outcomes?

- 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

- Each population in Section 6 is unique with regard to syncope, and within each of them we identified several key areas that are important for future research considerations.
- 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.

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FOOTNOTES

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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)

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Win-Kuang Shen, Chair	Mayo Clinic Arizona—Professor of Medicine; Mayo Clinic College of Medicine—Chair, Department of Cardiovascular Diseases	None	None	None	None	None	None	None
Robert S. Sheldon, Vice Chair	University of Calgary, Department of Medicine—Professor	None	None	None	None	None	None	None
David G. Benditt	University of Minnesota Medical School, Cardiovascular Division—Professor of Medicine	• Medtronic† • St. Jude Medical†	None	None	None	None	None	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
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	None	None	None	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	None
Roy Freeman‡	Harvard Medical School—Professor of Neurology; Beth Israel Deaconess Medical Center, Center for Autonomic and Peripheral Nerve Disorders—Director	• Lundbeck†	None	None	None	None	None	4.3.1–4.3.5, 5.1, 6.1, 10.1, 10.3, 10.5, 12
Zachary D. Goldberger	University of Washington School of Medicine, Harborview Medical Center Division of Cardiology—Assistant Professor of Medicine	None	None	None	None	None	None	None
Blair P. Grubb	University of Toledo Medical Center, Medicine and Pediatrics—Professor	• Biotronik • Medtronic	None	None	None	None	None	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
Mohamed H. Hamdan	University of Wisconsin School of Medicine, Cardiovascular Medicine—Professor and Chief of Cardiovascular Medicine	None	None	• F2 Solutions	None	None	None	2.3.3, 2.3.4, 12

(*Continued*)

Appendix 1. Continued

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
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	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
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	None
Brian Olshansky	University of Iowa Carver College of Medicine, Cardiovascular Medicine—Emeritus Professor of Internal Medicine; Mercy Hospital North Iowa—Electrophysiologist	• Lundbeck†	None	None	None	None	None	None
Satish R. Raj	University of Calgary, Cardiac Sciences—Associate Professor	• GE Healthcare • Lundbeck†	None	None	• Medtronic	None	None	2.3.2, 2.3.4, 3.2–3.2.5, 3.3.2, 4.1.1–4.1.3, 4.2.1–4.2.5, 4.3.1–4.3.5, 5.1–5.3, 6.1, 7, 10.1–10.3, 10.5, 12
Roopinder Kaur Sandhu	University of Alberta, Medical Division of Cardiology—Assistant Professor of Medicine	None	None	None	None	None	None	None
Dan Sorajja	Mayo Clinic Arizona, Cardiovascular Diseases—Assistant Professor of Medicine	None	None	None	None	None	None	None
Benjamin C. Sun	Oregon Health & Science University—Associate Professor	None	None	None	None	None	None	None
Clyde W. Yancy	Northwestern University Feinberg School of Medicine, Division of Cardiology—Professor of Medicine and Chief; Diversity & Inclusion—Vice Dean	None	None	None	None	None	None	None

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 ≥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.

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.

†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)

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Italo Biaggioni	Official Reviewer—AHA	Vanderbilt University School of Medicine—Professor of Medicine	• Lundbeck* • Shire Pharmaceuticals* • Theravance*	None	None	• Astellas Pharma (DSMB) • AstraZeneca* • Forest Pharmaceuticals* • Janssen Pharmaceuticals (DSMB) • Lundbeck* • Theravance*	None	None
Joaquin E. Cigarroa	Official Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Oregon Health & Science University—Clinical Professor of Medicine	None	None	None	None	• NIH† • AHA† • SCAI† • ASA† • Catheterization and Cardiovascular Intervention†	None
Kenneth A. Ellenbogen	Official Reviewer—AHA	VCU Medical Center—Director, Clinical EP Laboratory	• AHA • Atricure* • Biosense Webster* • Biotronik* • Boston Science* • HRS* • Janssen Pharmaceuticals • Medtronic* • Pfizer* • Sentra Heart • St. Jude Medical*	None	None	• Atricure* • Boston Science • Biosense Webster • Daiichi-Sankyo* • Medtronic (DSMB) • Medtronic • NIH • Sanofi-aventis	• AHA • American Heart Journal • Biosense Webster* • Boston Science* • HRS • JCE • Medtronic* • PACE • Sanofi-aventis	• Defendant, Catheter ablation complication, 2015 • Plantiff, Lead extraction complication, 2015
Rakesh Gopinathannair	Official Reviewer—HRS	University of Louisville School of Medicine and Jewish Hospital Division of Cardiovascular Medicine—Associate Professor of Medicine, Director of Cardiac EP	• Boston Scientific • Health Trust PG • St. Jude Medical*	• AHA • Bristol-Myers Squibb • Pfizer* • Zoll Medical	None	None	None	None
Robert Helm	Official Reviewer—HRS	Boston University School of Medicine—Assistant Professor of Medicine, Assistant Professor of Radiology	None	None	None	None	• Boston Scientific • St. Jude Medical	None
Dhanunjaya Lakkireddy	Official Reviewer—ACC Board of Governors	University of Kansas Medical Center—Professor of Medicine; Center for Excellence in AF and Complex Arrhythmias—Director	• Biosense Webster • St. Jude Medical	• Boehringer Ingelheim • Bristol-Myers Squibb • Janssen Pharmaceuticals • Pfizer	None	None	None	None
Thad Waites	Official Reviewer—ACC Board of Trustees	Forrest General Hospital—Director of Catheterization Laboratory	None	None	None	None	None	None

(*Continued*)

Appendix 2. Continued

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

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Appendix 2. Continued

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

(*Continued*)

Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Richard Page	Content Reviewer	University of Wisconsin School of Medicine & Public Health—Chair, Department of Medicine	None	None	None	None	• FDA	None
Antonio Raviele	Content Reviewer	Alliance to Fight Atrial Fibrillation—President; Venice Arrhythmias—President	None	None	None	None	None	None
Marwan Refaat	Content Reviewer—ACC EP Section Leadership Council	American University of Beirut—Faculty of Medicine and Medical Center	None	None	None	None	None	None
Melissa Robinson	Content Reviewer	University of Washington—Assistant Professor of Medicine; Director, Ventricular Arrhythmia Program	• Medtronic*	None	None	None	None	None
Paola Sandroni	Content Reviewer	Mayo Clinic—Professor of Neurology, Practice Chair of Neurology	None	None	None	None	None	None
Colette Seifer	Content Reviewer	University of Manitoba—Associate Professor, Section of Cardiology	None	None	None	None	None	None
Monica Solbiati	Content Reviewer	Fondazione IRCCS CA' Granda, Ospedale Maggiore Policlinico, Milano—Senior Physician	None	None	None	None	None	None
Richard Sutton	Content Reviewer	National Heart and Lung Institute, Imperial College London—Emeritus Professor	• Medtronic*	• St. Jude Medical*	• Boston Scientific* • Edwards Lifesciences* • Shire Pharmaceuticals • AstraZeneca	• Medtronic*	None	• Defendant, Fatal car accident caused by VVS patient, 3 trials in 2016*
Gaurav Upadhyay	Content Reviewer—ACC EP Section Leadership Council	University of Chicago—Assistant Professor of Medicine	• Biosense Webster • Biotronik • Boston Scientific • Medtronic • St. Jude Medical • Zoll Medical	None	None	• Biosense Webster • Biotronik* • Medtronic*	None	None

(*Continued*)

Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Paul Varosy	Content Reviewer	University of Colorado Hospital, Clinical Cardiac EP Training program—Associate Program Director; VA Eastern Colorado Healthcare System—Director of Cardiovascular EP	None	None	None	• AHA† • VA Office of Health Services Research and Development (PI)*	None	None

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; SCD, sudden cardiac death; VA, Veterans Affairs; VCU, Virginia Commonwealth University; and VVS, vasovagal syncope.

Appendix 3. Abbreviations

ACHD = adult congenital heart disease
ARVC = arrhythmogenic right ventricular cardiomyopathy
AV = atrioventricular
CHD = congenital heart disease
CPVT = catecholaminergic polymorphic ventricular tachycardia
CT = computed tomography
ECG = electrocardiogram/electrocardiographic
ED = emergency department
EEG = electroencephalogram/electroencephalography
EPS = electrophysiological study
GDMT = guideline-directed management and therapy
HCM = hypertrophic cardiomyopathy
HF = heart failure
ICD = implantable cardioverter-defibrillator
ICM = implantable cardiac monitor
LCSD = left cardiac sympathetic denervation
LQTS = long-QT syndrome
LV = left ventricular
MRI = magnetic resonance imaging
OH = orthostatic hypotension
QoL= quality of life
RCT = randomized controlled trial
POTS = postural tachycardia syndrome
SCD = sudden cardiac death
SVT = supraventricular tachycardia
VA = ventricular arrhythmia
VF = ventricular fibrillation
VT = ventricular tachycardia
VVS = vasovagal syncope

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2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society

Win-Kuang Shen, Robert S. Sheldon, David G. Benditt, Mitchell I. Cohen, Daniel E. Forman, Zachary D. Goldberger, Blair P. Grubb, Mohamed H. Hamdan, Andrew D. Krahn, Mark S. Link, Brian Olshansky, Satish R. Raj, Roopinder Kaur Sandhu, Dan Sorajja, Benjamin C. Sun and Clyde W. Yancy

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CORRECTION

Correction to: 2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society

In the article by Shen et al, "2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society," which published online March 9, 2017, and appeared in the August 1, 2017, issue of the journal (*Circulation.* 2017;136:e60–e122. DOI: 10.1161/CIR.0000000000000499), several corrections were needed.

1. In the table of contents and the corresponding headings in the text, a colon and the word "Recommendations" have been added to headers for the following sections: 3.2., 3.3., 4.1., 4.2., 4.3., 5., 6., and 10.
2. On page e64, in Section 1.2., the first sentence read, "The writing committee was composed of clinicians with expertise in caring for patients with syncope, including cardiologists, electrophysiologists, a neurologist, an emergency physician, and a pediatric cardiologist." The words "a neurologist" have been deleted. The sentence is updated to read, "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."
3. On page e64, in Section 1.3., second paragraph, the first sentence read, "This document was approved for publication by the governing bodies of the ACC, AHA, and HRS and was endorsed by the Pediatric and Congenital Electrophysiology Society." It is updated to read, "This document was approved for publication by the governing bodies of the ACC, AHA, and HRS and was endorsed by the American College of Emergency Physicians, the Society of Academic Emergency Medicine, and the Pediatric and Congenital Electrophysiology Society." The endorsing bodies text is also updated on page e60, the title page.
4. On page e70, in Table 5, "Short- and Long-Term Risk Factors," the column headed "Long-Term Risk Factors (>30 d)," the entry for "Older age" previously read, "Older age.[90]" It is updated to read, "Older age.[67,74,75,90]"
5. On page e77, in the Section 3.3.2. recommendation table, "Recommendations for Neurological Diagnostics," first IIa recommendation explanatory text, the second sentence read, "ECG findings are characteristic if an episode can be induced during the tilt-table testing.[261–263]" "ECG" has been replaced with "EEG." The sentence is updated to read, "EEG findings are characteristic if an episode can be induced during the tilt-table testing.[261–263]"
6. On page e79, in the Section 4.1.1. recommendation table, "Recommendation for Bradycardia," the first sentence of the explanatory text read, "A search and review of papers on syncope and bradycardia has been performed since the last guidelines were published in 2008 and 2012.[12,264]" It is updated to read, "A search and review of papers on syncope and bradycardia has been performed since the last updated guidelines were published in 2012.[12]"

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7. On page e82, the Section 4.3.2. recommendation table title read, "Recommendation for Short-QT Syncope." It is updated to read, "Recommendation for Short-QT Syndrome."
8. On page e82, Section 4.3.3., the second paragraph previously read, "Patients with LQTS and syncope should adhere to the lifestyle changes previously published, including avoidance of strenuous activity in LQT1, and drugs known to prolong QT interval in all patients with LQTS.[25]" "LQT1" is replaced with "LQTS1." It is updated to read, "Patients with LQTS and syncope should adhere to the lifestyle changes previously published, including avoidance of strenuous activity in LQTS1, and drugs known to prolong QT interval in all patients with LQTS.[25]" "LQT1" has also been replaced with "LQTS1" in the final sentence of explanatory text for the Class I recommendation on page e83 in this section.
9. On page e87, the Section 6.1. recommendation table, "Recommendations for Neurogenic OH," all recommendations in the table previously included the sentence, "See Online Data Supplements 33 and 34." That sentence is updated to read, "See Online Data Supplements 33–35."
10. On page e88, the Section 6.2. recommendation table, "Recommendations for Dehydration and Drugs," all recommendations previously included the sentence, "See Online Data Supplements 35 and 36." That sentence is updated to read, "See Online Data Supplements 36 and 37."
11. On page e89, the Section 8. recommendation table, "Recommendations for the Treatment of Pseudosyncope," both recommendations previously included the sentence, "See Online Data Supplements 37 and 38." That sentence is updated to read, "See Online Data Supplements 38 and 39."
12. On page e95, Table 9, "Conditions Uncommonly Associated With Syncope," the names of several diseases have been corrected. "Fabry's disease" is replaced with "Fabry disease"; "Kearns-Sayre" with "Kearns-Sayre Syndrome"; and "Lev's and Lenegre's diseases" with "Lenègre-Lev disease."
13. On page e98, in the list of American College of Cardiology/American Heart Association staff, the title for Abdul R. Abdullah, MD, is updated to read "Science and Medicine Advisor."
14. On page e99, reference 1, the abbreviation "ed." is deleted. It is updated to read, "1. Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, Institute of Medicine (U.S.). Clinical Practice Guidelines We Can Trust. Washington, DC: National Academies Press; 2011."
15. On page e99, reference 2, the abbreviation "ed." is deleted. It is updated to read, "2. Committee on Standards for Systematic Reviews of Comparative Effectiveness Research, Institute of Medicine (U.S.). Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: National Academies Press; 2011."
16. On page e99, reference 4, URL information has been added. It is updated to read, "4. ACCF/AHA Task Force on Practice Guidelines. Methodology Manual and Policies From the ACCF/AHA Task Force on Practice Guidelines. American College of Cardiology and American Heart Association, 2010. Available at: http://assets.cardiosource.com/Methodology_Manual_for_ACC_AHA_Writing_Committees.pdf and http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/documents/downloadable/ucm_319826.pdf. Accessed January 23, 2015."
17. On page e100, reference 45, the journal name and volume were added. It is updated to read, "45. Ruwald MH, Hansen ML, Lamberts M, et al. The relation between age, sex, comorbidity, and pharmacotherapy and the risk of syncope: Danish nationwide study. Europace. 2012;14:1506–14."
18. On page e100, reference 50, the journal name was added. It is updated to read, "50. Ruwald MH, Hansen ML, Lamberts M, et al. Accuracy of the ICD-10 discharge diagnosis for syncope. Europace. 2013;15:595–600."
19. On page e100, reference 54, the journal name and volume were added. It is updated to read, "54. Disertori M, Brignole M, Menozzi C, et al. Management of patients with syncope referred urgently to general hospitals. Europace. 2003;5:283–91."
20. On page e104, reference 264 read, "264. Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society [corrected]. Circulation. 2012;126:1784–800.)" It is updated to read, "Deleted in press."
21. On page e107, reference 409, the journal name, publication date, volume, and page numbers were added. It is updated to read, "409. Sutton R. Pacing in patients with carotid sinus and vasovagal syndromes. Pacing Clin Electrophysiol. 1989;12:1260–3."

These corrections have been made to the current online version of the article, which is available at http://circ.ahajournals.org/content/136/5/e60.

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

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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 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.

2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope - Data Supplement

(Section numbers correspond to the full-text guideline.)

Table of Contents

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, electrocardiogram, electrocardiography, electrophysiologic, electrophysiological, falls, florinef, fludrocortisone, fluoxetine, functional neurologic symptoms, heart rate, holter monitor, holter, hypertrophic cardiomyopathy, hypotension, 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 unit, syncope, 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 1° indicates primary; 2°, secondary; AAD, antiarrhythmic dug; AAI, atrioventricular interval; ACA, aborted cardiac arrest; ACS, acute coronary syndrome; ADE, indicates adverse drug events; AF, atrial fibrillation; AMI, acute myocardial infarction; ARVC, arrhythmogenic right ventricular cardiomyopathy; ARVC/D, arrhythmogenic right ventricular dysplasia/cardiomyopathy; ARVD, arrhythmogenic right ventricular dysplasia; AS, aortic stenosis; ASR, Anatolian Syncope Rule; 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; CCU, coronary care unit; CHD, congenital heart disease; 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 sarcoidosis; CSH, carotid sinus hypersensitivity; CSM, carotid sinus massage; CSR, carotid sinus reaction; CSS, Carotid Sinus Syndrome; CSSS, Calgary Syncope Symptom Score; CT, computed tomography; cTnThs, 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; EDOSP, emergency department observation syncope protocol; EEG, electroencephalogram; EF, ejection fraction; EGSYS, evaluation of guidelines of syncope study; ELR, external loop recorder; EP, electrophysiological; EPS, electrophysiological 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; LCS, left cervicothoracic sympathectomy; LCSD, left cardiac sympathetic denervation; LOC, loss of consciousness; LOS, length of stay; LQTS, 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;OHDAS, Orthostatic Hypotension Daily Activity Scale; OHQ, orthostatic hypotension questionnaire; OHSA, 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)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
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

Sheldon, et al. 2006 16223744 (4)	**Aim:** Establish historical criteria for diagnosis of VVS **Study type:** Prospective, used a Questioner of 118 items **Size:** 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	**Inclusion criteria:** Pts with syncope and no apparent structural heart disease **Exclusion criteria:** N/A	**Results:** The point score correctly classified 90 % of pts with an 89% sensitivity and 91 % specificity	The point scoring system can distinguish VVS from other causes of syncope with a high sensitivity and specificity
Sheldon, et al. 2002 12103268 (5)	**Aim:** Develop criteria that distinguish syncope due to VT from VVS in pts with SHD **Study type:** Prospective analysis **Size:** n=671 pts with a history of TLOC completed a 118 item historical questionnaire	**Inclusion criteria:** Pts with syncope and SHD **Exclusion criteria:** N/A	**Results:** • Cause of TLOC known in 539 pts • Seizures in 102 pts: Complex partial in 50 pts; Primary Generalized in 52 pts • Syncope in 437 pts: VVS in 267 pts; VT in 90 pts; Other in 80 pts	The point score based on symptoms alone correctly classified 94% of pts, diagnosing seizures with a 94% sensitivity and 94% specificity
FAST Van Dijk, et al. 2008 17916139 (6)	**Aim:** Assess yield and accuracy of an initial evaluation using : History, PE, and ECG **Study type:** Prospective analysis then a 2 y follow-up by an expert committee **Size:** n=503 pts (with a 2 y follow-up in 99%)	**Inclusion criteria:** Adults presenting with TLOC to the Academic Medical Center Amsterdam between February 2000 and May 2002 **Exclusion criteria:** N/A	**Results:** At initial evaluation: • 119 pts (24%) certain diagnosis • 199 pts (40%) had a highly likely diagnosis • Overall diagnostic accuracy was 88%	Attending physicians can make a diagnosis in 63% of pts with TLOC, with a diagnostic accuracy of 88%

Romme, et al. 2009 19687157 (7)	**Aim:** Evaluate the Calgary Syncope Symptom Score **Study type:** Prospective trial **Size:** n=380 pts with TLOC: • 237 pts (55%) were diagnosed with VVS using Calgary Score and then compared after 2 y of follow-up	**Inclusion criteria:** Pts with TLOC **Exclusion criteria:** N/A	**Results:** Sensitivity of Calgary score was 87% but the Specificity was 32%	• Sensitivity of the Calgary score similar to original study but the specificity less
Sheldon, et al. 2010 20586825 (8)	**Aim:** Evaluate evidence based criteria to distinguish syncope due to VT from VVS in pts with structural heart disease **Study type:** Prospective. 118 item questionnaire and an invasive and non-invasive diagnostic assessment **Size:** n=134 pts	**Inclusion criteria:** Pts with syncope and SHD **Exclusion criteria:** N/A	**Results:** • 21 pts with HUTT+VVS • 78 pts with clinical or EPS Induced VT • 35 pts with no cause identified	• Factors predicting VT were male gender and >35 y of age • Factors predicting VVS were Prolonged sitting or standing, pre-syncope preceded by stress, headaches and fatigue after syncope lasting >1 min • The point score identified 92% of pts correctly, diagnosing VT with 99% sensitivity and 68% specificity, negative predictive value of >96%
PLOS Berecki-Gisolf, et al. 2013 24223233 (9)	**Aim:** Develop a model for symptoms that associate with cardiac causes of syncope **Study type:** Literature based review **Size:** n=7 studies	**Inclusion criteria:** • 2 Pubmed searches using the following key words: 1. Diagnosis; signs and symptoms; vasovagal syncope 2. Clinical history; diagnosis; syncope • Pts with ≥1 transient loss of consciousness • A diagnosis of cardiac syncope vs. other causes • Degree of evidence accepted in each paper • Studies reporting ≥2 predictors of cardiac syncope **Exclusion criteria:** N/A	**Results:** A total of 10 variables were found associated with cardiac syncope : 1. Age >60 y 2. Male gender 3. Structural heart disease 4. Low number of spells 5. Brief or absent prodrome 6. Supine syncope 7. Effort syncope 8. Absence of nausea 9. Absence of diaphoresis 10. Absence of blurred vision	A model with 5 variables was as effective with moderate accuracy: • >60 y of age • Male gender • Structural heart disease • Low number of spells • Lack of prodromal symptoms

Data Supplement 2. Nonrandomized Trials, Observational Studies, and/or Registries of Electrocardiography – (Section 2.3.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
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	**1° endpoint:** frequency of use ofechocardiogram 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	**1° 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)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)

Grossman SA, et al. 2012 22981659 (12)	**Study type:** Prospective observational **Size:** n=244 ED pts with presyncope	**Inclusion criteria:** Presyncope, >18 y of age **Exclusion criteria:** None	**1° 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 12727148 (13)	**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	**1° 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 24862309 (14)	**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	**1° endpoint:** 30 d combined death, arrhythmia, severe outflow tract obstruction, MI, CPR, pulmonary embolism, aortic dissection, hemorrhage, syncope resulting in major trauma **Results:** "OESIL", "SFSR," "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 18206736 (15)	**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;	**1° endpoint:** 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

		refusal to provide consent		
D'Ascenzo F, et al. 2013 22192287 (16)	**Study type:** Pooled meta-analysis **Size:** n=11 studies	**Inclusion criteria:** Presentation of syncope to an ED **Exclusion criteria:** N/A	**1° endpoint:** Combined death, hospitalization/intervention related to arrhythmia, ischemic heart disease, or VHD. **Results:** Strongest predictors of an adverse outcome included palpitations preceding syncope, exertional syncope, history of HF or ischemic heart disease, evidence of bleeding	• These criteria may identify pts who might benefit from hospital admission
Da Costa A, et al. 2006 15975670 (17)	**Study type:** Prospective observational **Size:** n=305 pts	**Inclusion criteria:** Normal EPS after first onset of syncope or near-syncope **Exclusion criteria:** None	**1° endpoint:** Combined symptomatic AV block, conduction abnormalities requiring pacemaker therapy, sustained ventricular arrhythmia, sudden death **Results:** ECG is only independent predictor of long term adverse events	• 5% event rate at 2.5 y; normal EPS does not rule out dangerous conduction problems as cause of syncope
Del Rosso A, et al. 2008 18519550 (18)	**Study type:** Prospective observational **Size:** Derivation n=260 pts, validation n=256 pts	**Inclusion criteria:** Presentation of unexplained syncope to one of 14 ED's **Exclusion criteria:** None	**1° endpoint:** Cardiac cause of syncope **Results:** "EGSYS" 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)	• Risk of cardiac cause is <3% if EGSYS score <3, and >17% if EGSYS score ≥3
Derose S, et al. 2012 22594351 (19)	**Study type:** Retrospective observational **Size:** n=22,189 pts	**Inclusion criteria:** Primary ED diagnosis of syncope or near-syncope in an integrated health system **Exclusion criteria:** None	**1° endpoint:** 30 d mortality **Results:** Predictors of short term mortality included increasing age, male gender, recent visit for syncope, history of HF, DM, seizure, and dementia	• Pts without history of HF and <60 y of age had less than 0.2% risk of 30 d mortality
Dipaola F, et al. 2010 20466221 (20)	**Study type:** Prospective observational **Size:** n=488 pts	**Inclusion criteria:** >18 y of age presenting to one of 2 EDs with syncope of unknown cause **Exclusion criteria:** None	**1° endpoint:** 10 d combined death, CPR, pacemaker/ ICD placement, ICU admission, acute anti-arrhythmic therapy, readmission **Results:** Compared to the "OESIL" and "SFSR" risk scores, unstructured clinical judgment had similar sensitivity and higher specificity.	• Unclear whether these specific risk scores add value to clinical evaluation

Exposito V, et al. 2013 23478089 (21)	**Study type:** Prospective observational **Size:** n=180 pts	**Inclusion criteria:** >60 y of age with suspected VVS and undergoing tilt test **Exclusion criteria:** None	**1° endpoint:** Positive tilt test **Results:** CSSS score ≥ -2 has sensitivity of 50% and specificity of 73%	• Calgary Syncope Symptom score for VVS has lower sensitivity and specificity in elderly population than previously reported
Gabayan G, et al. 2010 20102895 (22)	**Study type:** Retrospective observational **Size:** n=35,330 pts	**Inclusion criteria:** Primary ED diagnosis of syncope or near-syncope in an integrated health system **Exclusion criteria:** None	**1° endpoint:** 7 d death, hospitalization, or procedure related to ischemic heart disease, VHD, or arrhythmia **Results:** Predictors included >60 y of age, male gender, Hx of HF, ischemic heart disease, arrhythmia, and VHD.	• Increasing age and presence of cardiac co-morbidities is associated with short term serious cardiac outcomes.
Grossman S, et al. 2007 17976548 (23)	**Study type:** Prospective observational **Size:** n=362 pts	**Inclusion criteria:** >18 y of age presenting to an ED with syncope **Exclusion criteria:** None	**1° endpoint:** 30 d pacemaker/ ICD placement, PCI, cardiac urgery, blood transfusion, CPR, change in anti-arrhythmic therapy, death, pulmonary embolus, stroke, sepsis, arrhythmia, intranial bleed, MI **Results:** Low risk pts (<3% event rate) had none of the following: 1. suspicion for ACS; 2. signs of conduction disease; 3. worrisome cardiac history; 4. VHD; 5. family Hx of sudden death; 6. persistent abnormal vital signs in ED; 7. volume depletion; 8. primary central nervous system event	• These criteria may identify low risk pts for whom discharge can be considered
Kayayurt K, et al. 2012 22520447 (24)	**Study type:** Prospective observational **Size:** n=231 pts	**Inclusion criteria:** >18 y of age presenting to one of 2 ED's with syncope of unknown cause **Exclusion criteria:** None	**1° endpoint:** 7 d rehospitalization, death, CPR, pacemaker/ ICD implantation, ICU admission, anti-arrhythmic therapy **Results:** The "ASR" risk score includes dyspnea (+1), OH (+1), precipitating cause for syncope (+1), pts >58 y of age (+1), Hx of CHF (+1), abnormal ECG (+2). ASR at a cut-point of >2 appears to similar test characteristics as the "OESIL,", "SFSR," and "EGSYS" risk scores.	• These criteria may identify pts who might benefit from hospital admission
Martin T, et al. 1997 9095005 (25)	**Study type:** Prospective observational **Size:** Derivation n=252, validation n=374l	**Inclusion criteria:** Presentation of syncope to an ED **Exclusion criteria:** None	**1° endpoint:** 1 y mortality or arrhythmia **Results:** Predictors include abnormal ECG, Hx of ventricular arrhythmia, >45 y of age, Hx of CHF. Pts without any of these risk factors had <8% risk of the	• These criteria may identify pts who might benefit from hospital admission or close outpatient follow-up.

			outcome.	
Moazez F, et al. 1991 1985382 (26)	**Study type:** Prospective observational **Size:** n=91 pts	**Inclusion criteria:** Syncope of unknown origin referred for EPS **Exclusion criteria:** None	**1° endpoint:** Inducible sustained monomorphic VT **Results:** Risk factors included abnormal signal averaged ECG; abnormal LVEF; prior sustained monomorphic VT	• These criteria may be used to identify pts who might benefit from EPS.
Numeroso F, et al. 2010 20515909 (27)	**Study type:** Retrospective observational **Size:** n=200 pts	**Inclusion criteria:** >18 y of age hospitalized for syncope **Exclusion criteria:** None	**1° endpoint:** Cardiac cause of syncope **Results:** OESIL score <2 had NPV of 98% to exclude cardiogenic cause. Prior syncope episodes and lack of prodrome were associated with increased risk of cardiogenic cause.	• These criteria may identify pts who might benefit from hospital admission
Oh J, et al. 1999 10030311 (28)	**Study type:** Prospective observational **Size:** n=275 pts	**Inclusion criteria:** >18 y of age with syncope of unknown origin after initial evaluation **Exclusion criteria:** None	**1° endpoint:** Arrhythmic syncope **Results:** Risk factors included absence of nausea/vomiting prior to syncope, and ECG abnormalities	• These criteria may identify pts requiring who might benefit from cardiac monitoring
Quinn J, et al. 2004 14747812 (29)	**Study type:** Prospective observational **Size:** n=684 visits	**Inclusion criteria:** Presentation of syncope to an ED **Exclusion criteria:** None	**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 **Results:** In this derivation study, "SFSR" risk score predictors include abnormal ECG, shortness of breath, hematocrit <30%, SBP <90 mmHg, Hx of CHF.	• Using a cutpoint of 0 risk scores, the "SFSR" risk score has 96% sensitivity and 62% specificity. Use of the "SFSR" in the derivation cohort may have reduced hospitalizations by 10%.
Quinn J, et al. 2006 16631985 (30)	**Study type:** Prospective observational **Size:** n=791 consecutive visits	**Inclusion criteria:** Presentation of syncope to an ED **Exclusion criteria:** None	**1° endpoint:** 30 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 **Results:** In this validation cohort, the "SFSR" risk score was 98% sensitive and 56% specific.	• Application of the "SFSR" risk score may have decreased hospitalizations by 7%

Reed M, et al. 2010 20170806 (31)	**Study type:** Prospective observational **Size:** n=550 pts	**Inclusion criteria:** >16 y of age presenting with syncope to an ED **Exclusion criteria:** None	**1° endpoint:** 30 d combined acute MI, dangerous arrhythmia, pacemaker/ICD placement, pulmonary embolus, neurologic event, hemorrhage requiring transfusion, emergent surgical or endoscopic procedure **Results:** The "ROSE" risk score predictors include BNP≥300, bradycardia ≤ 50, rectal exam with fecal occult blood, hemoglobin ≤ 90 g/l, chest pain, ECG with q waves, oxygen saturation ≤ 94% on room air. The validation cohort demonstrated sensitivity of 87% and specificity of 66%.	• These criteria may identify pts who might benefit from hospital admission
Ruwald M, et al. 2013 23450502 (32)	**Study type:** Retrospective registry **Size:** n=37,705 pts	**Inclusion criteria:** Discharged from an ED with first time diagnosis of syncope **Exclusion criteria:** None	**1° endpoint:** All-cause mortality **Results:** The CHADS2 score (HF [+1], hypertension [+1], age ≥75 [+1], DM [+1], prior TIA/ stroke [+2] associated with all-cause mortality.	• CHADS2=0 is associated with 1.5% 1 y mortality rate
Saccilotto R, et al. 2011 21948723 (33)	**Study type:** Meta-analysis **Size:** n=12 studies; n=5,316 pts	**Inclusion criteria:** External validation study of "SFSR" risk score **Exclusion criteria:** N/A	**1° endpoint:** Combined serious outcomes, definition varied by specific study **Results:** The "SFSR" risk score has a pooled sensitivity of 87% and specificity of 52%. Significant between-study heterogeneity was observed	• "SFSR" risk score appears to be less sensitive and specific in external validation studies than originally reported
Sarasin F, et al. 2003 14644781 (34)	**Study type:** Prospective observational **Size:** n=175 pts cohort to develop and cross-validate the risk score; 269 pts cohort to validate the system	**Inclusion criteria:** Unexplained syncope after ED evaluation **Exclusion criteria:** None	**1° endpoint:** Arrhythmic syncope **Results:** Predictors include abnormal ECG, Hx of CHF, ≥65 y of age	• Pts without any risk factors had <2% risk of arrhythmic syncope
Serrano L, et al. 2010 20868906 (35)	**Study type:** Meta-analysis **Size:** n=18 eligible studies	**Inclusion criteria:** ED cohort study of syncope/ near-syncope study for risk score derivation or validation **Exclusion criteria:** N/A	**1° endpoint:** Combined serious outcomes, definition varied by specific study **Results:** The "OESIL" risk score has a pooled sensitivity of 95% and specificity of 31%. The "SFSR" risk score has a pooled sensitivity of 86% and specificity of 49%. Large variations were noted in methodological quality of studies.	• These criteria may identify pts who might benefit from hospital admission

Sheldon R, et al. 2006 16223744 (4)	**Study type:** Prospective observational **Size:** n=418 pts	**Inclusion criteria:** Prior episode of syncope evaluated in cardiology clinic or hospital cardiology wards **Exclusion criteria:** None	**1° endpoint:** Positive tilt test **Results:** CSSS risk score predictors include: any of bifasciular block, asystole, SVT, DM (-5); blue color at time of event (-4); age at first syncope ≥35 (-3), intact memory of event (-2); presyncope/ syncope with standing (+1); sweating/ warm feeling before episode (+2); episode associated with pain or procedure (+3)	• CSSS ≥-2 has sensitivity of 89% and specificity of 91% for identifying tilt-positive syncope
Sule S, et al. 2012 22878409 (36)	**Study type:** Prospective observational **Size:** n=242 consecutive pts	**Inclusion criteria:** Hospitalized for syncope **Exclusion criteria:** None	**1° endpoint:** Mortality **Results:** Predictors included unexplained etiology, SFSR risk score, lack of hypertension, GFR (higher value reduces risk)	• These criteria may identify pts who might benefit from hospital admission
Sun B, et al. 2009 19766355 (37)	**Study type:** Retrospective observational **Size:** n=2,871 pts	**Inclusion criteria:** >60 y of age with unexplained syncope or near-syncope after ED evaluation **Exclusion criteria:** None	**1° endpoint:** 30 d combined death, arrhythmia, MI, new diagnosis of severe SHD, pulmonary embolism, aortic dissection, stroke/TIA, cerebral hemorrhage, significant anemia requiring blood transfusion **Results:** Risk predictors include age >90 (+1), male gender (+1), history of arrhythmia (+1), triage SBP >160 mmHg (+1), abnormal ECG (+1), abnormal troponin result (+1), complaint of near syncope (-1). Score of <1 was associated with 2.5% event rate	• These criteria may identify pts who might benefit from hospital admission

Data Supplement 4. Nonrandomized Trials, Observational Studies, and/or Registries of Risk Stratification - Long-Term Outcomes – (Section 2.3.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Numeroso F, et al. 2014 24489075 (38)	**Study type:** Prospective observational **Size:** n=200 consecutive pts	**Inclusion criteria:** ED syncope **Exclusion criteria:** None	**1° endpoint:** Recurrent syncope, trauma, major procedures, CV events, death **Results:** Any heart disease not associated with endpoints, but high risk heart disease (CAD, CHF, AS, cardiomyopathies, primary arrhythmic diseases) was.	• N/A

Ungar A, et al. 2010 20167743 (39)	**Study type:** Prospective observational **Size:** n=380 pts	**Inclusion criteria:** ED syncope **Exclusion criteria:** None	**1° endpoint:** Death **Results:** Predictors for recurrent syncope were prodromes and palpitations prior to syncope	Incidence of syncope recurrence not related to mechanism of syncope or EGSYS score < or ≥3.
Sule S, et al. 2011 21259276 (40)	**Study type:** Observational **Size:** n=325 pts	**Inclusion criteria:** Hospitalized for syncope **Exclusion criteria:** None	**1° endpoint:** Recurrent syncope **Results:** Associated with recurrent hospitalized syncope were DM, AF and smoking	• Syncope etiology found in 74%
Sumner G, et al. 2010 20662990 (41)	**Study type:** Observational **Size:** n=208 pts	**Inclusion criteria:** NCS with Positive tilt and > lifetime syncope **Exclusion criteria:** None	**1° endpoint:** Recurrent syncope **Results:** Number of syncope in prior y better predicted syncope recurrence compared to lifetime syncope episodes	• Syncope recurred in 22% of those with <2 episodes in the prior y compared to 69% in those with >6 episodes.
Koechl B, et al. 2012 22722821 (42)	**Study type:** Observational **Size:** n=242 pts	**Inclusion criteria:** Syncope **Exclusion criteria:** None	**1° endpoint:** Recurrent syncope **Results:** Increased syncope with age and disability	• Syncope recurrence was 32.5%
Khera S, et al. 2013 23332735 (43)	**Study type:** Observational retrospective **Size:** n=352 pts	**Inclusion criteria:** ED syncope **Exclusion criteria:** None	**1° endpoint:** Admission for syncope **Results:** 3% readmitted; CHF and ACS were risk factors	• Etiology of syncope found in 69%
Sorajja D, et al. 2009 19720940 (44)	**Study type:** Case control **Size:** n=3877 pts with syncope; of which 9.8% had syncope while driving	**Inclusion criteria:** Syncope **Exclusion criteria:** None	**1° endpoint:** Syncope while driving in followup **Results:** In the syncope while driving group (n=381 pts) 72 pts had recurrent syncope, including 10 while driving.	• Etiology of syncope while driving included neutrally mediated (37%) and arrhythmic (12%)
Lee S, et al. 2014 25402339 (45)	**Study type:** Observational **Size:** n=289 pts	**Inclusion criteria:** Syncope **Exclusion criteria:** None	**1° endpoint:** Recurrent syncope **Results:** 6.6% with recurrent syncope in 1 y. Syncope more common in those with ≥6 prior episodes and unexplained syncope	• Etiology of initial syncope 63% NMS, 12% OH, 12% cardiac, 12% unexplained

Ruwald MH, et al. 2013 24035171 (46)	**Study type:** Nationwide administrative registries **Size:** n=5141 pts >85 y of age n=23,454 <85 y of age	**Inclusion criteria:** Syncope **Exclusion criteria:** None	**1° endpoint:** Recurrent syncope **Results:** Predictors of recurrent syncope include: AS, kidney disease, AV or LBBB, Male, COPD, CHF, AF, Age, orthostatic medications	• N/A

Data Supplement 5. Nonrandomized Trials, Observational Studies, and/or Registries of Disposition After Initial Evaluation – (Section 2.3.4)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (include P value; OR or RR; and 95% CI)	Summary/Conclusion Comment(s)
Sun, et al. 2012 22687184 (47)	**Aim:** Create standardized reporting guidelines, including serious outcomes, for syncope research **Study type:** Expert consensus **Size:** n=24 panelists	**Inclusion criteria:** Convenience sample of 24 panelists with clinical or methodological expertise relevant to syncope research	**1° endpoint:** N/A **Results:** Modified Delphi consensus process identified final guideline elements from 183 candidate elements	• 23 serious conditions identified for research reporting
Daccarett, et al. 2011 21757485 (48)	**Study type:** Retrospective observational **Size:** n= 254 pts	**Inclusion criteria:** ED visit for syncope identified by ICD code 780.2 **Exclusion criteria:** Pts with secondary diagnosis of syncope	**1° endpoint:** Admission rate **Results:** 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%).	• A standardized evaluation algorithm that explicitly identified serious conditions which requires admission appears to be safe and reduces resource use.
Framingham Cohort Study Soteriades, et al. 2002 12239256 (49)	**Aim:** Describe prognosis of syncope in general population **Study type:** Prospective cohort	**Inclusion criteria:** Participants in the original Framingham Heart Study and the Framingham Offspring Study **Exclusion criteria:** N/A	**All-cause mortality** Over 25 y follow-up period, pts with presumptive VVS had similar risk-adjusted mortality risk as pts without syncope	• Syncope of vasovagal etiology does not appear to increase mortality risk

	Size: n=7,814 pts			
Morag, et al. 2004 15498613 (50)	**Aim:** Assess diagnostic benefit of admission for unexplained syncope **Study type:** Prospective cohort **Size:** n=45 pts	**Inclusion criteria:** ED visit for syncope, undergoing structured evaluation, age ≥ 50 **Exclusion criteria:** 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)	**1° endpoint:** Life threatening event or significant therapeutic intervention **Results:** Of 30 admitted pts, none experienced the primary endpoint as inpatient or at 30 d follow up	• Yield of diagnostic admission appears to be low
Shiyovich, et al. 2008 18432020 (51)	**Aim:** Assess diagnostic evaluation, costs, and prognosis of pts admitted for syncope **Study type:** Retrospective cohort **Size:** n=376 pts	**Inclusion criteria:** Hospital admission for evaluation of syncope **Exclusion criteria:** pre syncope, seizure, malignant arrhythmia	**1° endpoint:** Diagnostic evaluation, costs, 1 y mortality **Results:** 38% had no clear diagnosis at discharge.	• A significant proportion of pts have an unrevealing evaluation
Schillinger, et al. 2000 11098534 (52)	**Aim:** Assess evaluation and prognosis of pts admitted for syncope **Study type:** Retrospective cohort **Size:** n=127 pts	**Inclusion criteria:** Hospital admission for evaluation of syncope **Exclusion criteria:** Not admitted after ED evaluation	**1° endpoint:** No patient has inpatient death or recurrent syncope as inpatient. 2% of pts died within 30 days, all from known pre-existing disease **Results:** Of 376 pts, 48% had no clear diagnosis at discharge. Long term mortality was higher for pts with cardiac and neurologic etiology.	• Hospital evaluation had modest diagnostic yield; population had low short term mortality risk.
Ungar, et al. 2015 25976905 (53)	**Study type:** Observational **Size:** n= 362 pts	**Inclusion criteria:** ED evaluation for TLOC **Exclusion criteria:** N/A	**1° endpoint:** Disposition **Results:** Disposition included 29% admitted; 20%	• Presence of ED observation unit and hospital based syncope unit is associated with lower hospitalization rates compared to historical experience

			ED observation unit; 20% referred to hospital based syncope unit; 31% discharged. No 1 y death after evaluation in any setting appeared to be related to TLOC	
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 **Size:** n= 244 pts	**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)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
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	• Index hospital costs: $629 less in EDOSP vs. control **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)

Study Acronym; Author; Year Published	Aim of Study; Study Type*; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Pfister R, et al. 2009 18237792 (57)	**Aim:** Determine NT-pro-BNP role in the differential diagnosis of pts with syncope. **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
Thiruganasambandamoorthy 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

GESINUR Pérez-Rodon, et al. 2014 24993462 (11)	**Aim:** Determine outcome predictors on resting ECG **Study type:** Multicenter, prospective, retrospective observational cohort **Size:** n=524 pts	**Inclusion criteria:** Syncope in the ER with 1 y follow-up	**Intervention:** None	**1° endpoint:** Mortality: 33 total deaths (6.6%), 1 SCD	**Summary**: AF, IVCD, LVH and ventricular pacing an independent risk factors for mortality
Chiu DT, et al. 2014 24698512 (59)	**Aim:** Determine the yield of standard diagnostic tests **Study type:** Prospective, observational, cohort study of consecutive ED **Size:** n=570 pts	**Inclusion criteria:** ER presentation syncope **Exclusion criteria:** None	**Intervention:** None **Comparator:** None	**1° endpoint:** Yield of 3 diagnostic tests in those pts that had the test (no structured indication for why tests were performed). **Safety endpoint (if relevant):** None	**Summary**: Diagnosis in 73 pts (8%). Yield: echo 22%, telemetry 3%, troponin 3%.
SYSTEMA Fedorowski, et al. 2013 23510366 (60)	**Aim:** Determine role of biomarkers in pts with syncope **Study type:** Observational cohort **Size:** n=270 pts	**Inclusion criteria:** Unexplained syncope	**Intervention:** Tilt with CSM and biomarker analysis	**1° endpoint:** 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)	**Summary**: Biomarkers divided into quartiles, CT-proET-1 and MR-proANP were associated with diagnoses of OH, carotid sinus hypersensitivity and VVS.
Reed, et al. 2012 22962048 (61)	**Aim:** Assess whether plasma troponin concentration can predict 1 mo and 1 y serious outcome, or all-cause death **Study type:** Prospective observational cohort **Size:** n=261 pts	**Inclusion criteria:** Admitted pts with syncope	**Intervention:** None	**1° endpoint:** 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%).	**Summary**: 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.
Grossman, et al. 2003 14630890 (62)	**Aim:** Determine role of cardiac enzymes in elderly pts with syncope **Study type:** Retrospective chart	**Inclusion criteria:** Consecutive pts 65 y of age and older with syncope in an urban teaching hospital ED	**Intervention:** None	**1° endpoint:** 3 of 141 pts, or 2.1% (95% CI: 0.04%–6.09%), had positive cardiac enzymes during their hospitalization (CPK, not TpI study)	**Summary**: Author conclusion: Cardiac enzymes may be of little additional value if drawn routinely on elderly pts with syncope

	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)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Tanimoto K, et al. 2003 14715356 (64)	**Study type:** Retrospective observational **Size:** n=118 pts	**Inclusion criteria:** Pts with syncope **Exclusion criteria:** AF; renal failure; and who died within 24 h after admission	**1° endpoint:** To evaluate the feasibility of measuring BNP to identify cardiac syncope. **Results:**	**Limitations:** ● Retrospective study, and "unknown" causes could be cardiac **Conclusions:**

			● 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
Christ M, et al. 2015 25447619 (65)	**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

Data Supplement 9. Nonrandomized Trials, Observational Studies, and/or Registries of Cardiac Imaging – (Section 3.2.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Chiu DT, et al. 2014 24698512 (59)	**Study type:** Prospective observational **Size:** n=570 pts presenting to ED with syncope	**Inclusion criteria:** ≥18 y of age with syncope **Exclusion criteria:** Altered mental status; substance-induced LOC; seizure; coma; hypoglycemia; TLOC due to head trauma; near syncope	**1° endpoint:** Finding on diagnostic test (echocardiogram, troponin [suspected AMI], telemetry, ambulatory monitor) while inpatient or follow-up that identified etiology of syncope. **Results:** ● 73 positive tests (12.8%) ● Echo: 33/150 (22%), telemetry: 19/330 (5.7%), ambulatory ECG: 2/56 (3.6%), troponin: 19/317 (6%)	**Limitations:** Single-center study; small sample; no long-term follow-up; kappa rarely >0.80. **Conclusions:** ● Routing testing common, but diagnostic yield low, although they uncover significant causes of syncope. ● Echo the highest yield (low LVEF most common etiology of syncope).
Recchia D, et al.	**Study type:**	**Inclusion criteria:**	**1° endpoint:**	**Limitations:**

1995 8770716 (10)	Retrospective observational **Size:** n=128 pts	Admission for syncope **Exclusion criteria:** Syncope of a known cause, near-syncope or vertigo, clinically obvious seizure, or referred for ECG testing	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&P, and electrocardiography **Results:** ● Echocardiogram normal for 52% pts ● Echocardiograms of pts with syncope and no clinical evidence of heart disease by H&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&P, or ECG, the echocardiogram confirmed the suspected diagnosis for 48% and ruled out a suspected diagnosis for the remaining 52%. ● H&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.	● Single-center study; small sample **Conclusions:** ● For pts without suspected cardiac disease after H&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.
Sarasin FP, et al. 2002 12231593 (66)	**Study type:** Prospective observational **Size:** n=650 pts	**Inclusion criteria:** Adult pts (≥18 y of age) presenting with chief complaint of syncope **Exclusion criteria:** None specified	**1° endpoint:** To study the role of echocardiography in the stepwise evaluation of syncope **Results:** ● 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	**Limitations:** ● Relatively small sample size of pts with SUO and/or arrhythmias. ● EPS not performed. **Conclusions:** ● 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.

			systolic dysfunction and in 12/64 remaining pts (19%) (p<0.01).	
Probst MA, et al. 2015 25943042 (67)	**Study type:** Observational cohort **Size:** n=3,500 pts	**Inclusion criteria:** ED visits where any of the 3 pts "reasons for visit" 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 **Exclusion criteria:** None	**1° endpoint:** To identify temporal trends in syncope-related ED visits and associated trends in imaging, hospital admissions, and diagnostic frequencies. **Results:** ● 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<0.001).	**Limitations:** ● Registry study, potential for residual confounding, miscoding syncope diagnoses **Conclusions:** ● Resource utilization associated with ED visits for syncope appears to have increased, with no apparent improvements in diagnostic yield for admissions
Mendu ML, et al. 2009 19636031 (68)	**Study type:** Observational cohort study **Size:** n=2106 pts	**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. **Exclusion criteria:** Pts in whom absence of loss of consciousness (e.g. near syncope) was documented were excluded.	**1° endpoint:** 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. **Results:** ● ECG (99%), telemetry (95%), cardiac enzymes (95%), and head CT (63%) were the most frequently obtained tests. ● Cardiac enzymes, CTs, echocardiograms, carotid ultrasounds, and electroencephalography all affected diagnosis or management in <5% of cases and helped determine etiology of syncope <2% of the time. ●Postural BP, performed in only 38% of episodes, had highest yield in affecting diagnosis (18–26%) or management (25–30%) and determining etiology of the syncopal episode (15–21%). ● The cost per test affecting diagnosis or management was highest for electroencephalography ($32,973), CT ($24,881), and cardiac enzymes ($22,397) and lowest for postural BP ($17–$20). ●The yields and costs for cardiac tests were better among pts meeting, than not meeting, SFSR.	**Limitations:** ● Retrospective diagnosis of database of a single-center, with potential for misclassification of diagnosis by ICD codes ● No capturing of testing performed in pts not admitted through ED, or after hospitalization. **Conclusions:** ● 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

Data Supplement 10. Nonrandomized Trials, Observational Studies, and/or Registries of Stress Testing – (Section 3.2.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Woelfel, et al. 1983 6875122 (69)	**Study type:** Small case series **Size:** n=3 pts	**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	**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.
Kapoor WN , et al. 1983 6866032 (70)	**Study type:** Prospective cohort **Size:** n=204 pts	**Inclusion criteria:** Symptoms "comparable with syncope" **Exclusion criteria:** Tonic-clonic movements; post-ictal state; aura	**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<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).

Data Supplement 11. RCTs Comparing Cardiac Monitoring – (Section 3.2.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Krahn, et al. 2001 11435336 (71)	**Aim:** To compare ILR to conventional monitoring in SUO. **Study type:** RCT, cross-over **Size:** n=60 pts	**Inclusion criteria:** Recurrent SUO or a single episode of syncope associated with injury that warranted CV investigation. **Exclusion criteria:** LVEF <35%; unlikely to survive for 1 y; unable to provide follow-up or give informed consent.	**Intervention:** ILR with one y of monitoring (n=30). **Comparator:** "Conventional testing" with a 2 to 4 wk period of monitoring with an ELR, followed by tilt table, and EPS (n=30).	**1° endpoint:** ● 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).	**Limitations:** ● 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). **Conclusions**: ● 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
Krahn AD, et al. 2003 12906979 (72)	**Aim:** To compare cost-effectiveness of ILR to conventional testing. **Study type:** RCT, crossover **Size:** n=60 pts	**Inclusion criteria:** Recurrent SUO or a single episode of syncope associated with injury that warranted CV investigation. **Exclusion criteria:** LVEF <35%; unlikely to survive for 1y; unable to provide follow-up or give informed consent.	**Intervention:** ILR with one y of monitoring (n=30). **Comparator:** "Conventional testing" with a 2 to 4 wk period of monitoring with ELR, followed by tilt table, and EPS (n=30).	**1° endpoint:** ●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<0.0001) and $8,414 ±$2,527/diagnosis (p<0.0001).	**Limitations:** ● 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. **Summary**: ● A strategy of primary monitoring is more cost-effective than conventional testing in establishing a diagnosis in recurrent SUO.
Farwell, et al. 2006 16314338 (73)	**Aim:** To investigate the impact of ILR on pts with recurrent SUO.	**Inclusion criteria:** Consecutive pts presenting to single center, ≥16 y of age; acute syncope presentation; ≥2 SUO in 12 mo; no	**Intervention:** ILR (n=103) **Comparator:** Conventional (n=98)	**1° endpoint:** ● Time to diagnosis: 43% vs. 6% HR: 6.5; 95% CI: 3.7–11.4; p<0.001.	**Limitations:** ● Single center, non-blinded trial. **Summary**: ● ILR significantly increases diagnostic

	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	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.	rate and ECG directed treatments in a typical unselected syncopal population. ● Long-term follow-up demonstrated a significant subsequent reduction in syncopal events with improved QoL.
Da Costa A, et al. 2013 23582676 (74)	**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:** 2nd or 3rd 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.	**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.

Sivakumaran, et al. 2003 12867227 (75)	**Aim:** To compare diagnostic utility of ELR to Holter in determining arrhythmic cause of syncope. **Study type:** RCT **Size:** n=100 pts	**Inclusion criteria:** SUO: index symptoms of syncope, presyncope, or both, referred for ambulatory ECG monitoring. **Exclusion criteria:** None stated	**Intervention:** Initial 48 H Holter (n=51) **Comparator:** Initial 30 d ELR (n=49)	**1° endpoint:** ●63% ELR vs. 24% Holter had arrhythmia identified or excluded, p<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<0.00001).	**Limitations**: ● Non-blinding; pre-enrollment evaluation not standardized. **Conclusions**: ● 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.
Rothman SA, et al. 2007 17318994 (76)	**Aim:** To compare the relative value of a MCOT c/w ELR. **Study type:** Multicenter RCT **Size:** n=266 pts, 17 centers	**Inclusion criteria:** 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. **Exclusion criteria:** 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 <18 y of age, condition prohibiting completion of or compliance with protocol.	**Intervention:** MCOT (n=134) **Comparator:** Loop (n=132)	**1° endpoint:** ● 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<0.001.	**Limitations:** ● Neither patient nor investigator blinded (although independent strip review). Patient compliance not 100%. **Conclusions**: ● 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.

Data Supplement 12. Nonrandomized Trials, Observational Studies, and/or Registries of Cardiac Monitoring – (Section 3.2.3)

Study Acronym;	Study Type/Design;	Patient Population	Primary Endpoint and Results	Summary/Conclusion

Author; Year Published	Study Size		(P values; OR or RR; & 95% CI)	Comment(s)
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% vs. 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 bradyarrhythmia 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

		Exclusion criteria: None specified	● The most frequent finding, which was recorded in 46% and 62% of pts, respectively, was one or more prolonged asystolic pauses, mainly due to sinus arrest.	mediated, and the most frequent mechanism was a bradycardic reflex. In the other cases, a normal sinus rhythm was frequently recorded.
Brignole M , et al. 2001 11673344 (80)	**Study type:** Prospective observational **Size:** n=52 pts	**Inclusion criteria:** All pts with any type of BBB with QRS >100 ms, no documentation of 2nd or 3rd degree AV block, and a negative EPS, and SUO **Exclusion criteria:** None specified	**1° endpoint:** 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. **Results:** ● During a follow-up of 3–15 mo, syncope recurred in 22 pts (42%). ● The most frequent finding, recorded in 17 pts, was ≥prolonged asystolic pause mainly attributable to AV block. ● The median duration of the arrhythmic event was 47 s. An additional 3 pts developed nonsyncopal persistent 3rd degree AVB, and 2 pts had presyncope attributable to AVB with asystole. ● No pts suffered injury attributable to syncopal relapse.	**Limitations:** ● 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. **Conclusions:** ● 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.
Garcia-Civera R, et al. 2003 12628723 (81)	**Study type:** Prospective observational **Size:** n=184 pts	**Inclusion criteria:** 184 pts with SUO. EPS: Any of presence of structural heart disease or family Hx of SCD; abnormal ECG; significant non-symptomatic 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. **Exclusion criteria:** None	**1° endpoint:** Diagnostic yield of a protocol in which EPS, TTTs, and ILR are selectively used in SUO. **Results:** ● 32/72 with inclusion criteria had positive EPS. 80/112 had positive TTT. 23/40 with negative EPS had positive TTT. ILR implanted in 15/17 pts with negative EPS who subsequently had negative TTT, with diagnostic activation in 7. Overall, 143/184 pts with positive diagnosis.	**Limitations**: ● Authors feel no ATP testing was a limitation ● No follow-up of all pts with ILR to confirm diagnosis **Conclusions**: ● In SUO, selective use of EPS or TTT leads to positive diagnosis in >70% of cases. ILR can be useful in non-diagnosed cases.
Ermis C, et al. 2003 14516882	**Study type:** Prospective observational	**Inclusion criteria:** >2 syncopal episodes, or significant physical injury with event	**1° endpoint:** Evaluate relative utility of auto-activate ILR based on a arrhythmia grading system in terms of the likelihood that	**Limitations**: ● Small sample, unclear how generalizable scoring system is.

(82)	**Size:** n=50 pts	**Exclusion criteria:** None	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.
Boersma L, et al. 2004 14697729 (83)	**Study type:** Prospective observational **Size:** n=43 pts	**Inclusion criteria:** SUO, ≥3 episodes of syncope within 6 mo **Exclusion criteria:** None	**1° endpoint:** Diagnosis of arrhythmia by ILR **Results:** ● 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.	**Limitations**: ● Not all had full diagnostic workup 18 mo follow-up somewhat limited. Small sample **Conclusions**: ● 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.
Solano A, et al. 2004 15231369 (84)	**Study type:** Observational, prospective, 2-hospital **Size:** n=2057, 103 ILR	**Inclusion criteria:** High-risk syncope: (1) were very frequent, or (2) were recurrent and unpredictable or (3) occurred during the prosecution of a `high risk' activity **Exclusion criteria:** Presyncope	**1° endpoint:** ECG diagnosis made by analysis of the ECG tracing obtained during the first syncopal episode that was correctly recorded by the device. **Results:** ● 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.	**Limitations**: ● Limited to high-risk group **Conclusions**: ● Mechanism of SUO is different in pts with and without SHD, though diagnostic yield and safety are similar in both groups.
Krahn, et al. 2004 15309004 (85)	**Study type:** Prospective observational **Size:** n=60 pts	**Inclusion criteria:** ≥30 y, with LVEF ≥35% and SUO (negative 24 h ambulatory/inpatient monitor, echocardiogram) had ILR	**1° endpoint:** Prespecified arrhythmias: pause >5 seconds; 3rd degree AVB >10 seconds; Heart rate <30 beats/min for >10 seconds while awake;	**Limitations**: ● Population likely to have recurrence and arrhythmias. Asymptomatic arrhythmias considered diagnostic.

		Exclusion criteria: LVEF <35%; limited survival; neurally mediated syncope	wide complex tachycardia >10 beats; narrow complex tachycardia >180 beats/min for >30 beats. **Results:** ● Recurrent symptoms developed in 30 pts during the 1 y follow-up period (47%), with arrhythmias detected in 14 pts. Pre-specified significant asymptomatic arrhythmias developed in 9 pts with bradycardia in 7 pts who underwent pacemaker implantation. 20 pts had borderline asymptomatic arrhythmias. 5 of these pts went on to have more pronounced diagnostic arrhythmias of same mechanism during further follow-up, including pauses of 6–17 s duration in 3 pts.	**Conclusions**: ● 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.
Pierre B, et al. 2008 18325892 (86)	**Study type:** Prospective observational **Size:** n=95 pts	**Inclusion criteria:** SUO: ≥3 episodes of syncope, normal workup including EPS, CSM **Exclusion criteria:** LVEF ≤30–35%, candidates for primary ICD	**1° endpoint:** 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. **Results:** ● During an average follow-up period of 10.2±5.2 mo, 27/43 pts developed a new syncope associated with an arrhythmic event. ● Syncope no more frequent in subgroup of pts with cardiac conduction abnormalities on resting ECG, while the frequency of arrhythmic events was similar whether or not the ECG was normal.	**Limitations**: ● Relatively small size with extensive negative workup. **Conclusions**: ● ILR useful diagnostic tool for recurrent syncope of unknown etiology in pts with or without cardiac conduction abnormalities or cardiac disease. ● The absence of arrhythmic events was frequently reported in all patient subgroups. This argues against an empirical pacing strategy in pts with cardiac conduction abnormalities on resting ECG suffering from recurrent syncope, but normal EPS.
Pezawas T, et al. 2008 17947364 (87)	**Study type:** Prospective observational **Size:** n=70 pts	**Inclusion criteria:** SUO (ISSUE classification) with ≥2 episodes, then ILR implanted **Exclusion criteria:** None	**1° endpoint:** Stratify mechanisms and predictors of SUO documented by an ILR in pts with and without SHD. **Results:** ● Syncopal recurrence occurred during 16 mo in 30 pts (91%) with SHD and in 30 pts (81%) without SHD. ● 45% vs. 51%, respectively, had an ILR documented arrhythmia at time of recurrence which led to specific	**Limitations**: ● Not necessarily generalizable—referral center. **Conclusions**: ● Presence of SHD has little predictive value for the occurrence or type of arrhythmia in pts with SUO.

			treatment. ● The remaining 45% with SHD and 30% without SHD had normal sinus rhythm at the time of the recurrence. ● Major depressive disorder predictive for early recurrence during ILR follow-up (p=0.01, HR: 3.35; 95% CI: 1.1–7.1). ● 57% of pts with major depressive disorder had sinus rhythm during recurrence compared with 31% of pts without the disorder (p=0.01). ● Conversely, no patient with major depressive disorder had asystole compared with 33% without (p<0.001).	● Pts with major depressive disorder are prone to early recurrence of symptoms and have no evidence of arrhythmia in most cases.
Edvardsson N, et al. 2011 21097478 (88)	**Study type:** Multicenter prospective observational **Size:** n=570 pts	**Inclusion criteria:** Recurrent SUO or pre-syncope **Exclusion criteria:** None specified	**1° endpoint:** 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. **Results:** ● 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.	**Limitations**: ● 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. **Conclusions**: ● 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.
Linker NJ, et al. 2013 24182906 (89)	**Study type**: Multicenter observational registry (PICTURE) **Size:** n=514 pts with ILR (25% implanted during initial work-up, 75%	**Inclusion criteria:** Recurrent SUO or pre-syncope **Exclusion criteria:** No evidence of "unexplained syncope," no follow-up data, ILR implanted for another reason	**1° endpoint:** First recurrence of syncope leading to a diagnosis or for at least 1 y after implant **Results:** ● Initial (8 tests [IQR 6-14]) vs. Full (14 tests [IQR 10-21]), p<0.0001. ● Hospitalization and injury before implant less common in	**Limitations**: ● "Unexplained," "initial workup," or "full evaluation" not defined in protocol **Conclusions**: ● Diagnostic yield of ILR high in both protocols. ● High number of testing in both protocols may have been mitigated by earlier ILR.

	after "full evaluation"		pts with "initial work-up": 53 vs. 75%, p<0001, and 23% vs. 39%, p<0.001, as were visits to specialists, p<0.001. ● Recurrence rate:32 initial vs. 36% full at 12 mo Recurrence with ILR diagnosis: 52 vs. 75% at 12 mo; cardiac dx: 90 vs. 79%	
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.

Locati ET, et al. 2016 26519025 (93)	**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).	• 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.

Data Supplement 13. Nonrandomized Trials, Observational Studies, and/or Registries of In-Hospital Telemetry – (Section 3.2.4)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
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.

			monitoring time was 72 H (sensitivity 73%, specificity 86%).	
Lipskis DJ, et al. 1984 6711429 (95)	**Study type:** Prospective observational **Size:** n=205 pts	**Inclusion criteria:** Pts admitted to telemetry **Exclusion criteria:** None specified	**1° endpoint:** ● To determine the benefits of telemetry in terms of arrhythmia diagnosis and therapy administered. **Results:** ● 14 episodes of significant arrhythmias in 12 pts who required specific intervention were detected over 608 patient-days of monitoring. ● Significant arrhythmias occurred only in pts with known or suspected CAD or in those with previously documented arrhythmias.	**Limitations:** ● Older data, not limited to syncope **Conclusions:** ● The diagnostic yield of ECG monitoring in pts with syncope may be low in the absence of a high amount of suspicion about an arrhythmic cause.
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 specified	**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 pts	**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 AVB (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 ELR, shows utility in SUO.
Schuchert A , et al. 2003	**Study type:** Prospective observational	**Inclusion criteria:** ≥2 SUO within 6 mo, negative TTT,	**1° endpoint:** Assess diagnostic yield of ELR in pts with	**Limitations:** ● Low sample size, all ELR patient triggered.

12930497 (96)	**Size:** n=24 pts	no SHD, no VVS trigger **Exclusion criteria:** None specified	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)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (include P value; OR or RR; and 95% CI)	Summary/Conclusion Comment(s)
Linzer M, et al. 1997 9214258 (97)	**Study type:** Literature review (population studies, referral studies, or case series) **Size:** N/A	**Inclusion criteria:** Published papers were selected if they addressed diagnostic testing in syncope, near syncope, or dizziness **Exclusion criteria:** N/A	**1° endpoint:** To review the literature on diagnostic testing in syncope that remains unexplained after initial clinical assessment. **Results:** After a thorough H&P, and electrocardiography, the cause of syncope remains undiagnosed in 50% of pts. In such pts, information may be derived from the results of carefully selected diagnostic tests, especially 1) EPS in pts with organic heart disease, 2) Holter monitoring or telemetry in pts known to have or suspected of having heart disease, 3) loop monitoring in pts with frequent events and normal hearts, 4) psychiatric evaluation in pts with frequent events and no injury, and 5) TTT in pts who have infrequent events or in whom VVS is suspected. Hospitalization is indicated for high-risk pts, especially those with known heart disease and elderly pts.	**Limitations:** • Older data, methods unclear. **Conclusions:** • After a thorough H&P, and ECG, 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 **Size:** n=100 pts	**Inclusion criteria:** Pts with syncope of unclear etiology who underwent EPS. **Exclusion criteria:** Documented arrhythmia at	**1° 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. **Results:**	**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 only 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.
Click RL, et al. 1987 3825942 (99)	**Study type:** Prospective cohort **Size:** n=112 pts	**Inclusion criteria:** Syncope/near syncope, symptomatic pts with BBB undergoing EPS **Exclusion criteria:** CV collapse, or requiring resuscitation	**1° endpoint:** To determine the role of invasive EP testing in pts with symptomatic BBB. **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%	**Limitations:** • Older data, limited and specific population **Conclusions:** • In symptomatic pts with BBB and normal EP test results, prognosis is good without treatment. In pts undergoing permanent pacing based on EP testing, survival is good and rate of symptom recurrence is low. EP testing identifies pts with inducible VT for whom antiarrhythmic therapy is indicated but who nevertheless have a poor prognosis.
Reiffel JA, et al. 1985 4072872 (100)	**Study type:** Prospective cohort **Size:** n=59 pts	**Inclusion criteria:** 24 H ambulatory ECG monitoring and then EP testing for unexplained syncope. **Exclusion criteria:** None specified	**1° 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. **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.	**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 **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.

Gulamhusein S, et al. 1982 7137203 (101)	**Study type:** Prospective cohort **Size:** n=34 pts	**Inclusion criteria:** Unexplained syncope/near syncope who underwent PES **Exclusion criteria:** None specified.	**1° endpoint:** To assess the value of clinical EPS using intracardiac recording and PES in 34 pts who had unexplained syncope and/or presyncope. **Results:** • 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.	**Limitations:** • 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. **Conclusions:** • The diagnostic yield of EP testing is low in a patient population that has no ECG abnormality or clinical evidence of cardiac disease.
Sagrista-Sauleda J, et al. 2001 11350095 (102)	**Study type:** Retrospective cohort **Size:** n=600 pts	**Inclusion criteria:** Syncope of unknown etiology who underwent TTT, after H&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.	**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. **Results:** • 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<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<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<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<0.0005, OR: 7.1), and it was especially low in pts with a normal ECG and without organic heart disease (2.6%).	**Limitations:** • Retrospective study in very specific population of pts undergoing TTT. **Conclusions:** • 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.
Gatzoulis KA, et al. 19419396 (103)	**Study type:** Prospective cohort	**Inclusion criteria:** Syncope of unknown etiology who had an ECG,	**1° endpoint:** To assess the utility of noninvasive electrocardiographic evaluation (12-lead ECG and 24 H ambulatory	**Limitations:** • Specific population, unclear generalizability.

	Size: n=421 pts	an EPS, and 24 H ambulatory monitoring **Exclusion criteria:** None specified	electrocardiographic recordings) to predict electrophysiology study results in pts with undiagnosed syncope. **Results:** 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 ($p<0.001$), 17.8 ($p<0.001$), and 3.5 ($p=0.064$) for abnormal findings on EPS, respectively (first 3 groups vs. the 4th one).	**Conclusions:** ● 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.
Hess DS , et al. 1982 7148707 (104)	**Study type:** Prospective observational **Size:** n=32 pts	**Inclusion criteria:** Syncope of unclear etiology **Exclusion criteria:** None specified	**1° endpoint:** Detection of brady and tachyarrhythmias in EPS to elucidate cause of SUO. **Results:** ● 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	**Limitations:** ● Small study and most pts had organic heart disease (more inducible VT). ● Older data, medical therapy changed now. **Conclusions:** ● The study shows some value in EPS in elucidating cause of syncope, in selected population with SUO.
Gulamshusein S, et al. 1982 7137203 (101)	**Study type:** Prospective observational **Size:** n=34 pts	**Inclusion criteria:** 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 **Exclusion criteria:** None specified	**1° endpoint:** Assess diagnostic yield of EPS in SUO. **Results:** ● 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	**Limitations:** ● EPS less diagnostic than predicted: some pts required pacing despite normal or nondiagnostic EPS. **Conclusions:** ● Diagnostic yield of EPS testing is low in a patient population that has no ECG abnormality or clinical evidence of cardiac disease.
Akhtar M , et al.	**Study type:**	**Inclusion criteria:**	**1° endpoint:**	**Limitations:**

1983 6189057 (105)	Prospective observational **Size:** n=30 pts	SUO (≥ 2 episodes in preceding y); negative evaluation **Exclusion criteria:** None specified	To assess results of EPS with PES in pts with recurrent syncope **Results:** ● Sustained or nonsustained VT and/or VF induced in 11/30; SND in 4/30; Intra-His AVB in remaining 1/30. ● 14/16 remained free of symptoms following therapy based on results of EPS during a mean 16 mo f/u. ● In 2/16 syncope recurred (one arrhythmic and one non-arrhythmic) despite pacemaker therapy for SND detected during EPS. ● In remaining 14/30 pts, EPS and PES did not induce arrhythmia which could account for patient symptomatology. However, 11/14 pts experienced a recurrence of symptoms within a 6–25 mo period (mean 16.2±6.8). ● Of 15/16 pts with inducible arrhythmias considered clinically significant had structural heart disease. ● 3/14 pts without clinically significant arrhythmias had structural heart disease.	All pts received EPS, high risk group. **Conclusions:** EPS with PES can uncover type of arrhythmic disturbance in a significant number of cases.
Morady F, et al. 1984 6475778 (106)	**Study type:** Prospective observational **Size:** n=32 pts	**Inclusion criteria:** SUO undergoing EPS **Exclusion criteria:** 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	**1° endpoint:** Diagnostic yield of EPS with PES in pts with SUO **Results:** ● HV interval ≥70 ms or greater in 12 pts ● Pathologic infranodal AVB during atrial pacing occurred in 2 pts→PPM ● Monomorphic VT induced in 9 pts and polymorphic VT in 5→AAD ● Actuarial incidence of sudden death was 10% at 45 mo of follow-up ● Only 2 pts had recurrent syncope; both had normal EPS	**Limitations:** ● 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. ● In some pts, the decision to implant PPM was due to patient preference, not EPS testing. **Conclusions:** ● Approximately 50% of pts with BBB and unexplained syncope who undergo EPS are found to have a clinically significant abnormality. ● Long-term management guided by the results of ESP generally is successful in preventing recurrent syncope.
Doherty JU, et al. 1985 3976512 (107)	**Study type:** Prospective observational	**Inclusion criteria:** SUO undergoing EPS **Exclusion criteria:**	**1° endpoint:** EPS findings of pts with SUO **Results:**	**Limitations:** ● EPS negative group differed in the frequency of heart disease.

	Size: n=119 pts	Known cause of syncope	● 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.	**Conclusions:** ● EPS can identify a subgroup of pts at low risk of recurrence and sudden death in the absence of therapy.
Olshansky B, et al. 1985 3968306 (108)	**Study type:** Prospective observational **Size**: n=105 pts	**Inclusion criteria:** SUO undergoing EPS **Exclusion criteria:** None specified	**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).	**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. **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	**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).	**Limitations:** ● Observational data, limited sample, no control. **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.
Krol RB, et al. 1987	**Study type:**	**Inclusion criteria:**	**1° endpoint:**	**Limitations:**

3598006 (110)	Prospective observational **Size:** n=104 pts	≥1 SUO episode **Exclusion criteria:** Sustained VT; high grade AV block; CSH; vasovagal/vasodepressor syncope; QT prolongation; AS; HCM; symptomatic postural hypotension; brady/tachyarrhythmia known to cause syncope	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) **Results:** ● 31 pts had positive EPS, inducible VT most common finding (71% of positive studies). ● LVEF ≤40% most powerful predictor of a positive EPS (p<0.00001), followed by the presence of BBB (p<0.00003), CAD (p<0.0003), remote MI (p<0.00006), use of type 1 AAD (p<0.00003), injury related to LOC (p<0.01) and male sex (p<0.01). ● A negative EPS associated with LVEF >40% (p<0.00001), absence of structural heart disease (p<0.00001), normal ECG (p<0.0001) and normal ambulatory ECG monitoring (p<0.0001). ● Probability of a negative study increased as number and duration of syncopal episodes increased.	● No episodes of syncope with ECG recorded. **Conclusions:** ● 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.
Fujimura O, et al. 1989 2594030 (111)	**Study type:** Prospective observational **Size:** n=21 pts	**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 **Exclusion criteria:** None specified	**1° endpoint:** 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 syncope. **Results:** ● 3/8 with documented sinus pauses had abnormal EPS including a prolonged SNRT in 1 and carotid-sinus hypersensitivity in 2 pts. ● 3/8 pts had abnormalities unrelated to syncope. ● 2/13 with documented AVB had abnormalities suggesting correct diagnosis.	**Limitations:** ● Small study limited to pts with transient ECG findings. **Conclusions:** ● 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 syncope.
Moazez F, et al. 1991 1985382 (26)	**Study type:** Prospective observational **Size**: n=91 pts	**Inclusion criteria:** SUO undergoing EPS **Exclusion criteria:** BBB, unknown data on LVEF or SAECG	**1° endpoint:** To examine usefulness of clinical and noninvasive variables to predict EPS, and to compare EPS results and therapy with syncope recurrence **Results:** ● Multivariate analysis identified +SAECG, LVEF, and history of sustained monomorphic VT as risk factors for induction of	**Limitations:** ● BBB pts excluded. ● No TTT or isoproterenol infusion performed. **Conclusions:** ● Pts who have inducible sustained monomorphic VT at EPS can be identified using certain clinical and noninvasive variables.

			sustained monomorphic VT at EPS. ●17 pts had recurrence of syncope over 19.0±8.3 mo of follow-up. ● Recurrence rates among empiric, EP-guided (sustained monomorphic VT), and no therapy groups were similar.	● When these pts undergo EP-guided therapy, their rate of recurrence of syncope similar to pts who had no arrhythmia induced at EPS. ● Empiric therapy does not offer any benefit over no therapy in reducing the rate of recurrent of scope.
Sra JS, et al. 1991 2029096 (112)	**Study type:** Retrospective observational **Size**: n=86 pts	**Inclusion criteria:** SUO undergoing EPS, and HUTT if negative. **Exclusion criteria:** None specified	**1° endpoint:** To determine the clinical characteristics of subgroups of pts with SUO having EPS and HUTT and to assess efficacy of various therapies. **Results:** ● 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.	**Limitations:** ● Retrospective evaluation **Conclusions:** ● The combination of EPS and HUTT can identify the underlying cause of syncope in as many as 74% of pts presenting with SUO.
Muller T, et al. 1991 2044546 (113)	**Study type:** Prospective observational **Size:** n=134 pts	**Inclusion criteria:** SUO **Exclusion criteria:** None specified	**1° endpoint:** EPS findings of pts with SUO. **Results:** ● 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).	**Limitations:** ● Small sample, moderate follow-up **Conclusions:** ● 19% of pts will have a recurrent event. ● Female gender may be an independent predictor of favorable outcome.
Denniss AR , et al. 1992 1572741 (114)	**Study type:** Prospective observational **Size**: n=111 pts	**Inclusion criteria:** SUO undergoing EPS **Exclusion criteria:** None specified	**1° endpoint:** Compare incidence of EPS abnormalities in pts with and without heart disease, and the effect of treatment of these abnormalities on recurrence of syncope. **Results:**	**Limitations:** ● Failure to demonstrate mortality reduction may be due to high-risk group, refractory to treatment. **Conclusions:** ● Syncope pts with heart disease more likely to have a

			● Abnormalities detected in 31/73 with heart disease but in only 6/38 with no heart disease (p<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<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<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).	diagnostically useful study than pts with normal hearts. ● Treatment directed at correction of abnormalities detected at EPS reduced recurrence of syncope but did not significantly affect mortality.
Link MS, et al. 1999 10235091 (115)	**Study type:** Retrospective observational **Size:** n=68 pts	**Inclusion criteria:** Syncope or presyncope and CAD, with unclear etiology **Exclusion criteria:** Sudden cardiac death; spontaneous sustained VT; noninvasive testing explained syncope	**1° endpoint:** Long-term outcome of pts with CAD and non-diagnostic work-up, including EPS **Results:** ● At a mean follow-up of 30±18 mo, 17 pts had recurrence. ● All 4 arrhythmias occurred in pts with LVEF ≤25%. ● Predictors of all-cause mortality: age (p=0.05) and reduced LVEF (p=0.02). ● Predictors of ventricular arrhythmias: BBB (p=0.07), longer runs of NSVT (p=0.08), lower LVEF (22.5±3% vs. 43±16%), p=0.09).	**Limitations:** ● Retrospective, HV ≥90 ms excluded. **Conclusions:** ● In pts with CAD and syncope, noninducibility at EPS predicts a lower risk of SCD and VT/VF. ● In pts with a reduced LVEF, the risk remains up to 10%/y; these pts may warrant treatment with ICDs.
Knight BP, et al. 1999 10362200 (116)	**Study type:** Prospective observational **Size:** n=33 pts	**Inclusion criteria:** "Syncope Group": NICM, SUO, and negative EPS who underwent ICD (n=14); "Arrest Group": NICM with cardiac arrest and ICD (n=33) **Exclusion criteria:** None specified.	**1° endpoint:** Determine outcome of pts with NICM, negative EPS, and SUO treated with ICD **Results:** ● 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).	**Limitations:** ● Small size, unclear "appropriate" shocks in devices without stored EGM. **Conclusions:** ● The high incidence of appropriate ICD shocks and the association of recurrent syncope with ventricular arrhythmias support treatment of pts with nonischemic cardiomyopathy, SUO and a negative EPS with an ICD.
Sagristà-Sauleda J, et al. 2001 11350095 (102)	**Study type:** Observational cohort **Size:** n=600 pts	**Inclusion criteria:** Group I: first syncope at age ≤65 y (n=464 pts) Group II: first syncope at age >65 y (n=136 pts) 4 subgroups in both:	**1° endpoint:** To assess diagnostic yield of TTT and EPS in different groups of pts with SUO established according to simple clinical criteria. **Results:** ● Positive TTT-more common in (group I) than group II (47% vs.	**Limitations:** ● Retrospective, and only TTT pts studied. EPS done at physician discretion. **Conclusions:** ● The rate of positive responses to the head-up tilt test

		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%).	was higher in younger pts and in pts with a normal ECG and without organic heart disease (49%), while older pts with an abnormal ECG and with organic heart disease had the lowest rate of positive responses (18%). ● The diagnostic yield of EPS was higher in older pts, in pts with organic heart disease and with an abnormal ECG (26%); it was lowest in pts without organic heart disease and with a normal ECG (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.)

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

Kenny RA, et al. 1986 2872472 (118)	**Study type:** Case-control study **Size:** n=25 pts (15 test, 10 control)	**Inclusion criteria:** Syncope of unclear etiology **Exclusion criteria:** None specified	**1° endpoint:** To investigate the utility of syncope that remained unexplained despite full clinical and electrophysiological assessment. **Results:** ● In 10 pts and one control VVS developed after 29±19 min (p<0.001). In symptomatic pts SBP fell from 150 ± 32 to 56 ± 9 mm Hg (p<0.001) and heart rate from 62 ± 9 to 38 ± 12 bpm (p<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).	**Limitations:** ● Small sample, all with EPS **Conclusions:** ● 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.
Fitzpatrick A, et al. 1991 2040321 (119)	**Study type:** Retrospective cohort **Size:** n=322 pts	**Inclusion criteria:** Recurrent syncope **Exclusion criteria:** None	**1° endpoint:** To utilize TTT to discover the incidence of malignant VVS in pts with recurrent syncope. **Results:** ● 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<0.01).	**Limitations:** ● All pts underwent EPS, with a large percentage (70%) of abnormal findings (limited generalizability). **Conclusions:** ● 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.
Passman R, et al. 2003 12963568 (120)	**Study type:** Retrospective cohort **Size:** n=694 pts	**Inclusion criteria:** Pts with syncope **Exclusion criteria:** None	**1° endpoint:** To assess the prevalence and type of apparent neurologic events associated with tilt table testing. **Results:** ● 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	**Limitations:** ● 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 **Conclusions:** ● Neurologic events are common during episodes of neurocardiogenic syncope, and this diagnosis should be considered in the evaluation of unexplained seizure-like activity.

			neurologic events (p<0.01) than in those with positive test results and no provoked neurologic events, and asystole was provoked more frequently in these 2 patient populations (p=0.03).	
Grubb BP, et al. 1991 1952474 (121)	**Study type:** Prospective cohort **Size:** n=15 pts	**Inclusion criteria:** Recurrent unexplained seizure-like episodes, unresponsive to antiseizure medication. **Exclusion criteria:** None	**1° endpoint:** 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. **Results:** ● 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.	**Limitations:** ● Small sample, single center study **Conclusions:** ● Upright TTT combined with isoproterenol infusion may be useful to distinguish convulsive syncope from epileptic seizures
Song PS, et al. 2010 20046517 (122)	**Study type:** Retrospective cohort **Size:** n=226 pts	**Inclusion criteria:** Syncope during HUTT without any other cause of syncope **Exclusion criteria:** None	**1° endpoint:** To assess the incidence and characteristics of seizure-like activities during HUTT-induced syncope in pts with neurally mediated reflex syncope. **Results:** ● 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.	**Limitations:** ● 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. **Conclusions:** ● 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.
Zaidi A, et al. 2000 10898432 (123)	**Study type:** Prospective cohort **Size:** n=74 pts	**Inclusion criteria:** Diagnosis of epilepsy, with continued attacks despite adequate anticonvulsant drug treatment (n=36 pts) or uncertainty about the	**1° endpoint:** To investigate the value of CV tests to diagnose convulsive syncope in pts with apparent treatment-resistant epilepsy. **Results:** ● An alternative diagnosis was found in 31 pts (41.9%), including 13 (36.1%) of 36 pts taking an anticonvulsant medication.	**Limitations:** ● Small sample, single center; highly unique population **Conclusions:** ● A simple, noninvasive CV evaluation may identify an alternative diagnosis in many pts with

		diagnosis of epilepsy, on the basis of the clinical description of the seizures (n=38 pts) **Exclusion criteria:** Suspected psychogenic nonepileptic attack disorder	● 19 pts (25.7%) developed profound hypotension or bradycardia during the HUTT, confirming the diagnosis of VVS. ● 1 patient 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.	apparent epilepsy and should be considered early in the management of pts with convulsive blackouts.
Zaidi A, et al. 1999 10512777 (124)	**Study type:** Prospective cohort **Size:** n=21 pts	**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:** ● 17 pts (81%) experienced typical symptoms (non-epileptiform limb shaking in 15 pts, absence in one patient, myoclonic jerking in one patient) during head-up tilt without significant EEG abnormalities or hemodynamic changes.	**Limitations:** ● Small sample, select population. **Conclusions:** ● HUT 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.
Luzza F, et al. 2003 12846340 (125)	**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.
Tannemaat MR, et al. 2013 23873974 (126)	**Study type:** Prospective cohort **Size:** n=800 pts	**Inclusion criteria:** Episode 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:**	**Limitations:** ● 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

		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).	affected the prevalence of jerking movements. **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 7798528 (127)	**Study type:** Randomized double-blind crossover study **Size:** n=30 pts	**Inclusion criteria:** Syncope and a baseline positive HUTT. **Exclusion criteria:** Previous hypertension and 11 (11%) because of a cardioinhibitory response to HUTT.	**1° endpoint:** To assess the efficacy of oral etilefrine in preventing a positive response to HUTT. **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)	**Limitations:** ● Small sample, drug not used clinically in most centers. The statistical power of the study was only 10%. **Conclusions:** ● Oral etilefrine (10 mg 3x a day) was not superior to placebo in preventing a positive response to HUTT. Despite a low statistical power, the high rate of negative response with placebo (50%) suggests that controlled trials are needed to assess the real efficacy of any treatment in pts with VVS.
Morillo CA, et al. 1993 8245337 (128)	**Study type:** Double-blind randomized trial **Size:** n=22 pts, randomly allocated to receive either intravenous disopyramide or placebo	**Inclusion criteria:** Recurrent neurally mediated syncope and 2 or more successive positive HUTT responses **Exclusion criteria:** Failure to produce syncope or presyncope during testing	**1° endpoint:** To determine the efficacy of intravenous and oral disopyramide phosphate in preventing neurally mediated syncope induced by a HUTT. **Results:** ● 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%)	**Limitations:** ● 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.

			assigned to placebo and in 3 pts (27%) receiving disopyramide (p=0.54, 95% CI: -42%–24%). ● Syncope recurred in 3 (27%) of the 11 pts receiving disopyramide and 3 (30%) of the 10 pts not treated pharmacologically (p>0.05).	
Gibbons, et al. 2006 16832073 (129)	**Aims:** To investigate the prevalence, symptoms, and neurophysiologic features of delayed OH **Study type:** Retrospective, observational, mechanistic **Size:** n=230 pts	**"Inclusion criteria":** OH or delayed during a 60° head-up tilt performed for 45 min **Exclusion criteria:** None specified	**1° endpoint:** OH or delayed OH **Results:** ● 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	**Limitations:** ● Laboratory study ● Referral population **Conclusions:** ● Delayed OH occurred in 54% of tested population ● TTT duration should be extended ● Underlying mechanism possibly early or mild sympathetic adrenergic failure
Podoleanu, et al. 2009 19669396 (130)	**Aim:** To investigated the hemodynamic mechanisms that underlie delayed OH **Study type:** Prospective, case-control, mechanistic study in human pts **Size:** n=13 pts and 9 controls	**Inclusion criteria:** 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 **Exclusion criteria:** The inability of the patient to collaborate and to perform tilt testing.	**1° endpoint:** 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. **Results:** ● At the end of the test, in pts compared to controls, SBP was significant lower; TPR progressively decreased in pts but not in controls; SV and CO did not change in pts or in controls. Heart rate increased progressively in pts until the end of the test and remained unchanged in controls ● Administration of elastic compression to the legs counteracts the decrease in SBP and TPR.	**Limitations:** ● Laboratory study ● Small number of pts ● Blinding – not stated **Conclusions:** ● 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 decrease in SBP and decrease in TPR.
Gurevich T, et al. 2014 25531748 (131)	**Aim:** (1) To assess time-related patterns of SBP and DBP responses in pts referred for suspected OH to tilt testing	**"Inclusion criteria":** Syncope during angioplasty **Exclusion criteria:** None specified	**1° endpoint:** OH or delayed OH **Results:** ● 7% had OH within 3 min, 35% within 30 min, and 40% within 40 min. ● 270 OH pts, 43 and 91% were identified within 3 and 30 min, respectively	**Limitations:** ●Referral population. ● Laboratory study **Conclusions:** ●Tilt table testing to 30 minus identifies most but no all pts with delayed OH.

	(2) 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)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results	Summary/ Conclusion Comment(s)
Abubakr A, et al. 2005 15820355 (133)	**Study type:** Retrospective chart review **Size:** n=1,094 syncope pts	**Inclusion criteria:** Syncope pts selected from a larger population of EEG reports	**1° endpoint:** Classification of EEG findings including variants of normal. **Results:** 2 (1.5%) abnormal EEGs: one focal slowing, one diffuse slowing	Very few abnormal EEGs, but the larger population of syncope pts is not reported. Rare EEG abnormalities. No epileptiform features

Al-Nsoor, et al. 2010 20672498 (134)	**Study type:** Perhaps prospective cohort **Size:** n=292 pts	**Inclusion criteria:** Syncope in ED seen by a neurologist	**1° endpoint:** Abnormality contributing to diagnosis **Results:** 254 CT scans (87%); 10 (3.9% of ordered) helped.	Very high use of CT scans, and firmness of attribution not clear
Giglio P, et al. 2005 16292675 (135)	**Study type:** Retrospective chart review **Size:** n=128 pts	**Inclusion criteria:** Syncope pts in ED	**1° endpoint:** Proportion with CT scans; proportion abnormal related to syncope **Results:** 44 had CT; 1 showed old posterior infarction.	Fully 34% had CT, but only 1 (3% of ordered) had diagnostic utility relevance
Goyal N, et al. 2006 17111790 (136)	**Study type:** Retrospective chart review **Size:** n=117 pts with syncope and head CT	**Inclusion criteria:** Syncope diagnosis by ED MD	**1° endpoint:** Any clinically significant finding **Results:** 117 had CT; 0 (0% of ordered) helped.	Inclusion criteria based on CT use, but the larger population of syncope pts is not reported. CT had no diagnostic utility
Johnson PC, et al. 2014 25365440 (137)	**Study type:** Retrospective chart review **Size:** n=167 syncope pts of 1,038 adult Texan in-pts with "syncope" screened	**Inclusion criteria:** Syncope coded in billing records, and after non-syncopal diagnoses excluded on chart review	**1° endpoint:** Test contributed to alleged diagnosis **Results:** 131 CT scans (78.4%); 0% helped. 18 brain MRI (10.7%); 0% helped. 52 carotid ultrasounds (31.1%); 0% helped.	CT and MRI performed moderately frequently and of no diagnostic utility. Carotid ultrasound less frequently and of no diagnostic utility.
Kapoor WN, et al. 1983 6866032 (70)	**Study type:** Prospective cohort **Size:** n=204 pts in global population	**Inclusion criteria:** Diagnosis of syncope after inclusion for TLOC	**1° endpoint:** Diagnosis of cause of syncope **Results:** 65 CT scans (32%); 0% helped. 101 EEGs (49.5%); 1 (1% of ordered) helped.	The population was accumulated nearly 40 y ago. Tests are of minimal diagnostic utility.
Mecarelli O, et al. 2004 15639129 (138)	**Study type:** prospective observational controlled cohort **Size:** 43 pts with vasovagal syncope; 32 controls	**Inclusion criteria:** recurrent syncope, positive tilt test, negative brain MRI	**1° endpoint:** Abnormal EEG **Results:** 0 (0%) abnormal findings on routine EEG but increased slow wave activity during hyperventilation	The report is restricted to VVS pts, and is only one of several. Maybe should delete it, or include them all.
Mendu ML, et al. 2009 19636031 (68)	**Study type:** Retrospective chart review **Size:** n=1,920 pts	**Inclusion criteria:** ICD 9 in-hospital primary or secondary syncope diagnosis	**1° endpoint:** Chart documentation that the finding contributed to the diagnosis **Results:** 1327 CT scans (63%); 35 (2.6% of ordered) helped. 154 brain MRI (19%); 23 (15%	One of the largest, but retrospective, firmness of attribution not clear. CT, EEG, carotid ultrasound of minimal diagnostic utility. MRI provided some diagnostic utility

			of ordered) helped. 267 carotid ultrasounds (20%); 3 (1.1% of ordered) helped. 174 EEG (13%); 3 (1.7%) helped	
Pires LA, et al. 2001 11493131 (139)	**Study type:** Retrospective chart review **Size:** n=649 pts	**Inclusion criteria:** ICD 9 syncope in in-patients	**1° endpoint:** Apparently contributed to diagnosis of etiology. **Results:** 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	Weak methodology. All investigations of low diagnostic utility
Poliquin-Lasnierl L, et al. 2009 19960758 (140)	**Study type:** Retrospective chart review **Size:** n=517 pts	**Inclusion criteria:** Syncope or falls and EEG ordered	**1° endpoint:** "Yield" of EEGs **Results:** 0 (0%) EEGs showed epileptiform activity	EEG use an inclusion criterion, so studied population. does not represent the large syncope population
Scalfani JJ, et al. 2010 20625024 (141)	**Study type:** Part A retrospective chart review: Part B prospective post-CME cohort **Size:** Part A 721; Part B 371 pts; pooled 1092 because CME had no effect on test ordering	**Inclusion criteria:** ICD primary or secondary diagnosis of syncope	**1° endpoint:** Causative finding defined as probably contributing to syncope, OR identifying a high risk subject for arrhythmic death **Results:** 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.	Pooled sequential 2-stage study
Sheldon, et al. 1982 9676166 (142)	**Study type:** Prospective observational **Size:** n=18 pts	**"Inclusion criteria":** Syncope or presyncope during head up tilt with isoproterenol provocation **Exclusion criteria:** None specified	**1° endpoint:** EEG changes during syncopal episodes **Results:** ● No pts developed EEG abnormalities before the onset of presyncope, ● During presyncope, theta wave slowing (8/14) and delta wave slowing (9/14), and background suppression (1/14) were noted During syncope, theta wave slowing (9/18) and delta wave slowing (11/18), and background suppression (6/18) were noted ● Abrupt changes in the EEG rhythm occurred	**Limitations:** ● 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.

			within 15 s of the transition to syncope (14/18)	
Low PA, et al. 2004 15562211 (143)	**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	**Inclusion criteria:** Known diabetes and willingness to complete general medical and neurological evaluations, and a full autonomic reflex laboratory evaluation annually **Exclusion criteria:** None specified	**"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	**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.
Kim, et al. 2009 19618439 (144)	**Aims:** To assesses 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	**Inclusion criteria:** A diagnosis of transthyretin amyloid polyneuropathy **Exclusion criteria:** None specified	**"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	**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
Iodice V, et al. 2012 22228725 (145)	**Aim:** To evaluate the autonomic characterization of MSA in autopsy confirmed cases **Study type:**	**Inclusion criteria:** Autopsy confirmed cases of MSA who had undergone formal autonomic testing, including adrenergic, sudomotor and cardiovagal functions and Thermoregulatory Sweat Test	**1° endpoint:** Autonomic test results, clinical features **Results:** ● OH was present in 21 pts and symptomatic in 19 pts	**Limitations:** None **Conclusions:** Severe and progressive generalized autonomic failure with severe adrenergic

	Retrospective, observational, autopsy study in human pts **Size:** n=29 pts	**Exclusion criteria:** None listed.	● Norepinephrine normal supine (203.6±112.7pg/ml). Orthostatic increment of was reduced (33.5±23.2%) ● Severe generalized autonomic failure in most pts ● 20/22 had anhidrosis and 18 had thermoregulatory sweat test % anhidrosis >30%	and sudomotor failure combined with the clinical phenotype is highly predictive of MSA.
Thaisetthawatkul P, et al. 2004 15159482 (146)	**Aim:** To assess autonomic function in pts with dementia with Lewy bodies **Study type:** Retrospective, observational study in human pts **Size:** n=20 DLB pts, 20 age-matched MSA and PD pts	**Inclusion criteria:** Clinically probable dementia with Lewy bodies and MSA pts and clinically definite PD pts **Exclusion criteria:** Coexistent conditions, such as diabetes, that account for the symptoms of dysautonomia.	**1° endpoint:** Autonomic test results, clinical features **Results:** ● OH present in 10/20 dementia with Lewy bodies, 17/20 MSA, and 1/20 PD pts ● Most common abnormal TST pattern in dementia with Lewy bodies was distal pattern, found in 54% of pts; while in MSA the most common pattern was global pattern, found in 41% of pts	**Limitations:** Referral bias Clinical diagnoses Autonomic testing in demented pts **Conclusions:** ● Autonomic dysfunction is frequent in dementia with Lewy bodies and the severity is intermediate between that of multiple system atrophy and Parkinson disease.
Thieben MJ, et al. 2007 17352367 (147)	**Aim:** To evaluate the prevalence and pathogenetic mechanisms of POTS **Study type:** Observational, retrospective, mechanistic **Size:** n=152 pts	**Inclusion criteria:** 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. **Exclusion criteria:** (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	**1° endpoint:** Autonomic test results, clinical features **Results:** ● Mean orthostatic heart rate increment was 44 beats/min. ● 50% of pts had sudomotor abnormalities (apparent on both the quantitative sudomotor axon reflex test and TST), ● 34.9% had significant adrenergic impairment	**Limitations:** ● Referral population. ● Laboratory study **Conclusions:** ● Findings suggest a neuropathic basis for at least half the cases of POTS

Gibbons C, et al. 2013 24386408 (148)	**Aim:** To define the neuropathology, clinical phenotype, autonomic physiology and differentiating features in individuals with neuropathic and non-neuropathic POTS. **Study type:** Observational, mechanistic **Size:** n=24 pts and 10 controls	**Inclusion criteria:** POTS was defined as an increase in heart rate of >30 beats per min upon standing with symptoms of orthostatic intolerance, without any known medical condition or medication causing the tachycardia **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	**1° endpoint:** Autonomic test results, clinical features, nerve density from skin biopsy **Results:** ● Pts with neuropathic POTS and had significantly lower resting and tilted heart rates; reduced parasympathetic function; and lower phase 4 Valsalva maneuver overshoot compared with those with non-neuropathic POTS	**Limitations:** ● Referral population. ● Laboratory study **Conclusions:** ● POTS subtypes may be distinguished using small fiber and autonomic structural and functional criteria.
Martinez-Fernandez, et al. 2008 17974603 (149)	**Study type:** Prospective Registry **Size:** n=359 pts	**Inclusion criteria:** Symptomatic pts with TIA or non-invalidating stroke, asymptomatic pts. with 85% stenosis, TCD detected microemboli/ exhausted CVR or silent lesions **Exclusion criteria:** N/A	**1° endpoint:** Occurrence of CSR and/or syncope during internal CAA **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 ($p<0.001$), 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.	● Syncope is common in pts undergoing CAA and can be misdiagnosed as frontal seizures, cardio-inhibitory response most frequent mechanism of syncope. ● Limitations: Beat to beat analysis of BP was not performed.
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	**"Inclusion criteria":** OH during a 60° HUTT performed for 45 mins **Exclusion criteria:** None specified	**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	**Limitations:** ● Laboratory study ● Referral population **Conclusions:** ● Delayed OH frequently progresses to OH ● Delayed OH frequently progresses to an alpha-synucleinopathy (multiple system

	age- and sex-matched controls		● 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%.	atrophy, Parkinson's disease, dementia with Lewy bodies) ● Delayed OH has a high associated mortality particularly when it progresses to OH

Data Supplement 17. Nonrandomized Trials, Observational Studies, and/or Registries of ARVCD – (Section 4.2.4)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
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, IDCM, Uhl's anomaly	**1° 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	**1° 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).
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	**1° 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
Bhonsale A, et al. 2013 23671136 (153)	**Study type:** Retrospective **Size:** n=215 pts	**Inclusion criteria:** Diagnosed with ARVD/C **Exclusion criteria:** None	**1° 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).
Link MS, et al. 2014	**Study type:** Prospective observational	**Inclusion criteria:** ARVD/C	**1° endpoint:** Sustained ventricular arrhythmias	• Syncope was not a predictor of VA.

25011714 (154)	**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	
Corrado D, et al. 2015 26216213 (155)	**Study type:** Consensus statement **Size:** None	**Inclusion criteria:** None **Exclusion criteria:** None	**1° endpoint:** None **Results:** None	• In ARVC pts with syncope an ICD should be considered

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

Study Acronym Author, Year	Study Type/Design*; Study Size	Patient Population	Primary Endpoint and Results	Summary/ Conclusion Comment(s)
Winters SL, et al. 1991 1894867 (156)	**Study type:** Retrospective **Size:** n=7 pts	**Inclusion criteria:** Documented (n=6) or highly suspected (n=1) Sarcoidosis with ECG abnormalities	**1° 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
Koplan, et al. 2006 16876741 (157)	**Study type:** Retrospective **Size:** n=8 pts	**Inclusion criteria:** Cardiac sarcoidosis with recurrent VT	**1° 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 pts (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 **Size:** n=42 pts	**Inclusion criteria:** CS	**1° 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.

Furushima, et al. 2004 15119697 (159)	**Study type:** Retrospective **Size:** n=8 pts	**Inclusion criteria:** CS and sustained monomorphic VT	**1° endpoint:** Mechanism and outcome of VT associated with cardiac sarcoidosis **Results:** Most VT is due to reentry. The inducibility rate depends on the presence or absence of an active phase. ICD therapy is effective.	• While most VT is due to reentry, inducibility depends on the disease state including response to immunosuppressive therapy.
Hiramitsu S, et al. 2005 16315784 (160)	**Study type:** Questionnaire survey **Size:** n=49 pts	**Inclusion criteria:** CS treated with steroid therapy	**1° endpoint:** Steroid dose used and pts outcome **Results:** 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.	• There is a fairly uniform use of steroid therapy in the management of CS with clinical improvement in over one-half of the cases.
Kandolin R, et al. 2011 21427276 (161)	**Study type:** Retrospective study **Size:** n=72 pts	**Inclusion criteria:** Unexplained AV block	**1° endpoint:** To determine the prevalence of CS and giant cell myocarditis in young and middle-aged adults undergoing pacemaker implantation for AV block **Results:** 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 ($p<0.001$).	• CS and giant cell myocarditis account for >25% of young and middle-aged adults presenting with AV block. • These pts are at high risk of having major adverse events.
Chapelon-Abric C, et al. 2004 15525844 (162)	**Study type:** Retrospective **Size:** n=41 pts	**Inclusion criteria:** CS	**1° endpoint:** Clinical characteristics and response to therapy **Results:** 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.	• Most pts with CS respond to immunosuppressive therapy.
Yodogawa K, et al. 2011	**Study type:** Retrospective	**Inclusion criteria:** CS and VA	**1° endpoint:** Efficacy of corticosteroid therapy in the treatment of VA	• Corticosteroid therapy may be effective for VA in the early stage, but

21496164 (163)	**Size:** n=31 pts		**Results:** Overall, there were no significant differences in the number of PVCs and in the prevalence of NSVT before and after steroid therapy. However, in pts with LVEF ≥ 35% (n=17), there was a significant reduction in the number of PVCs (from 1820 ± 2969 to 742 ± 1425, p=0.048) and in the prevalence of NSVT (from 41 to 6%, p=0.039). The less advanced LV dysfunction group showed a significantly higher prevalence of gallium-67 uptake compared with the advanced LV dysfunction group (LVEF <35 %, n=14). In the advanced LV dysfunction pts, there were no significant differences in these parameters.	is less effective in the late stage.
Schuller JL, et al. 2012 22812589 (164)	**Study type:** Retrospective **Size:** n=112 pts	**Inclusion criteria:** CS and ICD for primary or secondary prevention of sudden death	**1° endpoint:** ICD therapy in pts with CS **Results:** Over a mean follow up period of 29.2 mo, 32.1% of pts received appropriate therapies. VT storms and inappropriate therapies occurred in 14.2 % and 11.6% of pts respectively. Covariates associated with appropriate ICD therapies included LVEF <55% (OR: 6.52; 95% CI: 2.43–17.5), right ventricular dysfunction (OR: 6.73; 95% CI: 2.69–16.8), and symptomatic HF (OR: 4.33 95% CI: 1.86–10.1).	• Almost one-third of pts with CS and ICD receive appropriate therapies. • Adjusted predictors for ICD therapies included left or right ventricular dysfunction.
Betensky BP, et al. 2012 22338670 (165)	**Study type:** Retrospective **Size:** n=45 pts	**Inclusion criteria:** CS and ICD for primary or secondary prevention of sudden death	**1° endpoint:** To determine the prevalence and incidence of ventricular tachy-arrhythmias in pts with CS and to identify predictors of appropriate therapy **Results:** Appropriate and inappropriate ICD therapies were observed in 37.8% (15% per y) and 13.3% of pts, respectively. Longer ICD follow-up (4.5 ± 3.1y vs. 1.5 ± 1.5y; p=0.001), depressed left ventricular EF (35.5% ± 15.5% vs. 50.9% ± 15.5%; p=0.002), and complete heart block (47.1% vs. 17.9%; p=0.048) were associated with appropriate ICD therapy.	• The annual incidence rate for appropriate ICD therapy is 15%. • Longer follow-up, left ventricular systolic dysfunction, and complete heart block were associated with appropriate ICD therapy.
Kron J, et al. 2013 23002195 (166)	**Study type:** Retrospective **Size:** n=235 pts	**Inclusion criteria:** Consecutive pts with CS and ICD	**1° endpoint:** To evaluate the efficacy and safety of ICD therapy in pts with CS **Results:** Over a mean follow-up of 4.2 ± 4.0 y, 36.2% pts	• Almost a third of pts with CS and ICD receive appropriate ICD therapy over a mean follow-up of 4.2 ± 4.0 y.

			received an appropriate ICD therapy and 24.3% received inappropriate shocks. 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.
Mehta D, et al. 2011 21193539 (167)	**Study type:** Retrospective **Size:** n=76 pts	**Inclusion criteria:** Evidence of CS but without symptoms	**1° endpoint:** To assess the role of programmed electrical stimulation study in risk assessment in pts with sarcoidosis **Results:** 11% of pts were inducible and received an ICD (LVEF 36.4±4.2% vs. 55.8±1.5%, p<0.05). Over a median follow-up of 5 y, 6 of 8 pts in the group with inducible VA had ventricular arrhythmia or died, compared with 1 death in the negative group (p<0.0001).	• 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)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Morita H, et al. 2008 18838563 (168)	**Study type:** Retrospective **Size:** n=115 pts	**Inclusion criteria:** Symptomatic and asymptomatic BS **Exclusion criteria:** N/A	**1° 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%).	• Fragmented QRS appears to be a marker for spontaneous VF and syncope
Gehi, et al. 2006 16836701 (169)	**Study type:** Meta-analysis assessing predictors of cardiac events **Size:** n=1,545 pts	**Inclusion criteria:** Studies were included if they m, et al.l of the following criteria: 1) prospective cohort studies of the natural history of pts with Brugada-type ECG, 2) studies included >10 pts, 3) primary data on cardiac events was provided	**1° 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	• Male sex, spontaneous Type I ECG pattern and Hx of SCD and syncope are good predictors of future cardiac events

		and 4) stated clearly that structural heart disease was ruled out. **Exclusion criteria:** If not all inclusion criteria are met	• Spontaneous compared with drug-induced Type I ECG (RR: 4.65; 95% CI: 2.25–9.58)	
Benito B, et al. 2008 19007594 (170)	**Study type:** Prospective follow up study **Size:** n=384 pts	**Inclusion criteria:** Pts with BS **Exclusion criteria:** N/A	**1° endpoint:** To assess phenotype and prognosis differences between men and women **Results:** Men had greater rates of spontaneous Type 1 ECG, ST elevation and VF inducibility (p<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.	• Men with BS present with a greater risk clinical profile than women and have a worse prognosis. • Conduction disturbances may be a marker of risk in the female population
Morita H, et al. 2008 18838563 (168)	**Study type:** Retrospective **Size:** n=115 pts	**Inclusion criteria:** Symptomatic and asymptomatic BS **Exclusion criteria:** N/A	**1° 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%).	• Fragmented QRS appears to be a marker for spontaneous VF and syncope
Sarkozy, et al. 2011 21727093 (171)	**Study type:** Registry **Size:** n=280 consecutive pts	**Inclusion criteria:** Type 1 ECG pattern **Exclusion criteria:** N/A	**1° endpoint:** Prevalence of family history of SD and its prognostic value **Results:** 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.	• Family Hx of SD is not predictive for future arrhythmic events even if considering only SD in first-degree relatives or SD in first-degree relatives at a young age.
PRELUDE Registry. Priori SG, et al. 2012 22192666 (172)	**Study type:** Registry **Size:** n=308 pts	**Inclusion criteria:** Spontaneous or drug-induced type 1 ECG **Exclusion criteria:** Hx of cardiac arrest	**1° endpoint:** Arrhythmic events in pts with and without inducible VT/VF **Results:** During a median follow up of 34 mo, there were 14 arrhythmic events. 9/14 occurred in non-inducible pts. • Arrhythmia inducibility was not a predictor of	• 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 <200 ms, and QRS fragmentation seem useful to identify candidates for primary

			arrhythmic events. • Syncope and spontaneous Type I ECG (HR: 4.20) and VERP<200ms (HR:3.91), fragmented QRS (HR: 4.94) were significant predictors of arrhythmias.	prevention ICD implants.
Sacher F, et al. 2006 17116772 (173)	**Study type:** Multicenter outcome report **Size:** n=220 pts including 88 with syncope	**Inclusion criteria:** BS with ICD implant **Exclusion criteria:** N/A	**1° endpoint:** Appropriate shocks and ICD complications including inappropriate shocks **Results:** 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).	• 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.
Sarkozy, et al. 2007 17251258 (174)	**Study type:** Retrospective single center study **Size:** n=47 pts	**Inclusion criteria:** 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 **Exclusion criteria:** N/A	**1° endpoint:** Appropriate and inappropriate ICD shocks. **Results:** 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	• 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.
Rosso R, et al. 2008 18669142 (175)	**Study type:** Retrospective multicenter study (12 Israeli centers) **Size:** n=59 pts	**Inclusion criteria:** 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%) **Exclusion criteria:** N/A	**1° endpoint:** Efficacy and complications of ICD therapy **Results:** 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.	• 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.
FINGER Brugada Syndrome Registry Probst V, et al. 2010	**Study type:** Registry from 11 tertiary centers in 4 European countries: France, Italy, Netherlands,	**Inclusion criteria:** Pts with spontaneous or drug-induced Type 1 ECG pattern	**1° endpoint:** SCD **Results:** 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

20100972 (176)	Germany Registry (FINGER) **Size:** n=1029 consecutive pts	**Exclusion criteria:** Diseases that mimic BS	0.5% in asymptomatic pts. •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.	not predictive of arrhythmic events.
Conte, et al. 2015 25744005 (177)	**Study type:** Retrospective single center **Size:** n=176 pts	**Inclusion criteria:** Pts with spontaneous or drug-induced Type 1 ECG pattern who underwent ICD implantation. **Exclusion criteria:** N/A	**1° endpoint:** Appropriate and inappropriate shocks and device complications **Results:** During a mean follow-up period of 83.8 ± 57.3 mo, spontaneous sustained VAs occurred in 30 pts (17%). 8 pts (4.5%) died. • 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. • 105 (59.7%) pts had syncope with 53 (50.4%) having a family Hx of SD. Spontaneous Type 1 pattern was present in 18.1%. Appropriate and inappropriate shocks occurred in 10.5% and 17.1% of cases. • In multivariate Cox regression analysis, aborted SCD and VA inducibility on EP studies were independent predictors of appropriate shock occurrence.	• ICD therapy was an effective strategy in BS, treating potentially lethal arrhythmias in 17% of pts during long-term follow-up. Risk stratification by EPS may identify asymptomatic pts at risk for arrhythmic events and could be helpful in investigating syncope not related to VAs.
Hiraoka, et al. 2013 23702150 (178)	**Study type:** Retrospective analysis of the Japan Idiopathic Ventricular Fibrillation registry **Size:** n=69 pts	**Inclusion criteria:** BS with age 35 y of age or younger **Exclusion criteria:** N/A	**1° endpoint:** Cardiac events (VF or SCD) **Results:** During a mean follow-up period of 43±27mo, cardiac events (VF and/or SCD) developed in 8 cases, with 5 of 12 cases in the VF (41.7%), 2 of 17 cases in the Syncope (11.8%) and 1 of 40 cases in the asymptomatic group (2.5%). • The VF group had a worse prognosis for cardiac events than the Syncope and Asymptomatic group. Multivariate analysis revealed symptoms as a risk factor for predicting cardiac events.	• The presence of SCD or syncope is a risk factor for cardiac events in pts with BS
Sacher F, et al.	**Study type:** Prospective	**Inclusion criteria:**	**1° endpoint:** Cardiac events including syncope	• VA occurred only in pts with syncope

2012 22504046 (179)	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)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
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	**1° 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.	**1° endpoint:** Comprehensive EP evaluation **Results:** At baseline ECG, all pts exhibited a QT interval ≤280 ms (QTc ≤300 ms). During EPS (n=4),	• The short QT syndrome is characterized by familial sudden death, short refractory periods, and inducible VF.

		Exclusion criteria: N/A	short atrial and ventricular refractory periods were documented in all and increased ventricular vulnerability to fibrillation in 3 of 4 pts.	
Brugada R, et al. 2004 14676148 (182)	**Study type:** Prospective **Size:** 3 families with hereditary short-QT syndrome and a high incidence of ventricular arrhythmias and SCD.	**Inclusion criteria:** Short QT interval and history of ventricular arrhythmias or SCD **Exclusion criteria:** N/A	**1° endpoint:** Characterization of the genetic basis for SQTS **Results:** 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_{Kr} channel HERG (KCNH2). The mutations dramatically increase I_{Kr}, leading to heterogeneous abbreviation of action potential duration and refractoriness, and reduce the affinity of the channels to I_{Kr} blockers.	• The authors demonstrated a novel genetic and biophysical mechanism responsible for SD in infants, children, and young adults caused by mutations in KCNH2.
Gallagher, et al. 2006 16996877 (183)	**Study type:** Retrospective **Size:** n=12,012 pts	**Inclusion criteria:** Pts who underwent routine medical examination for occupational reasons **Exclusion criteria:** N/A	**1° endpoint:** Survival **Results:** 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.	• QTc ≤ 330 ms is extremely rare • QT interval in the lowest 1/2 centile of the normal range does not imply a significant risk of SD.
Anttonen O, et al. 2007 17679619 (184)	**Study type:** Retrospective **Size:** n=10,822 pts	**Inclusion criteria:** Randomly selected middle-aged pts enrolled in a population study and followed up for 29±10 y **Exclusion criteria:** N/A	**1° endpoint:** All cause and CV mortality **Results:** 10,822 randomly selected and followed for 29±10 y. The prevalence of SQTS (<340ms) was 0.4% and (<320ms) 0.1%. There were no SD or aborted CA or documented VA during follow up.	• A short QT interval does not appear to indicate an increased risk for all-cause or CV mortality
Funada A, et al. 2008 18543308 (185)	**Study type:** Retrospective **Size:** n=10,984 pts	**Inclusion criteria:** Pts who had an ECG between February 2003 and May 2004 **Exclusion criteria:** Irregular rhythms, conduction disturbances and wide QRS	**1° endpoint:** Prevalence of SQTS (<300ms) **Results:** 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<300ms. None were symptomatic.	• SQTS is very rare
Kobza, et al. 2009	**Study type:** Retrospective	**Inclusion criteria:** Swiss male citizen 18–19 y of age.	**1° endpoint:** Prevalence of LQTS and SQTS	• Short QT syndrome is a very rare entity in the population of young male adults

19303371 (186)	**Size:** n=41,767 ECGs	**Exclusion criteria:** Artifact, pre-excitation and BBB.	**Results:** The prevalence of SQTS (<320ms) was 0.02% and none of the pts had a QTc<300ms	
Giustetto C, et al. 2011 21798421 (187)	**Study type:** Retrospective review from the European Short QT registry **Size:** n=53 pts	**Inclusion criteria:** QTc≤360ms with cardiac arrest (n=18) or syncope (n=8); Asymptomatic QTc≤340ms and Family members of affected pts (n=27) **Exclusion criteria:** N/A	**1° endpoint:** Prevalence of arrhythmic events **Results:** The event rate was 3.3% per y and was limited to pts who were not receiving Hydroquinidine. ● Of the 12 pts with a previous CA, 11 had an ICD with 1 receiving appropriate shocks during follow-up. ● Of the 8 pts with syncope, 4 received an ICD and only 1 received appropriate shock for VF.	● Symptomatic pts are at high risk ● Hydroquinidine is effective in preventing arrhythmic events

Data Supplement 21. Nonrandomized Trials, Observational Studies, and/or Registries of Long-QT Syndrome – (Section 4.3.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Ouriel K, et al. 1995 8574528 (188)	**Study type:** Retrospective **Size:** n=10 pts	**Inclusion criteria:** LQTS refractory (n=9) or intolerant (n=1) to BB therapy **Exclusion criteria:** N/A	**1° 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<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.	● 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.
Priori SG, et al. 2003 12736279 (189)	**Study type:** Retrospective **Size:** n=674 pts	**Inclusion criteria:** 193 consecutively genotyped families with LQTS in Pavia, Italy **Exclusion criteria:** N/A	**1° endpoint:** Cumulative probability of cardiac event defined as syncope, 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.	● The probability of having a cardiac event depends on the genotype and sex.

Locati EH, et al. 1998 9631873 (190)	**Study type:** Retrospective **Size:** n=479 probands and n=1041 affected family members with LQTS	**Inclusion criteria:** LQTS pts and affected family members **Exclusion criteria:** N/A	**1° endpoint:** To evaluate age and sex-related differences **Results:** • 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.	• Data derived from a large registry (LQTS International Registry) • In LQT1, male sex until puberty and female sex during adulthood increase the risk of cardiac events.
Jons C et al. 2010 20170817 (191)	**Study type:** Retrospective **Size:** n=1,059 pts	**Inclusion criteria:** LQTS pts with QTc>450 ms presenting with syncope as a first symptom were drawn from the International LQTS Registry **Exclusion criteria:** N/A	**1° endpoint:** To identify risk factors for fatal arrhythmias (aborted CA, appropriate ICD therapy and SCD) **Results:** • The lowest risk was in pts with 1 syncopal 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.	• Cohort limited to pts with syncope • ICD should not be the first line therapy in pts with a single episode of syncope as they have the lowest risk • ICD is likely to save lives in pts with syncope despite BB therapy.
Zareba W, et al. 2003 12741701 (192)	**Study type:** Outcome data **Size:** n=286 pts with LQTS; 125 with an ICD and 161 without an ICD	**Inclusion criteria:** 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 **Exclusion criteria:** N/A	**1° endpoint:** Death during follow up **Results:** 1 death (1.3%) over 3 y in 73 ICD pts and 26 deaths (16%) in non-ICD pts over 8-y follow up.	• ICD therapy saves lives
Schwartz, et al. 2010 20837891 (193)	**Study type:** Retrospective **Size:** n=233 pts	**Inclusion criteria:** LQTS with an ICD in the European LQTS Registry **Exclusion criteria:** N/A	**1° endpoint:** To determine the characteristics of LQTS pts receiving an ICD, indications and follow up **Results:** 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	• Cohort limited to pts with an ICD • Age<20 y, QTc >500ms, prior CA and cardiac events despite medical therapy were strong predictors of appropriate ICD therapy. • Absence of these risk factors indicates good prognosis.

			included age <20 y at implantation, QTc >500ms, prior CA and cardiac events despite therapy. • No appropriate ICD therapy within 7 y in pts with none of these factors.	
Horner JM, et al. 2010 20816872 (194)	**Study type:** Retrospective **Size:** n=459 pts	**Inclusion criteria:** Genetically confirmed LQTS including 51 pts (14 LQT1, 22 LQT2, and 15 LQT3) who received an ICD from 2000 to 2010 **Exclusion criteria:** N/A	**1° endpoint:** Report outcome **Results:** 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 >500ms, syncope, TDP and negative family Hx.	• Syncope was a predictor of appropriate therapy (p=0.05) • In 408 pts with no risk factors, no deaths were reported
Priori SG, et al. 2004 15367556 (195)	**Study type:** Retrospective **Size:** n=335 pts	**Inclusion criteria:** Genotyped LQTS pts treated with BB **Exclusion criteria:** N/A	**1° endpoint:** Incidence of cardiac events **Results:** Cardiac events occurred in 10%, 23% and 32% of pts with LQT1, LQT2 and LQT3. Predictors included non-LQT1 and QTc >500ms and first occurrence <7 y of age.	• Response to BB depend on the genotype • LQT1 pts are better responders when compared to LQT2 and LQT3. • QTc >500ms and first occurrence <7 y of age are predictors of future cardiac events
Vincent GM, et al. 2009 19118258 (196)	**Study type:** Retrospective **Size:** n=216 pts	**Inclusion criteria:** Genotyped long-QT1 treated with BB and followed for a median of 10 y **Exclusion criteria:** N/A	**1° endpoint:** Cardiac events on BB therapy **Results:** Cardiac events occurred in 157 pts (73%) at a median age of 9 y, with CA in 26 (12%). • 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<0.001). • 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.	• BB are extremely effective in long-QT syndrome type 1 and should be administered at diagnosis and ideally before the preteen years. • BB noncompliance and use of QT-prolonging drug are responsible for almost all life-threatening " beta-blocker failures."

Liu JF, et al. 2011 21329841 (197)	**Study type:** International Long QT registry **Size:** n=1,648 pts	**Inclusion criteria:** QTc ≥ 450 ms and/or documented LQTS-causing mutation and enrolled in registry before the 20 y age. **Exclusion criteria:** N/A	**1° endpoint:** Recurrence of syncope after the first event **Results:** Multivariate analysis demonstrated that QTc ≥ 500 ms was a significant predictor of a first syncope episode (HR: 2.16). • Pts who experienced ≥ 1 episodes of syncope had a 6- to 12-fold (p<0.001 for all) increase in the risk of subsequent fatal/near-fatal events independently of QTc duration. • BB therapy was associated with a significant reduction in the risk of recurrent syncope and subsequent fatal/near-fatal events.	• Children and adolescents who present after an episode of syncope should be considered to be at a high risk of the development of subsequent syncope episodes and fatal/near-fatal events regardless of QTc duration.
Chockalingam P, et al. 2012 23083782 (198)	**Study type:** Retrospective **Size:** n=382 (101 symptomatic) pts with LQT1/LQT2	**Inclusion criteria:** LQT1 and LQT2 pts on BB therapy (Proprnolol, Metoprolol and Nadolol) **Exclusion criteria:** Less than 1 y of age at BB initiation	**1° endpoint:** To compare the efficacy of Propranolol, Metoprolol and Nadolol in pts with LQT1/LQT2 **Results:** QTc shortening was significantly greater with Propranolol. • None of the asymptomatic pts had cardiac events. • 15% of the symptomatic had breakthrough with the greatest risk among those taking Metoprolol.	• Not all BB are the same • Propranolol appears to be better than Metoprolol and Nadolol
Schwartz P, et al. 2004 15051644 (199)	**Study type:** Retrospective **Size:** n=147 pts	**Inclusion criteria:** LQTS pts who underwent LCSD (99% symptomatic with 75% of those treated with BB remaining symptomatic **Exclusion criteria:** N/A	**1° endpoint:** Long-term efficacy of LCSD **Results:** Post-LCSD, 46% remained symptomatic. The mean yearly number of cardiac events per patient dropped by 91% (P<0.001). Among 74 pts with only syncope before LCSD, all types of cardiac events decreased significantly as in the entire group, and a post-LCSD QTc <500 ms predicted very low risk.	• 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. • However, LCSD is not entirely effective in preventing cardiac events including sudden cardiac death during long-term follow-up. • LCSD should be considered in pts with recurrent syncope despite β-blockade and in pts who experience arrhythmia storms with an implanted defibrillator.
Collura, et al. 2009 19467503	**Study type:** Retrospective	**Inclusion criteria:** Secondary prevention in 11 pts including 8 with LQTS and primary prevention	**1° endpoint:** Outcome with LCSD using video-assisted thoracic surgery	• Videoscopic denervation surgery, in addition to traditional LCSD, offers a safe and effective treatment option for the personalized medicine required for pts

(200)	**Size:** n=20 pts including 12 with LQTS, 2 JLNS, 4 genotype negative LQTS and 2 CPVT	in 9 pts. **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.
Abu-Zeitone A, et al. 2014 25257637 (201)	**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	**1° 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)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Padfield, GJ, et al. 2016 26416620 (202)	**Study type:** Retrospective **Size:** n=8 pts	**Inclusion criteria:** CPVT secondary to mutations in the *RyR2* gene who refused (n=1) or were intolerant to BB therapy (n=7) **Exclusion criteria:** N/A	**1° endpoint:** Safety of flecainide as mono-therapy in pts with CPVT **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-syncope, syncope, or CA occurred in pts on flecainide mono-therapy during the follow-up period of 37.1 mo (range1.4–75.5 mo).	• Flecainide mono-therapy is an option in pts with CPVT who are intolerant to BB therapy.

Leenhardt, et al. 1995 7867192 (203)	**Study type:** Observational **Size:** n=21 pts	**Inclusion criteria:** Syncope due to documented or suspected VA. **Exclusion criteria:** N/A	**1° endpoint:** Syncope recurrence and exercise induced VA **Results:** 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.	• 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
Priori, et al. 2002 12093772 (204)	**Study type:** Retrospective **Size:** n=30 probands and 118 family members	**Inclusion criteria:** Exercise or emotion induced bidirectional VT (n=14), PMVT (n=12) and catecholaminergic idiopathic VF (n=4) **Exclusion criteria:** N/A	**1° endpoint:** Clinical and genetic characterization **Results:** 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.	• 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.
Sumitomo, et al. 2003 12482795 (205)	**Study type:** Questionnaires were sent to major Japanese pediatric centers **Size:** n=29 centers	**Inclusion criteria:** 1) Exercise or catecholamine induced VA (>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. **Exclusion criteria:** N/A	**1° endpoint:** Questionnaire responses and ECG characteristics **Results:** 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 in	• Pts with CPVT have a poor prognosis. BB do not always control symptoms thus the need for other pharmacological and non-pharmacological therapies.

			autosomal dominant cases.	
Hayashi, et al. 2009 19398665 (206)	**Study type:** Multicenter observational study **Size:** n=101 pts	**Inclusion criteria:** Exercise induced polymorphic ventricular arrhythmias or identification of a mutation in the *RYR2* or *CASQ2* gene **Exclusion criteria:** >55 y of age	**1° endpoint:** Incidence of cardiac events (exertional or stress induced syncope, aborted CA, appropriate ICD shocks or SCD) **Results:** 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.
van der Werf, et al. 2012 21893508 (207)	**Study type:** Meta-analysis including 11 studies using BB and review of other therapies **Size:** n=403 pts	**Inclusion criteria:** CPVT pts **Exclusion criteria:** N/A	**1° endpoint:** Arrhythmic, non-fatal and fatal events **Results:** 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.
van der Werf, et al. 2011 21616285 (208)	**Study type:** Chart review from 8 tertiary referral centers	**Inclusion criteria:** 1) Exercise induced PMVT or bidirectional VT 2) Mutation in the gene encoding *RyR2* or cardiac Calsequestrin	**1° endpoint:** Reduction of VA during exercise testing **Results:** Exercise tests comparing flecainide in	• Flecainide reduced exercise-induced VA in pts with CPVT not controlled by conventional drug therapy.

	Size: n=33 pts	**Exclusion criteria:** N/A	addition to conventional therapy with conventional therapy alone were available for 29 pts. • The median daily flecainide dose in responders was 150 mg (range 100 to 300 mg). • 22 pts (76%) had either partial (n=8) or complete (n=14) suppression of exercise-induced VA with flecainide (p<0.001). • No pts experienced worsening of exercise-induced VA.	
Swan, et al. 2005 15720454 (209)	**Study type:** Prospective physiology study in human pts **Size:** n=6 pts	**Inclusion criteria:** Pts with clinical diagnosis of CPVT and carrying a *RyR2* mutation **Exclusion criteria:** N/A	**1° endpoint:** Effect of verapamil and magnesium on exercise induced VA. **Results:** Premature ventricular complexes appeared later and at higher heart rate during verapamil compared to baseline (119 ± 21 vs. 127 ± 27 min−1, p<0.05). Magnesium did not inhibit the arrhythmias.	• First study to demonstrate in vivo that verapamil can suppress premature ventricular complexes and non-sustained ventricular salvoes in CPVT caused by *RyR2* mutations. • Physiology study with no long-term follow up
Rosso, et al. 2007 17765612 (210)	**Study type:** Retrospective 2 center study **Size:** n=5 pts	**Inclusion criteria:** CPVT pts with a Hx of syncope or CA and exercise induced ventricular ectopy despite maximally tolerated BB therapy **Exclusion criteria:** N/A	**1° endpoint:** Exercise induced arrhythmias and clinical outcome **Results:** 1) 3 pts had non-sustained VT on _-blockers, and none of them had VT on combination therapy. 2) The number of ventricular ectopic beats during the whole exercise test went down from 78 ± 59 beats to 6 ± 8 beats. 3) 1 pts with recurrent spontaneous VT leading to multiple shocks from her ICD despite maximal blocker therapy remained free of arrhythmias for 7 mo since the addition of verapamil therapy.	• The combination of calcium channel blockers with BB might be better than BB alone. • Short-term study
Sy R, et al. 2011 21315846 (211)	**Study type:** Retrospective **Size:** n=27 pts	**Inclusion criteria:** 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. • First-degree relatives of affected individuals	**1° endpoint:** Long-term outcome and relation between age and clinical presentation **Results:** Presentation was CA in 33% and syncope in 56%, and 11% were asymptomatic. • Polymorphic or bidirectional VT was provoked with exercise in 63% and adrenaline in 82%.	• Despite BB therapy and selective ICD implantation, breakthrough arrhythmias occur and may be associated with adverse outcomes

		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)	**Study type:** Retrospective cohort study **Size:** n=226 pts	**Inclusion criteria:** 170 probands and 56 relatives **Exclusion criteria:** N/A	**1° endpoint:** Treatment outcome **Results:** Symptomatic presentation was reported in 176 (78%). Syncope (p<0.001), cardiac arrest (p<0.001), and treatment failure (p=0.008) occurred more often in probands. • BB were prescribed in 205 of 211 pts (97%) on medication, and 25% experienced at least 1 treatment failure event. ICDs were placed in 121 (54%) and were associated with electrical storm in 22 (18%). Flecainide was used in 24% and LCSD in 8%. 6 deaths (3%) occurred during a cumulative follow-up of 788 pts-y.	• BB were almost universally initiated; however, treatment failure, noncompliance and sub-therapeutic dosing were often reported. • Treatment failure was rare in the quarter of pts on flecainide. • LCDS was not uncommon although the indication was variable. • ICDs were common despite numerous device-related complications.

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

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Moray A, et al. 2011 21478052 (213)	**Study type:** Retrospective Case report **Size:** n=1 patient	**Inclusion criteria:** 10 y of age boy with CPVT **Exclusion criteria:** N/A	**1° endpoint:** Safety of simultaneous ICD insertion and thoracoscopic sympathectomy **Results:** The procedure was safe suggesting that it is a better approach than sequential procedures	• Simultaneous ICD insertion and thoracoscopic sympathectomy is feasible and safe in pts with CPVT

Celiker A, et al. 2009 19102802 (214)	**Study type:** Retrospective **Size:** n=16 children pts	**Inclusion criteria:** Diagnosis of CPVT **Exclusion criteria:** N/A	**1° endpoint:** Clinical features, treatment and outcome **Results:** 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%.	• 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.
Wilde AA, et al. 2008 18463378 (215)	**Study type:** Retrospective single center experience **Size:** n=3 pts	**Inclusion criteria:** CPVT with symptoms despite BB therapy 3/3) and mexiletine (1/3) **Exclusion criteria:** N/A	**1° endpoint:** Cardiac events **Results:** LCSD resulted in marked reduction in cardiac arrhythmias and improvement in QOL.	• 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.
De Ferrari, et al. 2015 26019152 (216)	**Study type:** Retrospective including pts from 11 centers worldwide **Size:** n=63 pts	**Inclusion criteria:** Asymptomatic and symptomatic pts **Exclusion criteria:** N/A	**1° endpoint:** Cardiac events **Results:** 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 <0.001) after LCSD.	• 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.
Waddell-Smith, et al. 2015 26224781 (217)	**Study type:** Retrospective Survey-based **Size:** n=47 pts who underwent LCSD including 40 with LQTS and 7 with CPVT	**Inclusion criteria:** Underwent video-assisted thoracoscopic LCSD and completion of a telephone survey **Exclusion criteria:** N/A	**1° endpoint:** Physical and psychological effects of LCSD and pts satisfaction. **Results:** 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	• Despite significant morbidity resulting from LCSD, pts with LQTS and CVPT have high levels of post-operative satisfaction.

			(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.	
Marai, et al. 2012 22481011 (218)	**Study type:** Retrospective **Size:** n=27 pts	**Inclusion criteria:** CPVT **Exclusion criteria:** N/A	**1° endpoint:** Death **Results:** 27 pts were followed for 1-15 y (median 9). 20 were symptomatic at baseline and 13 remained symptomatic after treatment with high dose BB. • 8 pts refused ICD with 6 eventually dying. 5 received an ICD with 4/5 experiencing a VT storm not responsive to ICD shocks but with spontaneous termination. No death occurred in the ICD group.	• 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.
Roses-Noguer, et al. 2014 24120999 (219)	**Study type:** Retrospective **Size:** n=13 pts	**Inclusion criteria:** CPVT with an ICD implant for cardiac arrest (7 pts) and syncope (6 pts) **Exclusion criteria:** N/A	**1° endpoint:** Effectiveness of ICD shocks **Results:** Among appropriate shocks, 20 (32%) were effective in terminating sustained arrhythmia and 43 (68%) were ineffective. • Shocks delivered to triggered arrhythmias nearly always failed (1 of 40; 3% effective), while shocks delivered to VF were usually successful (19 of 23; 83% effective; p<0.001). No pts died.	• The effectiveness of ICD shock therapy in CPVT depends on the mechanism of the rhythm treated. Shocks delivered to initiating triggered arrhythmias nearly always fail, whereas those for subsequent VF are usually effective.

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

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Mahida S, et al. 2015	**Study type:** Retrospective	**Inclusion criteria:** ER syndrome with a history of aborted sudden	**1° endpoint:** Inducibility of VA	• Programmed stimulation protocols do not enhance risk

25593056 (220)	multicenter study **Size:** n=81 pts	death due to ventricular fibrillation **Exclusion criteria:** Structural heart disease and >60 y of age.	**Results:** VF was inducible in only 18 of 81 (22%) pts. During follow-up of 7.0±4.9 y, 6 of 18 (33%) pts with inducible VF during EPS experienced VF recurrences, whereas 21 of 63 (33%) pts who were non-inducible experienced recurrent VF (p=0.93).	stratification in pts with ER syndrome.
Morady F, et al. 1986 3717024 (221)	**Study type:** Retrospective **Size:** n=109 pts	**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. **Exclusion criteria:** N/A	**1° endpoint:** Characteristics of coupling intervals that induce clinical and non-clinical VT and VF **Results:** The mean coupling intervals of the first, second and third extra stimuli that induced nonclinical VT/VF were significantly shorter than the corresponding coupling intervals that induced the clinical VTs. • Regardless of the basic drive cycle length, the shortest coupling interval required to induce a clinical VT was 180 ms. Depending on the drive cycle length, 29 to 70% of nonclinical VT/VF induced by 3 extrastimuli required a coupling interval of less than 180 ms to induce.	• The results of this study demonstrate that the coupling intervals required to induce non-clinical forms of VT or VF are often shorter than the coupling intervals required to induce clinical VT raising concerns about the specificity of EP studies when aggressive stimulation protocols are used.
Nunn LM, et al. 2011 21737021 (222)	**Study type:** Retrospective **Size:** n=363 pts	**Inclusion criteria:** Families of sudden arrhythmic death syndrome probands **Exclusion criteria:** N/A	**1° endpoint:** The prevalence of J-point elevation among the relatives of sudden arrhythmic death syndrome probands **Results:** A total of 363 first-degree relatives from 144 families were evaluated. J-point elevation in the inferolateral leads was present in 23% of relatives and 11% of control pts (OR: 2.54, 95% CI: 1.66–3.90; p<0.001).	• J-point elevation is more prevalent in the relatives of sudden arrhythmic death syndrome probands than in controls. This indicates that ER is an important potentially inheritable pro-arrhythmic trait or marker of pro-arrhythmia in sudden arrhythmic death syndrome.
Haissaguerre M, et al. 2008 18463377 (223)	**Study type:** Retrospective **Size:** n=206 case pts and 412 control pts matched for age, sex, race and level of physical activity	**Inclusion criteria:** Resuscitated from cardiac arrest due to idiopathic VF **Exclusion criteria:** Age >60 y of age	**1° endpoint:** Prevalence of ER **Results:** ER was more frequent in case pts with idiopathic ventricular fibrillation than in control pts (31% vs. 5%, p<0.001). • During a mean follow-up of 61 ± 50 mo, defibrillator monitoring showed a higher incidence of recurrent ventricular fibrillation in case pts with a repolarization abnormality than in those without such an abnormality (HR: 2.1; 95% CI: 1.2–3.5; p=0.008).	• Among pts with a Hx of idiopathic VF, there is an increased prevalence of early repolarization.
Rosso, et al. 2008 18926326. (224)	**Study type:** Case control study **Size:** n=45 pts with	**Inclusion criteria:** Idiopathic VF compared with age and sex matched control pts	**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%,	• J-point elevation is found more frequently among pts with idiopathic VF than among healthy control pts. The frequency of J-

	idiopathic VF and 121 young athletes	**Exclusion criteria:** The presence of an etiology for the cardiac arrest	p=0.001). This was true for J-point elevation in the inferior leads (27% vs. 8%, p=0.006) and for J-point elevation in leads I to aVL (13% vs. 1%; p=0.009). J-point elevation in V(4) to V(6) occurred with equal frequency among pts and matched control pts (6.7% vs. 7.3%; p=0.86). • The presence of ST-segment elevation or QRS slurring did not add diagnostic value to the presence of J-point elevation.	point elevation among young athletes is higher than among healthy adults but lower than among pts with idiopathic VF.
Merchant FM, et al. 2009 19892058 (225)	**Study type:** Retrospective **Size:** n=39 cases of idiopathic VF	**Inclusion criteria:** Idiopathic VF and ICD implant **Exclusion criteria:** Structural heart disease, CAD or the presence of an arrhythmia susceptibility syndrome (LQTS, SQTS, WPW, BS or ARVD)	**1° endpoint:** Prevalence of ER and QRS notching **Results:** 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).	• Left precordial terminal QRS notching is more prevalent in malignant variants of ER than in benign cases.
Tikkanen, et al. 2009 19917913 (226)	**Study type:** Retrospective **Size:** n=10,864 middle-aged pts	**Inclusion criteria:** Community based general population **Exclusion criteria:** N/A	**1° endpoint:** Prevalence and prognostic significance of ER including death from cardiac cause, death from arrhythmia and death from any causes **Results:** 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%). • 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). • 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<0.001) and from arrhythmia (adjusted RR: 2.92; 95% CI: 1.45–5.89; p=0.01).	• 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.
Patel, et al. 2010 20657030 (227)	**Study type:** Case Control design **Size:** n=60 pts (CAD + ICD + sustained arrhythmic events) and n=60 control pts (CAD + ICD + no arrhythmic events)	**Inclusion criteria:** CAD + ICD implant + sustained arrhythmic events **Exclusion criteria:** Pts who had an acute MI during follow up, suspected BS and pts with QRS ≥120 ms	**1° endpoint:** Prevalence of ER **Results:** 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).	• 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.
Tikkanen, et al.	**Study type:**	**Inclusion criteria:** Pts participating	**1° endpoint:** Mortality over a 30±11 y follow up period	• ST-segment morphology

2011 21632493 (228)	Retrospective **Size:** n=10,957 pts	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 20668657 (229)	**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.

Data Supplement 25. RCTs Comparing Vasovagal Syncope – (Section 5.1.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Lu CC, et al. 2008 18772858 (230)	**Aim:** Assess whether glucose water ingestion will reduce orthostatic tolerance in young healthy volunteers **Study type:** Analytical,	**Inclusion**: Healthy male **Exclusion**: Hx of syncope, any medications	**Intervention:** Ingestion of 10% glucose water before 70 degree HUTT **Comparator:** Ingestion of pure water 5 mins before 70 degree	**1° endpoint:** 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	Glucose water attenuates reflex role of PVR during orthostatic stress, perhaps by vasodilatation in splanchnic circulation or raising plasma osmolality which may enhance

	Randomized controlled crossover, prospective cohort, **Size:** n=15 pts		HUTT	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. **Safety endpoint:** N/A	barorefex control of SNS.
Schroeder, et al. 2002 12451007 (231)	**Aim:** To assess water drinking on orthostatic tolerance in healthy pts **Study type:** Analytical, randomized controlled, prospective crossover **Size:** n=13 pts	**Inclusion**: Healthy volunteers **Exclusion**: Regular medication except oral contraceptives	**Intervention:** 500 mL nonsparkling mineral water at room temperature **Comparator:** 50 mL nonsparkling mineral water • then 60 degree HUTT for 20 min followed by LBNP for 10 min each at -20, then -40, -60 mmHg	**1° endpoint:** Drinking 500 mL water prolonged time to presyncope in 11 pts from 31 +/-3 min to 36+/-3 min (P<0.001). Supine heart rate, BP, SV, and cardiac output were not significantly different with 500 mLwater drinking. With HUTT, 500 mL water drinking blunted decrease in SV from -45+/-2% to -38+/-3%, p<0.01 **Safety endpoint:** N/A	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.
El-Sayed, et al. 1996 8673750 (232)	**Aim:** To evaluated salt supplementation in syncope with orthostatic intolerance, **Study type:** Analytical, Randomized placebo controlled, prospective cohort, **Size:** n=20 pts; **Study type:** Analytical, observational, open label, prospective cohort **Size:** n=11 pts	**Inclusion**: Recurrent syncope without etiology **Exclusion**: None	RDBPCT: **Intervention:** Sodium chloride 10 mmol **Comparator:** Placebo 12x daily then 60 degree HUTT with LBNP up to -40 mmHg Open label: **Intervention:** Slow sodium 10 mmol 12x daily (pts told it was a "mineral dietary supplement") then 60 degree HUTT with LBNP up to -40 mmHg	**1° endpoint:** 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) **Safety endpoint:** N/A **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
Brignole M, et al. 2002 12475469 (233)	**Aim:** Whether handgrip or arm-tensing would increase BP during impending syncope and avoid LOC **Study type:** Randomized;	**Inclusion criteria:** ≥1 episode of syncope; ≥1 syncopal episodes preceded by prodromal; syncope reproduced during 2 tilt tests performed on different days	**Intervention:** Hand-grip or arm-tensing **Comparator:** Placebo	**1° endpoint:** Syncope or presyncopal recurrence with maneuver **1° Safety endpoint:** N/A	• 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

	single-blind, placebo-controlled; cross-over tilt efficacy study **Size:** n=19 pts	≥18 y. **Exclusion criteria:** N/A			**Summary**: Isometric arm contraction helps to abort impending syncope BP increased
Van Dijk, et al. 2006 17045903 (234)	**Aim:** Assess effectiveness of PCM in daily life **Study type:** Randomized (multicenter) **Size:** n=223 pts standard n=117; standard+PCM n=106	**Inclusion criteria:** Recurrent syncope and prodome (≥3 syncope episodes in 2 y or (≥1 syncope and ≥3 presyncope in 1 y **Exclusion criteria:** Heart disease, OH, other causes for syncope, life-expectancy <1; unable to follow-up	**Intervention:** Conventional therapy+ PCM (leg-crossing, hand grip, arm tensing **Comparator:** Conventional therapy	**1° endpoint:** Syncope recurrence **1° Safety endpoint:** N/A	• 32% PCM vs. 51% control (p=0.005); median yearly syncope burden lower in PCM group (p<0.004); RRR: 39% in PCM group. **Summary**: PCM effective, safe in VVS with prodrome.
Foglia-Manzillo, et al. 2004 15121070 (235)	**Aim:** Efficacy of tilt training in preventing tilt-induced syncope **Study type:** Randomized (multicenter) **Size:** n=68 pts; tilt-training n=35; controls n=33	**Inclusion criteria:** Recurrent syncope; 2 consecutive positive nitrate-potentiated head-up tilt test **Exclusion criteria:** Other causes of syncope	**Intervention:** Tilt-training (30min standing against wall 6 days a 1 wk x 3 wk). **Comparator:** No tilt-training	**1° endpoint:** Positive tilt test; syncope recurrence **1° Safety endpoint:** N/A	• F/U 1 y; syncope recurrence 28%; presyncope 45%; 17% performed tilt-training; of the 5 compliant 3 neg tilt table; none had recurrence. **Summary**: Tilt-training not effective in reducing tilt-testing positivity because of poor compliance.
On YK, et al. 2007 17461874 (236)	**Aim:** Effectiveness of repeated home orthostatic self-training **Study type:** Randomized **Size:** n=33 pts; tilt-training n=16; control n=17	**Inclusion criteria:** VVS by positive HUTT **Exclusion criteria:** Other causes of syncope after comprehensive evaluation, structural heart disease.	**Intervention:** Daily sessions x 4 wk. Standing against wall 1–2 times a day until prodrome of for up to 30 min **Comparator:** No tilt-training	**1° endpoint:** Tilt response at 1 min; syncope recurrence **1° Safety endpoint:** N/A	• 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. **Summary**: Tilt-training ineffective in reducing positive HUT response.
Duygu, et al. 2008	**Aim:** Effectiveness of repeated orthostatic self-	**Inclusion criteria:** Recurrent syncope (≥2 events in 6m)	**Intervention:** Conventional+tilt-training (Standing against wall 1-	**1° endpoint:** Syncope recurrence	• Follow up 12±2 m; syncope recurrence 56% control and

18439174 (237)	training **Study type:** Randomized **Size:** n=82 pts; 1:1	and + HUTT **Exclusion criteria:** Other causes of syncope after comprehensive evaluation	2X a d until prodrome of for up to 30 min x 1m; then every other day x2 m then 2x a wk) **Comparator:** Conventional	**1° Safety endpoint:** N/A	37% tilt-training (p=0.1); frequency of recurrence similar in all types of VVS; rate of episodes higher in vasodepressor type. **Summary**: Tilt-training did not reduce syncope recurrence
Salim, et al. 2005 15708690 (238)	**Aim:** Effectiveness of salt and fludocrotisone in prevention of VVS in children **Study type:** Randomized (pediatric) **Size:** n=32 pts; florinef 0.1mg/day and salt 1g/d n=18; control n=14	**Inclusion criteria:** ≥1 syncope or presyncope ; +HUTT; <18 y of age; no prior therapy for syncope **Exclusion criteria:** No structural heart disease	**Intervention:** florinef 0.1mg/day and salt 1g/d **Comparator:** Placebo	**1° endpoint:** Syncope or pre-syncope recurrence **1° Safety endpoint:** N/A	• Follow up 176±117d ; recurrence 36% in controls and 55% active arm (p<0.04). **Summary**: Symptoms were more frequent in the placebo group.
Romme JJ, et al. 2011 21752826 (239)	**Aim:** Effectiveness of midodrine in pts not responding to non-pharmacological treatment (STAND-trial) **Study type:** randomized, double-blind crossover (3 m then 1 wk washout) **Size:** n=23 pts	**Inclusion criteria:** ≥3 syncope in 2 y; prodrome in 80% episodes; +HUTT **Exclusion criteria:** LOC not due to VVS; already using pharmacotherapy for rx VVS	**Intervention:** Midodrine **Comparator:** Placebo	**1° endpoint:** Recurrence of syncope or presyncope, side effects and QoL **1° Safety endpoint:** N/A	• Syncope and presyncope 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. **Summary**: Addition of midodrine to non-pharmacological therapy not effective
Kaufman H, et al. 2002 12205647 (240)	**Aim:** Efficacy of midodrine **Study type:** Randomized, double-blind cross-over **Size:** n=12 (5 mg or placebo day 1 and opposite on day 3)	**Inclusion criteria:** ≥2 syncope in 1 y; +HUT **Exclusion criteria:** N/A	**Intervention:** Midodrine **Comparator:** Placebo	**1° endpoint:** Recurrence of syncope **1° Safety endpoint:** N/A	• Midodrine produced no significant change in BP or heart rate • Response to HUT: NMS 67% on placebo and 17% on midodrine (p<0.02)

	and 1 h after HUTT				
Perez-Lugones, et al. 2001 11513446 (241)	**Aim:** Efficacy of midodrine **Study type:** Randomized **Size:** n=61 pts; midodrine n=31; conventional n=30	**Inclusion criteria:** ≥1 syncope per mo and (2) a positive HUTT. **Exclusion criteria:** 1) other causes of syncope; 2)CVD and /or systemic disease; or 3) SBP150 mmHg or dBP 95 mmHg	**Intervention:** Midodrine (5 mg pot id titrated up to 15 tid if required) q 6 daytime **Comparator:** Conventional	**1° endpoint:** Syncope recurrence **1° Safety endpoint:** N/A	• F/u 6m; 81% midodrine and 4% in conventional remained asymptomatic (p<0.001) **Summary**: Midodrine provides a significant benefit compared to conventional therapy.
Ward, et al. 1998 9505918 (242)	**Aim:** Benefit of midodrine on symptom frequency and hemodynamic response during HUTT **Study type:** Randomized (double-blind placebo controlled cross over) **Size:** n=16 pts	**Inclusion criteria:** >2 pre-syncope or syncope; no HTN meds; reproducible syncope with GTN on HUTT **Exclusion criteria:** Did not meet inclusions	**Intervention:** midodrine x 1 mo **Comparator:** Placebo	**1° endpoint:** Symptom frequency and hemodynamic response HUTT **1° Safety endpoint:** N/A	• Midodrine 7.3 symptom free days than placebo (p<0.0001); QoL improved with midodrine; 14 placebo group tilt-induced syncope vs. 6 midodrine (p=0.01) **Summary**: Midodrine associated with reduced symptom frequency; symptom HUTT and improved QoL.
Qingyou, et al. 2006 17137891 (243)	**Aim:** Effectiveness of midodrine in prevention of VVS in children **Study type:** Randomized (open-label) (pediatric) **Size:** n=26 pts; midodrine+ conventional n=13; conventional n=13	**Inclusion criteria:** ≥3 syncope/y **Exclusion criteria:** Other causes of syncope after comprehensive evaluation	**Intervention:** 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) **Comparator:** Conventional	**1° endpoint:** Syncope recurrence **1° Safety endpoint:** N/A	• Follow up 10±8 m; 80% controls vs. 22% midodrine (p=0.023) **Summary**: Midrodrine effective in treating VVS in children.

Madrid, et al. 2001 11216978 (244)	**Aim:** Efficacy of atenolol **Study type:** Randomized (double-blind and placebo-controlled) **Size:** n=50 pts; atenolol n=26; placebo n=24	**Inclusion criteria:** ≥2 syncope 1 y **Exclusion criteria:** PAD, DM, AV disease, autonomic dysfunction, neoplastic or psych, drug addiction	**Intervention:** Atenolol 50 mg/d **Comparator:** Placebo	**1° endpoint:** Time to syncope recurrence **1° Safety endpoint:** N/A	• ITT, syncope recurrence similar both groups; KM p value 0.45 for time to first recurrence **Summary**: Recurrence of syncope similar in pts treated with atenolol compared to placebo.
Flevari, et al. 2002 12142117 (245)	**Aim:** Efficacy of propranolol, nadolol and placebo in recurrent VVS **Study type:** Randomized 3 mo cross-over **Size:** n=33	**Inclusion criteria:** ≥2 syncope 3m; +HUTT **Exclusion criteria:** Autonomic failure, HTN, COPD, PVD	**Intervention:** Propranolol, nadolol, placebo 3 mo cross-over **Comparator:** See above	**1° endpoint:** Syncope and pre-syncope recurrence **1° Safety endpoint:** N/A	• Follow up 3m periods syncope and pre-syncope reduced by all drugs; [ANOVA]: chi-square =67.4; p<0.0001 for syncopal attacks; chi-square =60.1; p<0.0001 for presyncopal attacks **Summary**: B-blockers and placebo equally effective in decreasing syncope and pre-syncope
Brignole, et al. 1992 1632399 (246)	**Aim:** Efficacy of medical treatment in preventing VVS **Study type:** Randomized **Size:** n=30 pts; 1:1	**Inclusion criteria:** Frequent, unexplained syncope or pre-syncope; 2 +HUTT **Exclusion criteria:** Other causes of syncope after comprehensive evaluation	**Intervention:** Drugs: atenolol n=7;dihyroergotamine n=2;domperidone n=2; cafedrine n=1; stocking ± drug n=3 **Comparator:** Placebo	**1° endpoint:** Syncope recurrence **1° Safety endpoint:** N/A	• Follow up 10±7m; absence of syncope recurrence after 20m 70% treatment and 67% placebo **Summary**: Outcomes similar in either medically treated or placebo groups.
POST Sheldon, et al. 2006 16505178 (247)	**Aim:** Effectiveness of b-blockers in prevention VVS **Study type:** Randomized (multicenter) **Size:** n=208 pts; metoprolol n=108; placebo n=100	**Inclusion criteria:** ≥2 syncope over lifetime or ≥1 syncope 6 mo; +HUTT **Exclusion criteria:** Oother cause of syncope; PPM, contraindication to b-blocker; prior trial b-blocker ≥25 mg bid	**Intervention:** Metoprolol **Comparator:** Placebo	**1° endpoint:** Syncope recurrence **1° Safety endpoint (:** N/A	• 36% in control and 36% metoprolol (p=0.99) **Summary**: Syncope recurrence did not differ between metoprolol or placebo groups.

Theodorakis, et al. 2006 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 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 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 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

	Size: n=45	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)

Study Acronym; Author; Year Published	Study Type/Design*; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Pitt, et al. 2004 15316842 (252)	**Study type:** Observational Determine whether syncope pts and control pts show different responses of BP to postural maneuvers; carbohydrate or water **Size:** n=7 pts	**Inclusion criteria:** syncope or presyncope related to upright posture; ≥episode in prior 6 m; +HUTT: drop in SBP <80 mmHg with symptoms **Exclusion criteria:** Evidence of cardiac or neurological etiology on work-up	**1° endpoint:** BP response **Results:** Carbohydrate : 85% meal or 500 ml of tap water alternated 1-2 wk; before and after crouching • Before meal or water no difference btw groups in BP or in response to maneuvers; in pts standing BP did increase after water; BP after crouch increased largely after meal but smaller after water.	• In pts with posturally related syncope unlike in control; carbohydrate ingestion and water result in opposite effects on BP during postural maneuvers.
Krediet, et al. 2002 12270863 (253)	**Study type:** Observational Effects of leg crossing and lower body tensing 30s **Size:** n=21 pts	**Inclusion criteria:** Recurrent VVS syncope; positive tilt table **Exclusion criteria:** Other causes of syncope after comprehensive evaluation	**1° endpoint:** Syncope or presyncope recurrence after tilt test and use of counter-maneuvers **Results:** 5/20 (25%) vasovagal reaction averted by maneuver prior to tilt; In follow up (10m) 13 pts used counter-maneuver in daily life and 2 fainted; 10 with presyncope benefited.	• Counter-maneuvers can help to alleviate prodromal symptoms and can prevent in some recurrent syncope. • BP increased
Di Girolamo, et al. 1999 10534467 (254)	**Study type:** Controlled Study, standing against wall up to 40 min **Size:** n=47 pts; consent n=24 and refusal (n=23)	**Inclusion criteria:** Refractory VVS syncope; positive nitrate-potentiated head-up tilt test **Exclusion criteria:** Other causes of syncope after comprehensive evaluation	**1° endpoint:** Syncope recurrence **Results:** HUTT response evaluated at 1m: 26.1% of control group and 95.8% of training group became tilt-neg (p<0.0001); syncope recurrence (18.2±5.3 m) 56.3% control vs. 0% in training group (p<0.0001)	• Tilt training significantly improves symptoms in those unresponsive or intolerant of medications.
Reybrouck, et al. 2002 12418741 (255)	**Study type:** Observational (long term f/u); 1-2m against will **Size:** n=38	**Inclusion criteria:** Recurrent VVS syncope and positive tilt without pharmacological provocation **Exclusion criteria:** Other causes of syncope after comprehensive evaluation	**1° endpoint:** Syncope recurrence **Results:** Follow up (43±7.8 m); 29/38 abandoned tilt training; 82% free of syncope; 6/7 recurrent syncope discontinued training; 19 compliant for 1 y no syncope recurrence reported	• Syncope recurrence may improve symptoms.
Kinay, et al. 2004 15557724 (256)	**Study type:** Observational In-hospital training: 3 consecutive session w/o	**Inclusion criteria:** Recurrent VVS syncope; positive nitrate-potentiated head-up tilt test	**1° endpoint:** Syncope recurrence **Results:** F/U 356 ±45 d;81% free of recurrent syncope.	• Short-term tilt-training is effective.

	syncope; home: 2 session standing against wall 15 min 2m; no activity **Size:** n=32	**Exclusion criteria:** Other causes of syncope after comprehensive evaluation		
Samniah, et al. 2001 11423066 (257)	**Study type:** Observational **Size:** n=20	**Inclusion criteria:** Recurrent VVS syncope ≥1 y; failed ≥2 meds **Exclusion criteria:** BP >160/90; symptomatic IHD; CVA	**1° endpoint:** Syncope recurrence **Results:** Follow up 21.9 (15,36); 14/18 resolution of symptoms; 4 partial response	• Midodrine effective and safe in pts with VVS refractory to standard drug therapy.
Sheldon, et al. 1996 8806338 (258)	**Study type:** Non-randomized **Size** n=153; 52 received b-blocker; 101 control	**Inclusion criteria:** ≥2 VVS syncope or 1 syncope and ≥4 presyncope; +Iso HUTT **Exclusion criteria:** Other causes of syncope after comprehensive evaluation	**1° endpoint:** Syncope recurrence **Results:** Event occurred 17/52 b-blockers; 28/101 pt control; actuarial probability of remaining syncope similar in both groups	• B-blocker may not have significant effects in preventing syncope recurrence after a positive HUT.
Sheldon, et al. 2012 22972872 (259)	**Study type:** Post-hoc POST; retrospective observational **Size:** n=160; BB=52 in obs; POST n=108; <42 or >42 y of age	**Inclusion criteria:** Obs: ≥2 VVS syncope or 1 syncope and ≥4 presyncope or 1 syncope with trauma; +HUTT Inclusion POST **Exclusion criteria:** Other cause of syncope; PPM, contraindication to b-blocker; prior trial b-blocker ≥25 mg bid	**1° endpoint:** Syncope recurrence **Results:** A pooled analysis of both studies yielded an estimate of the HR: 1.58 (CI: 1.00–2.31) for <42 y, and HR: 0.52 (CI: 0.27–1.01) for ≥42.	• B-blocker prevents syncope recurrence in middle-aged pts (>42 y of age).

Data Supplement 27. RCTs Comparing Pacemakers in Vasovagal Syncope – (Section 5.1.2)

Study Acronym Author Year	Aim of Study; Study Type*; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (include Absolute Event Rates, P value; OR or RR; and 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Connolly, et al. 1999 9935002 (260)	**Aim:** Effectiveness of PPM compared with pharmacological therapy in recurrent VVS	**Inclusion criteria:** ≥6 lifetime syncope; +HUTT **Exclusion criteria:** Other causes of syncope after comprehensive evaluation	**Intervention:** PPM with rate drop **Comparator:** Placebo	**1° endpoint:** Syncope recurrence	• Adjusted RRR 90.8% (CI: 71.0%–97.1%, p<0.0001); effect on presyncope NS (p=0.56) • Mean age no PPM 40 and PPM 46 y of age.

	Study type: Randomized **Size:** n=54;1:1 (terminated early)				**Summary**: In severely symptomatic, PPM significantly reduces syncope recurrence.
Sutton R, et al. 2000 10899092 (261)	**Aim:** Effectiveness of DDI pacemaker with rate drop on syncope recurrence **Study type:** Randomized (multicenter) **Size:** n=42; PPM n=19; no PPM=23	**Inclusion criteria:** :≥3 syncope 2 y; + cardio inhibitory response (HUTT) **Exclusion criteria:** Other causes of syncope after comprehensive evaluation; recent MI, HF (NYHA III-IV), chronic disease	**Intervention:** DDI + hysteresis **Comparator:** placebo	**1° endpoint:** Syncope recurrence	•1 (5%) PPM vs. 14 (61%) non-PPM, p<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. **Summary**: In those with cardio-inhibitory response, DDI pacing with hysteresis reduces likelihood of syncope.
Ammirati, et al. 2001 11435337 (262)	**Aim:** Effectiveness of PPM compared with pharmacological therapy in recurrent VVS **Study type:** Randomized (multicenter) **Size:** n=93; PPM n=46; no PPM n=47 terminated early	**Inclusion criteria:** >35 y of age; ≥3 syncope 2 y; +HUTT with syncope and bradycardia **Exclusion criteria:** Other causes of syncope after comprehensive evaluation	**Intervention:** PPM with rate drop **Comparator:** atenolol	**1° endpoint:** Syncope recurrence	•2 (4.3%) PPM vs. 12 (25.5%) drug; OR 0.133 (0.028–0.632), p=0.004. **Summary**: DDD with rate drop more effective than atenolol for prevention of syncope.
Connolly, et al. 2003 12734133 (263)	**Aim:** If pacing reduces syncope recurrence **Study type:** Randomized (multicenter, double-blind) **Size:** n=100 pts; DDD n=48; ODO n=52	**Inclusion criteria:** ≥6 lifetime syncope;3 in 3 y; +HUTT **Exclusion criteria:** Other causes of syncope after comprehensive evaluation, valvular, coronary, myocardial, major non CVD, ECG abnormalities	**Intervention:** DDD with rate drop **Comparator:** ODO	**1° endpoint:** Syncope recurrence	• Cumulative risk at 6m 40% (25%–52%) ODO and 31% (-33%–63%) DDD, p=0.14. **Summary**: Pacing did not reduce risk of recurrent syncope.
Raviele A, et al. 2004 15451153 (264)	**Aim:** if pacing reduces syncope recurrence **Study type:** Randomized (multicenter, double-blind,	**Inclusion criteria:** ≥6 lifetime syncope; 1 in last y; +HUTT(asystole or mixed) **Exclusion criteria:** Other causes of syncope after comprehensive evaluation	**Intervention:** DDD with rate drop **Comparator:** OOO	**1° endpoint:** Syncope recurrence	• Follow up med 715d, 8(50%) on vs. 5(38%) off (p=NS); no difference in the mixed and asystole subgroups. **Summary**: Active pacing was not

	placebo-controlled) **Size:** n=29 pts; on n=16; off n=13				significant associated with reduction in syncope recurrence compared to inactive pacing.
Brignole, et al. 2012 22565936 (265)	**Aim:** effectiveness of cardiac pacing in NMS and asystole **Study type:** Randomized (multicenter, double-blind, placebo-controlled) **Size:** n=77; on n=16; off n=13	**Inclusion criteria:** :≥40 y of age; ≥3 syncope in 2 y; ILR with ≥3s asystole or ≥6s asystole w/o syncope **Exclusion criteria:** ≥1 cardiac abnormalities that suggested cardiac syncopesinus bradycardia <50 bpm or sinoatrial block; Mobitz I second-degree AV block; BBB; rapid paroxysmal SVT or VT; preexcited QRS complexes; prolonged QT interval; BS; ARVC); nonsyncopal loss of consciousness; CSS	**Intervention:** DDD with rate drop **Comparator:** ODO	**1° endpoint:** Syncope recurrence	•2 y estimated recurrence 57% (40%-74%) ODO and 25% (13%-45%) DDD, p=0.039. absolute RR 32% and relative RR 57% with DDD **Summary**: DDD effective in reducing recurrence of syncope in ≥40 y of age with severe asystolic component.
Flammang, et al. 1999 11228858 (266)	**Aim:** Effectiveness of pacing in symptom recurrence with abnormal adenosine 5-triphosphate **Study type:** Randomized (open label) **Size:** n=20; Dual chamber Pacemaker on n=10; Pacemaker off n=10	**Inclusion criteria:** VVS and abnormal cardioinhibitory (i.e. electrocardiographic) response during ATP test. **Exclusion criteria:** Syncope due to neurological, metabolic or arrhythmic etiology	**Intervention:** Pacemaker on **Comparator:** Pacemaker off	**1° endpoint:** Syncope recurrence	• Follow up mean 52m; syncope recurrence PPM 0 (0%); No PPM 6 (60%) •All-cause mortality: Pacemaker 3 (30%); No Pacemaker 1 (10%) **Summary**: PPM in pts with abnormal ATP have fewer syncope recurrences
Flammang, et al. 2012 22086879 (267)	**Aim:** effectiveness of pacing in unexplained syncope and positive adenosine 5-triphosphate **Study type:** Randomized (single blind ,multicenter) **Size:** n=80; active n=39; passive n=41	**Inclusion criteria:** syncope of unknown origin; AV or SA block >10s under ATP administration **Exclusion criteria:** ≥1+EPS, carotid sinus hypersensitivity, sustained or episodic atrial or VT documented sinus or AV node conduction disorders (including first-degree AV block), + PPM and ICD ,heart transplant list, pregnancy, asthma or	**Intervention:** DDD 70 bpm **Comparator:** back-up 30 bpm	**1° endpoint:** Syncope recurrence	• Follow up mean 16m; 8/39 (21%) active vs. 27/41 (66%) HR: 0.25 (0.12–0.56) **Summary**: Dual chamber PPM reduces syncope by 75%.

		severe chronic bronchitis, systemic infection, or DM			
Occhetta, et al. 2004 15519257 (268)	**Aim:** To determine whether dual-chamber rate adaptive CLS prevents recurrence of VVS CLS – tracks variation of intracardiac impedance during systolic phase of cardia 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) • Randomization between DDD (9/26) (17/26) and DDI only during 1st y • 24 pts recruited in 2nd y programmed to DDD-CLS	**1° endpoint:** 2 VVS during 1 y follow-up.	• Follow up mean 44 m; 7/9 DDI had met primary endpoint; 41 pts programmed to DDD-CLS none had VVS **Summary**: Effectiveness of DDD-CLS in preventing VVS with cardioinhibition
Russo, et al. 2013 23723446 (269)	**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	**1° 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)

Study Acronym (if applicable) Author; Year	Study Type/Design*; Study Size	Patient Population	Primary Endpoint and Results (include P value; OR or RR; and 95% CI)	Summary/Conclusion Comment(s)
Deharo, et al. 2013	**Study type:** Observational	**Inclusion criteria:** Sudden onset syncope without prodrome and normal	**1° endpoint:** Pathophysiology of sudden-onset syncope	• Low adenosine plasmatic levels defines distinct form syncope from

23810895 (270)	**Size:** n=15 pts with syncope without prodrome and normal heart and ECG compared to n=31 VVS	heart and ECG; VVS **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.
Brignole, et al. 2011 21570228 (271)	**Study type:** Observational **Size:** n=18 pts	**Inclusion criteria:** Syncope; normal ECG, no structural heart disease, paroxysmal 3AVB associated with syncope **Exclusion criteria:** Other causes of syncope after comprehensive evaluation	**1° endpoint:** Clinical characteristics unexplained syncope with paroxysmal AVB **Results:** Follow up mean 4±4 y; AVB without P-P cycle or PR interval prolongation; 17 pts had dual-chamber PPM no syncope recurrence.	• Efficacy of PPM in idiopathic AVB.
Lelonek M, et al. 2007 (272)	**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	**Inclusion criteria:** Tilt-induced cardio depressive syncope with asystole >3 s (2B VASIS) **Exclusion criteria:** Other causes of syncope after comprehensive cardiac and neurological evaluation	**1° endpoint:** Syncope recurrence **Results:** Syncope recurrence at 18 mo: Pacemaker 5 (23%); No pacemaker 3 (25%); p>0.05 No injury in either group	• Pacemaker or pharmacological treatment effective

Data Supplement 29. RCTs Comparing Carotid Sinus Syndrome – (Section 5.1.3)

Study Acronym Author Year	Aim of Study; Study Type*; Study Size (N)	Patient Population	Study Intervention (include # patients) / Study Comparator (include # patients)	Endpoint Results (include Absolute Event Rates, P value; OR or RR; and 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Brignole, et al. 1992 1561975 (273)	**Aim:** Efficacy of permanent pacing. **Study type:** RCT **Size:** n=60 pts; no pacing=28; pacing 32 (VVI=18, DDD=14)	**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	**Intervention:** Pacing **Comparator:** No pacing	**1° endpoint:** Symptom recurrence **1° Safety endpoint:** N/A	• Syncope recurrence in 57% of the non-pacing group and 9% of the pacing group (p=0.0002); the actuarial rate of absence of syncopal recurrence after 1,2,3 and 4 y was 64%, 54%, 36%, and 38%, respectively, for the nonpacing group, and 100%, 97%, 93%, and 64%, respectively, for the pacing group (p=0.0001). **Summary**: Permanent pacing effective in CSS

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 CSS
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	● 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 bradyarrhythmias ● 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 (CI: 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

					(4.5%) • Pts with soft tissue injury due to fall at 12 mo: pacemaker 26 (29.9%); no pacemaker 32 (36.4%) • All-cause mortality at 12 mo: pacemaker 5 (5.7%); No pacemaker 3 (3.4%) **Summary**: Pacing associated with less falls and injury; no reduction in syncope events
Ryan, et al. 2010 19933747 (277)	**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	**1° endpoint:** Number of falls after implant. **2° endpoint:** Time to fall event, presyncope, quality of life and cognitive function **1° Safety endpoint:** N/A	• 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) **2° endpoints:** • Pts with falls at 24 mo: Pacemaker 44 (67%); No pacemaker 33 (53%); RR 1.25 (95% CI: 0.93–1.67) • Syncope-related falls at 24 mo: pacemaker 4.33 events; No pacemaker 6.52 events; RR: 0.79 (95% CI: 0.41–1.5) **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)

Study Acronym (if applicable) Author, Year	Study Type/Design*; Study Size	Patient Population	Primary Endpoint and Results (include P value; OR or RR; and 95% CI)	Summary/Conclusion Comment(s)
Sugrue, et al. 1986	**Study type:** Retrospective, observational study of untreated	**Inclusion criteria:** ≥1 episodes of syncope or presyncope;	**1° endpoint:** Symptom recurrence	• PPM effective in CSS predominately cardioinhibitory

3941204 (278)	compared to pacing or anticholinergic drugs **Size:** n=56 untreated=13 anticholinergic=20 pacing=23	cardioinhibitory, vasodepressor or mixed; no other cause **Exclusion criteria:** N/A	**Results:** Incidence of recurrence 27% no treatment, 22% drug group, 9% pacing group; those with cardioinhibitory CSS had no recurrence of syncope with DVI pacing (9/9) and 8 of 10 were asymptomatic with VVI pacing	
Blanc, et al. 1984 6424619 (279)	**Study type:** Retrospective, observational **Size:** n=54 pts; no pacing=33 pacing=21	**Inclusion criteria:** Cardio inhibitory **Exclusion criteria:** N/A	**1° endpoint:** Symptom recurrence after pacemaker implant **Results:** 50% of pts had recurrence of syncope with no pacing vs. 0% in pacing group	• PPM effective in CSS
Morley, et al. 1982 7073901 (280)	**Study type:** Prospective, observational **Size:** n=70 pts; pacing mode (VVI, DVI, DDD, AAI)	**Inclusion criteria:** Cardioinhibitory with pacemaker **Exclusion criteria:** N/A	**1° endpoint:** Symptom persistence, vasodepressor response, pacemaker effect **Results:** Persistence of symptoms with a final pacing mode VVI 11%; 8% DVI and 8% DDD, AV sequential pacing eliminated hypotensive effects of VVI pacing	• PPM effective in CSS; AV sequential pacing preferred
Gaggioli, et al. 1995 7572635 (281)	**Study type:** Retrospective, observational **Size:** n=169 pts; VVI n=59 DDD n=110	**Inclusion criteria:** Cardioinhibitory or mixed; no other cause **Exclusion criteria:** N/A	**1° endpoint:** Symptom recurrence after pacemaker implant **Results:** Syncope recurrence was 7% at 1 y, 16% at 3 y, and 20% at 5 y; 21% syncope recurrence in pts with vasodepressor response.	• PPM effective in CSS; recurrence does occur in mixed type
Maggi, et al. 2007 17507364 (282)	**Study type:** case-control (age-sex matched 2:1) **Size:** n=18 pts	**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	**1° endpoint:** Syncope recurrence **Results:** Asystole 89% CSS and 50% controls; 14 of CSS with asystole DCH PPM; f/u 35 ±22m syncope burden decreased 1.68 (1.66–1.70) episodes to 0.04 (0.038–0.042) with PPM (98% RR)	• Cardio inhibitory CSS predicts associated with asystole during spontaneous syncope benefit from pacing
Lopes, et al. 2011 21169606 (283)	**Study type:** Retrospective observational **Size:** n=138 pts	**Inclusion criteria:** Cardio inhibitory or mixed in whom pacemaker implanted	**1° endpoint:** Symptom recurrence after pacemaker implant **Results:** Syncope recurrence 10.9%; 5.8% minor	• Permanent pacing effective in CSS; recurrence does occur in mixed type

		Exclusion criteria: N/A	symptoms/presyncope; mixed CSS predicted recurrence (HR: 2.84; 1.20–6.71; p=0.017)	
Brignole, et al. 2011 21570228 (271)	**Study type:** Systematic review **Size:** 12 studies; n=601 pts with pacing and 305 untreated	**Inclusion criteria:** Cardioinhibitory or mixed **Exclusion criteria:** Case reports	**1° endpoint:** Syncope recurrence; up to 5 y follow-up **Results:** 0–20%in pacing group and 20-60% in untreated group; 3 studies with control groups RR 0.24 (0.12–0.48)	• Benefit of cardiac pacing with significant reduction in recurrence; lead to reduced morbidity • Recurrence 20% of paced pts at 5 y
Menozzi, et al. 1993 8237805 (284)	**Study type:** Prospective observational **Size:** n=23 pts	**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. **Exclusion criteria:** No other identifiable cause	**1° endpoint:** Occurrence of asystolic episodes **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%)	• Asystolic response to vasovagal maneuvers predicts occurrence of spontaneous asystolic episodes. Spontaneous episodes are asymptomatic and incidence is low.
Striyger, et al. 1986 2429277 (285)	**Study type:** Prospective observational **Size:** n=20 pts	**Inclusion criteria:** Repeated syncope of unknown cause; CSM asystole of ≥4 sec; cardioinhibitory based on EPS **Exclusion criteria:** N/A	**1° endpoint:** Efficacy of VVI pacing in preventing recurrence **Results:** Mean 20 mo; no pts had reoccurrence of syncope	• VVI pacing for isolated form of cardioinihibitory syncope results in complete resolution of symptoms.
Walter, et al. 1978 356576 (286)	**Study type:** Prospective observational **Size:** n=21 pts	**Inclusion criteria:** Syncope of unknown cause or pre-syncope; CSM ventricular asystole of >3 sec **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** 17 pts had cardio inhibitory, 2 vasodepressor and 2 mixed. 11 pts PPM 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.	• PPM in cardio inhibitory syncope is associated with less reoccurrences.
Crilley, et al. 1997 9338027 (287)	**Study type:** Prospective observational **Size:** n=42 pts	**Inclusion criteria:** recurrent falls, pre-syncope or syncope and CSM >3 s ventricular asystole **Exclusion criteria:** N/A	**1° endpoint:** Outcomes of DCH PPM on elderly with falls, pre-syncope and syncope associated with cardioinhibitory syncope **Results:** All pts had DDI pacemaker implant; 84% no longer had further syncope mean follow up 10 mo and	• DCH PPM is effective for hypersensitive cardioinhibitory syncope.

			symptoms unchanged in 22%	

Data Supplement 31. RCTs for Type of Permanent Pacing in Carotid Sinus Hypersensitivity – (Section 5.2.2)

Study Acronym Author Year	Aim of Study; Study Type*; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (include Absolute Event Rates, P value; OR or RR; and 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Brignole, et al. 1988 2463565 (288)	**Aim:** Evaluate importance of atrial synchronism for mixed CSS **Study type:** RCT (single blind, cross-over) **Size:** n=23 pts	**Inclusion criteria:** Mixed CSS **Exclusion criteria:** Isolated cardioinhibitory or vasodepressor	**Intervention:** DVI/DDD **Comparator:** VVI	**1° endpoint:** Symptom recurrence; VA conduction, OH, pacemaker effect **1° Safety endpoint :** N/A	• DVI vs. VVI, syncope occurred in 0% vs. 13% (p= 0.25); pre-syncope in 48% vs. 74% (p=0.04); DVI was the modepreferred 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
McLeod, et al. 2012 22548372 (289)	**Aim:** Investigate impact of pacing modes (DDDR, DDR with sudden brady response and VVI) on syncope recurrence and QoL **Study type:** RCT (double-blind, sequential cross over – 6 m) **Size:** n=21 pts	**Inclusion criteria:** Cardioinhibitory/ mixed CSS; symptoms reproducible CSM **Exclusion criteria:** Isolated vasodepressor response to CSM; another cause for LOC; structural heart disease, PPM	**Intervention:** DDDR, DDR with sudden brady response and VVI **Comparator:**	**1° endpoint:** Syncope and pre-syncope recurrence; QoL 9SF-36) **1° Safety endpoint :** N/A	• 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<0.001) and presyncope (258–17; p<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

Data Supplement 32. Observational studies, for Type of Permanent Pacing in Carotid Sinus Hypersensitivity – (Section 5.2.2)

Study Acronym; Author; Year Published	Study Type/Design*; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
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 syncope compatible with cardiac origin **Exclusion criteria:** N/A	**1° 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. DDD vs. VVI **Size:** n=202 pts	**Inclusion criteria:** syncope or pre-syncope 98%; positive CSM; pacemaker inserted **Exclusion criteria:** N/A	**1° 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° 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)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
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° 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

	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
Lu CC, et al. 2008 18772858 (230)	**Aim:** Assess whether glucose water ingestion will reduce orthostatic tolerance in young healthy volunteers **Study type:** Analytical, Randomized controlled crossover, prospective cohort **Size:** n=15 pts	**Inclusion**: Healthy male **Exclusion**: Hx of syncope, any medications	**Intervention:** 10% glucose water **Comparator:** Pure water 5 min before 70 degree HUTT	**1° endpoint:** 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.	• Glucose water attenuates reflex role of PVR during orthostatic stress, perhaps by vasodilatation in splanchnic circulation or raising plasma osmolality which may enhance barorefex control of SNS.
Raj SR, et al. 2006 16785332 (294)	**Aim:** To assess if ingestion of salt with water would increase magnitude of acute pressor response compared with water in OH **Study type:** Analytical, randomized controlled, prospective crossover **Size:** n=9 pts	**Inclusion**: 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. **Exclusion**: None	**Intervention:** Distilled water mixed with 2 g of NaCl added, **Comparator:** 16 ox (473 mL) of distilled water then noninvasive heart rate and BP were measured for ≥ 60 mins after ingestion	**1° endpoint:** Hemodynamic response to water: SBP increased from 92±8 mmHg at baseline to 129±9 mmHg 30 min after ingestion (p<0.001), and 110±12 mmHg 60 min after ingestion (p=0.022). Plasma norepi significantly increased at 30 min (p=0.018) after water ingestion **1° endpoint:** Hemodynamic response to salt water: • SBP increased from 94 ±9 mmHg as baseline to 112 ±9 mmHg 30 min after ingestion (p=0.005), and 104 ±9 mmHg (p=0.139)	• Water and salt water both increased SBP at 30 min post ingestion, with water having double the effect of salt water. By 60 m, only water ingestion continued to show significant increase in SBP. The osmolality of salt water may have reduced the gastropressor response which likely is not just due to blood volume.
Schroeder C, et al. 2002	**Aim:** To assess water drinking on orthostatic tolerance in healthy pts	**Inclusion**: Healthy volunteers	**Intervention:** 500 mL nonsparkling mineral water at room temperature	**1° endpoint:** Drinking 500 mL water prolonged time to presyncope in 11 pts from 31 ±3 min to 36 ±3 min (p<0.001). Supine	• Water drinking 500 mL increases orthostatic tolerance, with the effect apparently

12451007 (231)	**Study type:** Analytical, randomized controlled, prospective crossover, **Size:** n=13 pts	**Exclusion**: Regular medication except oral contraceptives	**Comparator:** 50 mL nonsparkling mineral water, then 60 degree HUTT for 20 min followed by LBNP for 10 m each at -20, then -40, -60 mmHg	heart rate, BP, SV, and cardiac output were not significantly different with 500 mLwater drinking. With HUTT, 500 mL water drinking blunted decrease in SV from -45+/-2% to -38 ±3%, p<0.01	mediated with factors beyond increasing plasma volume. Increase in peripheral resistance and vasoconstrictor tone may have role.
Jankovic JJ, et al. 1993 7687093 (295)	**Aim:** Effect of midodrine in neurogenic OH **Study type:** Analytical, Randomized double-blind placebo controlled, prospective cohort, **Size:** n=97 pts	**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) **Exclusion**: Pre-existing supine hypertension (>180/110 mmHg), renal or hepatic impairment, pheochromocytoma, or severe cardiac abnormalities	**Intervention:** Midodrine 2.5 mg, 5 mg, or 10 mg 3x daily, for 4 wk **Comparator:** Placebo for 4 wk	**1° endpoint:** Midodrine increased standing SBP by 22 mmHg vs. 3 mmHg for placebo (p<0.001). Midodrine increased standing DBP by 15 mmHg vs. 3 mmHg for placebo (p<0.001). Supine SBP increased 13 mmHg vs. -2mmHg for placebo (p<0.001). Symptom improvement was significant with 10 mg for blurred vision, syncope, and energy level (p<0.01). Improvement with energy level occurred with midodrine 2.5 and 5 mg doses.	• Scalp tingling (13.5%), supine HTN (8%) Midodrine significantly improves standing SBP and symptoms of OH.
Jordan J, et al. 1998 9774366 (296)	**Aim:** To assess volume loading and alpha-adrenergic agonism in idiopathic orthostatic intolerance **Study type:** Analytical, Randomized placebo controlled, cross-sectional cohort **Size:** n=9 pts	**Inclusion**: Idiopathic OI (>30 bpm increase in heart rate within 5 min of standing without a concomitant decrease in SBP/DBP >20/10 mmHg); plasma norepi level >600 pg/mL with standing; at least 6 mo Hx of typical symptoms of OI with standing, which were significantly relieved by lying down **Exclusion**: Systemic illness	**Intervention:** Phenylephrine (infusion rate increased until either heart rate decreased by 5-10 bpm or SBP increased by 5-10 mmHg, **Comparator 1:** Phentolamine (infusion rate increased until heart rate increased by 5–10 bpm or SBP decreased by 5–10 mmHg) or **Comparator 2:** Normal saline (placebo at rate similar to pheylephrine or phentolamine	**1° endpoint:** At 5 m HUTT compared to placebo, volume loading significantly blunted the increased upright heart rate (-20+/-3.2 bpm, p<0.001) as did phenylephrine (-18+/-3.4 bpm, p<0.001), but effect diminished at end of HUTT. Phentolamine significantly increased upright heart rate at 5 min (20+/-3.7 bpm, p<0.01) and at end of HUTT (14+/-5 bpm (p<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	• 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

		that could affect the autonomic nervous system (DM, amyloidosis)	infusion). **Comparator 3:** All pts were volume loaded with 2000 mL normal saline over 3 H,then 75 degree HUT for 30 m	cerebral artery velocity with upright posture ($p<0.05$ for each).	
Jordan J, et al. 1998 9727818 (297)	**Aim:** To assess various medication effect in severe OH from autonomic failure **Study type:** Randomized placebo controlled, prospective cohort, **Size:** n=35 pts	**Inclusion**: severe OH due to multiple system atrophy or PAF **Exclusion**: Secondary causes of autonomic failure (DM, amyloidosis), contraindications to pressor agents (CAD, CHF)	Seated BP effect of **Intervention:** Phenylpropanolamine 12.5 mg (25 mg in pts not responsive to 12.5 mg), **Comparator 1:** yohimbine 5.4 mg, **Comparator 2:** indomethacin 50 mg, **Comparator 3:** Ibuprofen 600 mg, **Comparator 4:** Caffeine 250 mg, **Comparator 5:** Methylphenidate 5 mg, **Comparator 6:** Midodrine 5 mg	**1° endpoint:** Compared to placebo, the pressor response was significant for phenylpropanolamine (12.5 mg, standing SBP +37+/-12 mmHg, $p<0.05$), yohimbine (standing SBP 36+/-13 mmHg, $p<0.05$), and indomethacin (standing +28+/-2 mmHg, $p<0.05$). Phenylpropanolamine and midodrine elicited similar pressor responses. No association between drug response and autonomic function testing, or plasma catecholamine levels	• Not every pts received each drug so direct comparison was not possible. Midodrine was described as having similar effect to phenylopropanolamine with somewhat less effect seen in figure 4, but without specific hemodynamic numbers.
Kaufmann H, et al. 1988 2452997 (298)	**Aim:** To assess the effect of midodrine OH in autonomic failure **Study type:** Analytical, Randomized double-blind placebo controlled crossover, prospective cohort, **Size:** n=7 pts	**Inclusion**: Several OH with multiple system atrophy, or idiopathic OH. **Exclusion**: None Low dose fludrocortisone 0.1 mg daily continued	**Intervention:** Midodrine titrated from 2.5 mg 4x daily to total daily dose of 0.5 mg/kg (25-40 mg/d) for 7 days, **Comparator:** Placebo	**1° endpoint:** Midodrine increased standing BP significantly in 3 of 7 pts ($p<0.05$) 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.	• Midodrine improves BP and symptoms of OH in selected pts with autonomic failure. Pts with increasing severity of autonomic function may not respond to midodrine, and may worsen OH due to extracellular fluid loss
Low PA, et al. 1997 9091692 (299)	**Aim:** Assess midodrine in neurogenic OH **Study type:** Multicenter analytical, randomized double-blind placebo controlled, prospective cohort	**Inclusion**: 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	**Intervention:** Midodrine 10 mg 3x daily **Comparator:** Placebo	**1° endpoint:** Primary: improvement in standing SBP: mean increased SBP of 21.8 mmHg, $p<0.001$. Midodrine effect was independent of fludrocortisone (mean dose 0.35+/-0.33 mg) and independent of wearing compression garments. Symptoms of lightheadedess improved over entire study, and reached significance at second wk of	• Piloerection 13%, pruritus (scalp) 10%, paresthesia 9%, supine HTN 4% • Midodrine 10 mg 3 x daily increases standing BP and improves symptoms of OI.

	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.	
Phillips AA, et al. 2014 24436297 (300)	**Aim:** Assess effect of midodrine on OH and cerebral blood flow in SCI compared to able-bodied **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 orthostatic tolerance index 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	**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	• Atomoxetine improved DBP and symptoms greater than midodrine. Supine BP was not assessed. BP was measured beyond 1 h after medication administration

	Size: n=65 pts	amyloidosis, or paraneoplastic syndrome			
Singer W, et al. 2006 16476804 (302)	**Aim:** To assess pyridostigmine alone or in combination with midodrine in neurogenic OH **Study type:** Analytical, randomized, double-blind, placebo controlled, prospective crossover, **Size:** n=58 pts	**Inclusion**: Adults >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. **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	**Intervention:** Pyridostigmine 60 mg **Comparator 1:** Pyridostigmine 60 mg + midodrine 2.5 mg **Comparator 2:** Pyridostigmine 60 mg + midodrine 5 mg **Comparator 3:** Placebo	**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	• Pyridostigmine alone and in combination with midodrine with resultant improvement in symptoms without significantly affecting supine HTN.
Wright RA, et al. 1998 9674789 (303)	**Aim:** To assess dose effect of midodrine in neurogenic OH **Study type:** Analytical, randomized, double-blind, placebo-controlled, prospective	**Inclusion**: >18 y of age, neurogenic OH (≥15 mmHg SBP drop with standing; PAF, n=14, and multiple system atrophy n=7), and symptoms of OH, postmenopausal if a woman or taking	**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

	crossover, **Size:** n=25 pts	contraception **Exclusion**: Pregnancy, lactating, supine hypertension ≥ 180/110 mmHg, concomitant administration of sympathomimetics or vasoactive drugs, significant systemic, cardiac, renal, or gastrointestinal illness, or clinically significant abnormalities on exam.		mean increase of 43 mmHg, p<0.05. Significant improvement in symptoms occurred with 10 mg and 20 mg doses.	standing in dose-dependent fashion with improvement in symptoms. With increasing dose, there is also increased frequency of supine HTN.
Biaggioni I, et al. 2015 25350981 (304)	**Aim:** To evaluate whether droxidopa is beneficial in treatment of neurogenic OH **Study type:** Multinational, Analytical, Randomized placebo controlled, prospective cohort; parallel-groups phase 3 study **Size:** n=101 pts	**Inclusion**: 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 **Exclusion**: Severe HTN ≥ 180/110 mmHg; AF, or significant cardiac arrhythmia, current use of TCA, norepi reuptake inhibitors, current use of anti HTN meds, use of vasoconstrictive agents within 2 d.	**Intervention:** Droxidopa 100 mg TID and adjusted upward; mean dose at randomization was 389.6 +/- 180.9 mg 3x daily, then randomized to continue droxidopa **Comparator:** After upward adjustment of droxidopa adjustment then withdraw to placebo for 14 days	Self Rated OH Questionnaire [6-item OHSA and 4-item OHDAS: Primary: pts change on OHSA item 1: dizziness/lightheadedness **Primary:** OHSA item 1 increased by 1.3+/-2.8 in droxidopa group vs. 1.9 +/-3.2 in placebo (p=0.509); Secondary: Favored droxidopa but not statistically **Secondary:** Change in OHSA items 2–6: vision disturbance, weakness, fatigue, trouble concentrating, and head/neck discomfort).	• 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%) • 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.
Freeman R, et al. 1999 10599797	**Aim:** To assess DL-DOPS in neurogenic OH,	**Inclusion**: Autonomic failure pts with severe, symptomatic OH (n=6,	**Intervention:** 3-4-DL-threodihydroxyphenylserine (DL-DOPS) 1000 mg	**1° 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.

(305)	**Study type:** Analytical, Randomized double-blind, placebo controlled crossover, prospective cohort, **Size:** n=10 pts	multiple system atrophy; n=4, PAF) **Exclusion**: Alternative cause OH, systemic illness affecting autonomic function, significant CAD, cerebrovascular disease, or peripheral vascular disease, or malignant cardiac arrhythmias, pregnancy or child-bearing potential not on birth control, medication impairing vasomotor function except fludrocortisone	**Comparator:** Placebo then 60 degree tilt table	peak SBP occurring 300 m after medication ingestion. Plasma norepi increased in supine and tilt after DL-DOPS ingestion (p<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<0.06)	
Hauser RA, et al. 2014 24326693 (306)	**Aim:** To assess droxidopa effect in neurogenic OH in Parksonson disease, **Study type:** Multicenter analytical, randomized double-blind placebo controlled, prospective cohort phase 3 trial, **Size:** n=51 pts	**Inclusion**: 51 pts with Parkinson disease enrolled in clinicaltrials.gov NCT01176240, droxidopa for neurogenic OH in Parkinson disease interim analysis; **Exclusion**: N/A	**Intervention:** 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 **Comparator:** Placebo	**Primary:** Change in OH questionnaire composite score from baseline to wk 8 **Secondary:** OH questionnaire item 1 (dizziness, lightheadedness) and pts reported falls Mean OH qiestionnaire composite score change at wk 8 was -2.2 vs. -.21 (p=0.98). Droxidopa group with 1.0 falls/wk vs. 1.9 falls/wk in placebo (p=0.16).	• 17 droxidopa recipients (71%) with AE, nausea in 3 (13%), headache in 3 (13%), dizziness in 2 (8%) • There was no benefit of droxidopa as measured by OHQ. There was a lower (insignificant) rate of falls with droxidopa, but this subgroup was too small to analyze benefit of droxidopa. • 98% of falls occurred in 22 pts (43%).
Kaufmann H, et al. 2003 12885750 (307)	**Aim:** To assess L-DOPS effect on BP and orthostatic tolerance in severe neurogenic OH **Study type:** Analytical, Randomized double-blind placebo controlled	**Inclusion**: Severe symptomatic OH (n=11 with multiple system atrophy, n=8 with PAF **Exclusion**: Sustained, severe HTN (>180/110 mmHg while sitting),	**Intervention:** L-threo-3,4-dihydroxyphenylserine (L-DOPS) with dose based on dose ranging study **Comparator:** Placebo, then active standing	**1° endpoint:** L-DOPS significantly increased mean BP in supine (101+/-4 to 141 +/-5 mmHg) and standing (60 +/-4 to 100+/-6 mmHg, p<0.001) • At 3 m of standing, 94% of pts were able to stand compared to 84% with placebo, p<0.001. • L-DOPS showed increase in plasma NE	• Supine HTN 45% vs. 23% in placebo, hyponatremia in 1 pts • L-DOPS improves BP and orthostatic tolerance in severe neurogenic OH, but the administration of carbidopa (which inhibits conversion of L-

	crossover, prospective cohort **Size:** n=19 pts	clinically significant CAD, cerebrovascular disease, peripheral vascular disease, or cardiac arrhythmias		level that remained significantly elevated for at 46 H. Cardidopa abolished pressor response to L-DOPS.	DOPS to norepi peripherally) may limit L-DOPS effect in Parkinson disease pts
Kaufmann H, et al. 2014 24944260 (308)	**Aim:** To determine whether droxidopa improves neurogenic OH **Study type:** Analytical, Randomized placebo controlled, prospective cohort; parallel-group trial of droxidopa responders, **Size:** n=162 pts	**Inclusion**: Symptomatic neurogenic OH due to Parkinson disease, multiple system atrophy, PAF, or non-diabetic autonomic neuropathy **Exclusion**: 95 titration failures (50 had treatment failure, 12 AEs, 6 withdrew consent, 4 protocol violations, 23 other failures, 6 randomized in error	Open-label droxidopa dose optimization (100 to 600 mg 3x daily) followed, in responders by 7 day washout and then **Intervention:** 7 d double blind trial of droxidopa **Comparator:** Placebo	**1° endpoint:** Responders to droxidopa defined as improvement on OHQ item 1 ≥ 1 unit, plus a ≥ 10 mmHg increase from baseline in standing SBP **Primary:** OHQ improvement from randomization to end of study • Secondary: changes in symptom and symptom-impact composite scores, and individual OHQ items • OHQ composite score improvement (1.83 vs. 0.93 units, p=0.003). Mean standing SBP increase of 11.2 vs. 3.9 mmHg, p <0.001)	• Headache (9.9%), dizziness (6.5%), nausea (4.6%), palpitations (1.9%) • Only 1 w duration of therapy. No continuous BP monitoring
Figueroa JJ, et al. 2015 25448247 (309)	**Aim:** Assess effect of abdominal compression on postural changes in SBP with OH, **Study type:** Analytical, Randomized controlled, prospective crossover cohort **Size:** n=13 pts	**Inclusion**: 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 OH defined as SBP ≥ 30 mmHg or DBP ≥ 15 mmHg **Exclusion**: pregnancy, lactation, motor impairment affecting hand coordination, dementia, severe systemic illness, inability to tolerate	Moving from supine to standing **Comparator 1:** Without abdominal compression; **Comparator 2:** With abdominal binder in place; **Comparator 3:** With maximal tolerable abdominal compression; **Comparator 4:** With abdominal compression that pts believed would be tolerable for prolonged period	**Primary:** Postural changes in SBP. Mild abdominal compression (10 mmHg) prior to rising blunted drop in BP from -57 mmHg to -50 mmH (p=0.03) but other levels of compression did not have additional benefit. **Secondary:** Pts assessment of preferences and ease of use. There was no difference in preference or ease of use. • Standing without binder: -57 mmHg (interquartile -40 to -76 mmHg). With 10 mmHg compression: -50 mmHg (interquartile range -33 to -70 mmHg, p=0.03)	• Abdominal binders at minimal compression of 10 mmHg may blunt drop in BP. Additional compression did not have increasing effect unlike specialized shock garments which apply pressure over larger areas.

		withholding of anticholinergic-/alpha- and beta-adrenergic agonists for 5 half-lives prior to study, inability to withhold midodrine night before evaluation			
Platts SH, et al. 2009 19456003 (310)	**Aim:** To assess ability of 2 compression garments to prevent hypovolemia-related OI **Study type:** Analytical, randomized controlled, prospective cohort **Size:** n=35 pts	**Inclusion**: n=19 healthy volunteers, 32–54 y of age, and passing a modified Air Force Class III physical; and n=16 hypovolemic control pts **Exclusion**: none	(To mimic plasma volume loss due to spaceflight) pts given furosemide 0.5 mg/kg, consumed low-salt diet for 36 H **Intervention:** NASA antigravity suit inflatable in 25.9 mmHg increments, n=9 **Comparator:** Russian Kentavr – non-inflatable elastic shorts and gaiters, n=10 then did 15 m 80 degree HUTT	**1° endpoint:** No significant difference in plasma volume loss between control (17.1%), antigravity suit (16.9%), or Kentavr (18.4%). • Only 9 of 16 (56%) control pts were able to complete HUT. All antigravity suits (9 pts) and Kentavr (10 pts) were able to complete HUTT: antigravity suit vs. control, p=0.03, Kentavr vs. control, p=0.02. Change in SBP of control pts (-16 mmHg) was greater than antigravity suits group (8 mmHg, p=0.005) and Kentavr group (2 mmHg, p=0.035). No difference in diastolic BP.	• Both the antigravity suit and Kentavr suits were able to resolve orthostatic intolerance during HUT, although the Kentavr provided same benefit at approximately ½ of the compressive force. • Pts not exposed to all deconditioning effect of microgravity, just acutely reduced plasma volume
Podoleanu C, et al. 2006, 17010806 (311)	**Aim:** To assess lower limb compression bandage effect on OH in elderly persons **Study type:** Analytical, randomized controlled cross-over, prospective cohort **Size:** n=21 pts	**Inclusion**: 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 **Exclusion**: Inability of pts to collaborate and to perform tilt testing	**Intervention:** Leg compression bandages at 40 -60 mmHg for 10 m and then of the abdomen too (20 – 30 mmHg) for 10 m **Comparator:** Sham compression, then measured effect on 60 degree modified Italian HUTT	**1° endpoint:** Sham placebo leg bandage and placebo abdominal bandage: SBP decreased from 125 +/- 18 mmHg to 112 +/-25 mmHg with tilt for 10 m then to 106 +/- 25 mmHg after 20 m. With active bandage: SBP was 129 +/-19 mmHg, then 127 +/-17 mmHg (p=0.03) at 10 m tilt, and then 127 +/- 21 mmHg, (p=0.02) at 20 min. Symptom burden vis SSS-OI questionnaire decreased from 35.2 to 22.5 (p=0.01) after 1 mo of leg compression stocking therapy.	• Leg compression stocking is able to decrease the SBP drop with postural change, and reduce symptoms over 1 mo follow-up
Protheroe CL, et al. 2011 22194814	**Aim:** To assess effect of graded calf compression stockings on orthostatic tolerance	**Inclusion**: Healthy volunteers **Exclusion**: CV or	HUTT and LBNP (-20 mmHg, -40 mmHg, and -60 mmHg for 10 min each) on 3 occasions with different types of stocking:	**1° endpoint:** Time to presyncope was not significantly different between compression stocking 26 +/- 2.0 m, calf placebo 29.9 +/- 1.8 m, and ankle placebo 27.6 +/- 2.4 m. Smaller	• There was no significant difference in time to presyncope between compression stockings to placebo.

(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)	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	**1° 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.	Orthostatic tolerance challenged at same time **Intervention:** With leg crossing **Comparator 1:** Without leg crossing **Comparator 2:** Placebo table	**1° 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	**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	**1° 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%). Pursed lips during inspiration increased MAP	• 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.

	Size: n=20 pts	(n=10) **Exclusion**: Cardiac disease or used antihypertensive medications	legs without leg crossing **Comparator 3:** Breathing through pursed lips during inspiration **Comparator 4:** Inspiratory sniffing	by 1 mmHg (-7 to 8 mmHg), mCBFV by 2% (-11 to 9%). No significant difference in symptom scores was noted between maneuvers	
Tutaj M, et al. 2006 16096819 (316)	**Aim:** Assess effect of countermaneuveres in familial dysautonomia and active standing **Study type:** Analytical, randomized controlled, prospective crossover **Size:** n=17 pts	**Inclusion**: Familial dysatuonomia with IKBKAP gene mutation **Exclusion**: Pts unable to comply with discontinuation of fludrocortisone or midodrine for 18 h.	Physical countermaneuvers **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 countermanuevers. 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).	• 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
Singer W, et al. 2006 16476804 (302)	**Aim:** To assess pyridostigmine alone or in combination with midodrine in neurogenic OH **Study type:** Analytical, randomized, double-blind, placebo controlled, prospective crossover, **Size:** n=58 pts	**Inclusion**: Adults >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. **Exclusion**: Pregnant, lactating, evidence of failure of other organ systems or of systemic illness that	**Intervention:** Pyridostigmine 60 mg, **Comparator 1:** pyridostigmine 60 mg + midodrine 2.5 mg, **Comparator 2:** pyridostigmine 60 mg + midodrine 5 mg, **Comparator 3:** Placebo	**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.	• Pyridostigmine alone and in combination with midodrine with resultant improvement in symptoms without significantly affecting supine HTN.

		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)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
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

11904109 (319)	observational, prospective cohort **Size:** n=27 pts Protocol 2: **Study type:** Analytical, observational, prospective cohort **Size:** n=27 pts	(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, **Exclusion criteria:** None	**Intervention:** 480 mL tapwater at room temperature in <5 min **Comparator:** no tapwater then active standing Protocol 2: **Intervention:** eat a meal then 480 mL tapwater at room temperature **Comparator:** no tapwater then active standing **Results:** Protocol 1: Seated BP increased from 117/67 mmHg before water drinking to 150/78 mmHg with water drinking (P<0.01). After 1 min of standing, BP increased from 83/53 mmHg before water drinking to 114/66 mmHg with water drinking (p<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	improves orthostatic tolerance in pts with autonomic failure as well as post-prandial hypotension
Young TM, et al. 2004 15548493 (320)	**Study type:** Analytical, observational, prospective cohort **Size:** n=14 pts	**Inclusion criteria:** chronic autonomic failure (7 pts with multiple system atrophy [MSA] which is preganglionic, and 7 pts with PAF which is postganglionic **Exclusion criteria:** None	**1° endpoint:** 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) **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<0.01. Water ingestion raised SBP and DBP and lowered heart rate at 3 min of Stand 2 compared to before water, all p<0.01, but at 5 min, only SBP and DBP had significance, p<0.01.	• 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)
Humm AM, et al. 2008 18469030	**Study type:** Analytical, randomized controlled crossover,	**Inclusion**: PAF with sympathetic and parasympathetic dysfunction with severe OH.	**1° endpoint:** 480 mL distilled room temperature water, then supine cycle ergometer followed by active standing	• N/A

(321)	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)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Axelrod FB, et al. 1995 8690848 (322)	**Aim:** To assess midodrine effect in treating OH in familial dysautonomia, **Study type:** Analytical, observational, open label, prospective cohort **Size:** n=9 pts	**Inclusion**: Familial dysautonomia, OH **Exclusion**: None 5 pts were on fludrocortisone which was continued	**Intervention:** Midodrine 2.5 3x daily titrated up **Comparator:** No midodrine	**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.	No placebo control, but most pts noted symptomatic improvement in this small open label study
Fouad-Tarazi FM, et al. 1995 7503082 (323)	**Aim:** To assess efficacy of midodrine with ephedrine, **Study type:** Analytical, Randomized double-blind, placebo controlled crossover, prospective cohort **Size:** n=8 pts	**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 >180/100 mmHg unrelated to	**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 <100 mmHg and standing SBP≥ 80 mmHg	**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<0.01 for both) not significantly different from each other. Ephedrine (vs. placebo) did not increase standing BP but did heart rate (p<0.05). Midodrine increased standing SBP and DBP vs. placebo (p<0.001) and vs. ephredine (p<0.001). Only midodrine produced a significant reduction in postural symptoms as	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

		drug therapy, symptomatic CAD, acute or chronic renal failure, thyrotoxicosis, significant liver disease, pheochromocytoma, dementia, concomitant MAO inhibitors		shown by increased ability to stand (5.3+/-4.4% vs. 14.2+/-8.4%, p<0.01 vs. placebo) which correlated in increased percentage with standing SBP ≥ 80 mmHg	
Denq JC, et al. 1997 9430805 (324)	**Aim:** Whether compression of different capacitance beds can improve symptomatic neurogenic OH **Study type:** Analytical, observational, prospective cohort, **Size:** n=14 pts	**Inclusion**: Pts with neurogenic OH (multiple system atrophy, PAF, or autonomic neuropathy) **Exclusion**: None OH defined as decrement in SBP ≥ 30 mmHg or mean BP ≥ 20 mmHg	**Intervention/ Comparator:** G suit with 5 separate compartments (lower abdominal, 2 thigh, and 2 calf bladders). Compartments were inflated to 40 mmHg as 1) bilateral calves; 2) bilateral thighs, 3) combination of 1) and 2); 4) low Abdomen; 5) All sites combined; 6) baseline tilt (80 degrees for 5 min) without compression	**Results:** Order of efficacy in reducing orthostatic symptoms from best to worst: All (13 of 14, 93%) > abdomen (9 of 14, 64%) > calves + thighs = calves alone > thighs. Maximal improvement in orthostatic BP occurred with All (115.9+/-7.4 mmHg, p<0.005)) followed by Abdomen 102.0+/-6.7 mmHg, p<0.01) vs. noncompression (89.6+/-7.0 mmHg). The other compartments compression results were not significantly different from noncompression. Improvement correlated to increase in TPR.	Compression of abdomen and legs, and even abdominal compression alone improves orthostatic symptoms and improves BP.
Mathias CJ, et al. 2001 11710796 (325)	**Aim:** Effect of L-DOPS in management of neurogenic OH **Study type:** Multicenter, analytical, observational, open-label, prospective cohort **Size:** n=33 pts	**Inclusion**: 18–75 y of age with autonomic failure and symptoms (dizziness, syncope) and OH (drop in SBP ≥20 mmHg) **Exclusion**: idiopathic Parkinson's disease, prior use or current use of any antiparkinsonian drugs, mental disorder, AF, serum creatinine >130 micromol/L, narcotic abuse, > moderate alcohol consumption (>1 L of beer or equivalent daily), child-bearing potential, drug hypersensitivity	**Intervention:** L-threo-DOPS from 100 mg BID to 300 mg BID	**Results:** L-DOPs blunted SBP decrease with standing (22+/-28 mmHg, p=0.0001) compared to baseline SBP. L-DOPs blunted DBP decrease with 2-min standing (8.1+/-17.2 mmHg, p=0.0124) compared to baseline DBP. In 25 pts (78%), there was a decrease in OH. In 14 ps (44%), OH was no longer observed by BP definition. Symptoms of light-headedness, dizziness, and blurred vision improved significantly from baseline with L-DOPS, but no correlation was found between change in postural SBP decrease and change in clinical symptom scores.	Increase lactate dehydrogenase (12.1%), urinary tract infection (12.1%), akinesia (9.1%), headache (9.1%), and stomach upset (9.1%) L-DOPS reduces OH and related symptoms in pts with autonomic failure. No supine HTN was seen.
Henry R, et al. 1999 10406369	**Aim:** Effect of compression hosiery in elderly persons with OH	**Inclusion**: elderly pts with reproducible, symptomatic OH (>20 mmHg)	**Intervention:** Graduated elastic compression hose	**Results:** Mean: 77.2 y of age (range 62-89 y of age). Compression hosiery resolved symptoms of orthostatic dizziness in 7 of 10	Graduated elastic compression hose improves orthostatic tolerance and symptoms

(326)	**Study type:** Analytical, observational, open label, prospective cohort **Size:** n=10 pts	**Exclusion**: None	**Comparator:** baseline without compression hose then 90 degree HUTT	pts. Mean fall in SBP was 20.3+/-3.8 mmHg at baseline to 0.4 mmHg+/-8.2 mmHg with compression hose (p=0.005). Mean fall was significantly blunted with compression at HUTT mins 1, 2, and 3 (p<0.01, p<0.005, and p=0.01 respectively)	acutely. Long term studies are required.
Yamamoto N, et al. 2006 17003821 (327)	**Aim:** To assess abdominal compression with inflatable abdominal band in hemodialysis pts with OH **Study type:** Analytical, observational, prospective cohort **Size:** n=25 pts	**Inclusion**: Hemodialysis pts and OH for at least 6 mo before study enrolling between 7/2004 to 8/2004. **Exclusion**: severe anemia (Hematocrit <25%), bleeding tendency, hypervolemic symptoms such as leg edema and pleural effusion, poor compliance, treatment for apparent infection, admission to hospital, chronic hypotension (defined as pre-dialysis SBP of <100 mmHg)	**Intervention:** Inflatable abdominal band then active standing test. **Intervention 2:** Some pts received antihypotensive medications (L-threo-3,4-dihydroxyphenylserine [L-DOPS], n=5, **Intervention 3:** midodrine, n=3	**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<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	Inflatable abdominal band was able to reduce post dialysis OH, in pts already receiving antihypotensive medications
Ten Harkel AD, et al. 1994 7874844 (328)	**Aim:** Effect of leg muscle pumping and tensing on orthostatic pressure **Study type:** Analytical, observational, cross-sectional cohort **Size:** n=13 pts	**Inclusion**: normotensive pts (n=6); hypoadrenergic OH (OH, n=7) of which PAF comprised n=4. **Exclusion**: None	**Intervention:** leg crossing **Comparator:** no leg crossing	**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.	Leg crossing increases BP and cardiac output in both normal and hypoadrenergic OH.
Van Lieshout, et al. 1992 1348300 (329)	**Aim:** Whether physical maneuvers can improve orthostatic tolerance in autonomic failure **Study type:** Analytical,	**Inclusion**: autonomic dysfunction (hypoadrenergic) with OH, n=7; healthy pts, n=6 **Exclusion**: None	**Comparator:** Standing upright until presyncopal, followed by **Intervention 1:** leg-crossing and then standing upright	**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	Both leg crossing and squatting improved symptoms of orthostatic intolerance and improved BP, with squatting having larger effect.

	observational, prospective cohort, **Size:** n=13 pts		until presyncopal **Intervention 2:** followed by squatting and then standing upright until presyncopal	presyncope, BP was 74/47 mmHg with MAP 56 mmHg. Squatting increased BP to 131/81 mmHg (MAP 100 mmHg). Symptoms improved with both maneuvers. In healthy, there was much milder increase with leg-crossing (+4/0 mmHg) and with squatting (+12/4 mmHg).	
Singer W, et al. 2006 17016160 (330)	**Aim:** To assess acetylcholinesterase inhibition in orthostatic intolerance during HUTT **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 Then 70 degree HUTT for 5 mins	**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)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Anley C, et al.	**Aim:** To assess which	**Inclusion**: All	**Intervention:** OT, oral fluid and	**1° endpoint:** Time to discharge from the	• With no difference in time to

2011 20584756 (293)	treatment protocol for exercise-associated postural hypotension results in earlier discharge **Study type:** Analytical, randomized, prospective cohort **Size:** n=28 pts	collapsed athletes at two Ironman Triathlon competitions and one ultra-distance footrace in 2006 and 2007 **Exclusion**: Abnormal serum sodium	Trendelenburg position **Comparator:** IV	medical tent (in min) **Results:** No significant difference between IV (52.5 +/- 18 min) and OT group (58+/-23 min), p=0.47 **Secondary endpoint**: Heart rate and BP changes: **Results:** No significant 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.	discharge, but significantly less fluid given in OT group compared to IV group, the probable cause of exercise associated postural hypotension is peripheral vasodilatation resulting in venous pooling
Atherly-John YC, et al. 2002 12444837 (331)	**Aim:** To compare oral rehydration therapy with IV therapy for moderate dehydration in children **Study type:** Analytical, randomized, prospective cohort **Size:** n=34 pts	**Inclusion**: Children with moderate dehydration (having at least 4 standard published criteria) at single center **Exclusion**: Chronic illness, severe dehydration or shock, protracted vomiting, absent bowel sounds, no accompanying guardian, no contact telephone number, and those requiring IV access for reasons other than hydration	**Intervention:** Oral replacement therapy: 5 mL every 5 min if <4 y of age, 10 mL every 5 mins if ≥4 y of age, and intake was advanced to twice the initial volume if there was no vomiting during the first H; n=18 **Comparator:** IV therapy (initial bolus of 20 mL/kg of isotonic sodium chloride over 30 min period, and second bolus was given per treating physician discretion. This was followed by IV solution of 5% dextrose in 0.45% or 0.33% saline depending on age at a rate of 1.5 times daily maintenance; n=16	**1° endpoint:** Duration of pediatric emergency department stay: **Results**: Oral replacement therapy: 224.7 +/- 77.8 min vs. IV 358 +/-160 min, p<0.01 **Secondary endpoints:** Staff time require for pts care: **Results:** ORT: 35.8+/-32 min vs. IV: 65+/-44 min, p=0.03 Parent satisfaction: **Results:** ORT: 77.7% vs. IV: 37.5%, p=0.01 Hospital admission rate: **Results:** ORT: 11.1% vs. IV: 25%, p=0.2 Relapse after being discharged: **Results:** 0% in both ORT and IV groups	• Oral rehydration therapy shortens emergency department stay, reduces staff time required for pts care, and improves satisfaction with pts care compared to intravenous rehydration for pediatric pts presenting with moderate dehydration.
Keneflick RW, et al. 2006 17146319 (332)	**Aim:** To determine effects of rapid (<30 min) IV vs oral rehydration immediately after dehydration during subsequent exercise in	**Inclusion**: Healthy non heat acclimated men **Exclusion**: N/A	Each subject performed 3 trials: **1) Dehydration phase**, pts walked or ran for 75 min at 50% VO_2 max with airflow directed to enhance evaporative sweat loss	**1° endpoint:** To determine effects of rapid (<30 min) IV vs. oral rehydration immediately after dehydration, on CV, thermoregulatory, and perceptual responses during subsequent exercise	• Although IV hydration restored plasma volume more quickly than oral rehydration, there was no significant effect on exercise duration. Sensation of thirst was

	the heat **Study type:** Analytical, randomized, prospective cohort **Size:** n=8 pts		**2) Rehydration phase** Rehydration treatments were randomly assigned to receive amount of fluid lost during dehydration: **Intervention 1:** IV rehydration (0.45% saline) **Intervention 2:** Oral rehydration (0.45% saline) **Intervention 3:** No fluid Then: **3) heat-tolerance test:** immediately after 30 min rehydration period, pts performed a 75 min heat tolerance test in 37°C chamber	**Results:** IV rehydration resulted in more rapid plasma volume restoration ($p<0.05$) 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. Sensation of thirst was significantly lower in oral rehydration than IV fluid ($p<0.05$)	improved with oral rehydration.
Maughan RJ, et al. 1995 8549573 (333)	**Aim:** To study the effect of sodium content of drinks on rehydration after exercise **Study type:** Analytical, randomized, prospective cohort **Size:** n=6 pts	**Inclusion**: Healthy males **Exclusion**: N/A	Pts were dehydrated by intermittent cycle exercise in warm and humid environment then ingested 1.5 times body mass loss of: **Intervention 1:** Na content 2 mmol/L (108 mosmol/kg) **Intervention 2:** Na content 26 mmol/L (158 mosmol/kg) **Intervention 3:** Na content 52 mmol/L (206 mosmol/kg) **Intervention 4:** Na content 100 mmol/L (300 mosmol/kg)	**1° endpoint:** Effect of sodium content of drinks on rehydration after exercise **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 • Plasma volume was higher with sodium contents of 52 and 100 mmol/L compared to 2 mmol/L • Cumulative urine output was higher on sodium content 2 mmol/L than with 52 mmol or 100 mmol/L.	• Rehydration and retained volume is greater with ingestion of fluid with increasing sodium concentration
Merson SJ, et al. 2008 18463891 (334)	**Aim:** To investigate differing sodium chloride concentrations affect rehydration **Study type:** Analytical, randomized, prospective	**Inclusion**: Healthy men without Hx of CV or renal disease **Exclusion**: N/A	Exercise via cycle ergometer with measured VO_2 max then drinking 150% of fluid lost as sweat: **Intervention 1:** NaCl 0 mmol **Intervention 2:** NaCL 30 mmol/L **Intervention 3:** 40 mmol/L **Intervention 4:** 50 mmol/L	**1° endpoint:** Sodium chloride concentration effect on rehydration after exercise and subsequent exercise capacity **Results:** • Pts retained more of test drink as the sodium concentration of the drink increased	• 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.

	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 8673750 (232)	**Aim:** To evaluated salt supplementation in syncope with OI **Study type:** Analytical, Randomized placebo controlled, prospective cohort, **Size:** n=20 pts **Study type:** Analytical, observational, open label, prospective cohort **Size:** n=11 pts	**Inclusion**: Recurrent syncope without etiology **Exclusion**: N/A	RDBPCT: **Intervention:** sodium chloride 10 mmol **Comparator:** Placebo 12x daily then 60 degree HUTT with LBNP up to -40 mmHg Open label: **Intervention:** slow sodium 10 mmol 12x daily (pts told it was a "mineral dietary supplement") then 60 degree HUTT with LBNP up to -40 mmHg	**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

Data Supplement 37. Nonrandomized Trials, Observational Studies, and/or Registries of Dehydration and Drugs – (Section 6.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Greenlead JE, et al. 1998 9737753 (335)	**Aim:** To evaluate various carbohydrate electrolyte fluid formulations for consumption by astronauts to restore plasma	**Inclusion**: Healthy young men, nonsmokers, no drug use	Pts 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.

	volume **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).	
Jeukendrup AE, et al. 2009 19232115 (337)	**Aim:** To study the effects of increasing carbohydrate and sodium content on fluid delivery **Study type:** Analytical, observational, prospective case control, **Size:** n=20 pts	**Inclusion**: Healthy males **Exclusion**: N/A	Each subject undertook 4 trials each >7 days apart Carbohydrate group (CHO, n=10 pts) **Intervention 1:** G0: water + 20 mmol/L sodium **Intervention 2:** G3: 3% glucose + 20 mmol/L sodium **Intervention 3:** G6: 6% glucose + 20 mmol/L sodium **Intervention 4:** G9: 9% glucose + 20 mmol/L sodium Sodium group (Na, n=10 pts) **Intervention 1:** Na0: 6% glucose **Intervention 2:** Na20: 6% glucose + 20 mmol/L sodium **Intervention 3:** Na40: 6% glucose + 40 mmol/L sodium **Intervention 4:** Na60: 6% glucose + 60 mmol/L sodium **1° endpoint:** Fluid delivery surrogately measured by plasma deuterium enrichment **Results:** • Glucose group: trend for time to plateau with increasing carbohydrate concentration (GO:34 min, G3: 35 min, G6:43 min, G9:51 min) • Plasma deuterium enrichment was significantly greater with 3% glucose ($p<0.001$) than no carbohydrate, 6% glucose, or 9%	• 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.

			glucose. • Sodium group: trend for decrease in time to plateau with increasing sodium content (Na0: 23 min, Na20:19 min, Na40:18 min, Na60:16 min) • Plasma deuterium enrichment did not differ between groups (p=0.121)	
Beckett NS, et al. 1999 10618673 (338)	**Aim:** To assess OH prevalence and associated factors in elderly hypertensive pts, **Study type:** Analytical, observational, cross-sectional study **Size:** n=1,241 pts	**Inclusion**: Pts in HYVET trial (Hypertension in the Very Elderly Trial); at least 80 y of age with sustained systolic (average SBP 160-219 mmHg) and diastolic hypertension (average DBP 90-109 mmHg) **Exclusion**: Pts on BP lowering treatment for reasons other than HTN	**1° endpoint:** Orthostatic fall in BP in hypertensive pts **Results:** Mean sitting BP was 182/100 mmHg. Average fall in SBP on standing was 8 mmHg (95% CI: 7.3–8.3) and in DBP was 1.3 mmHg (95% CI: 1.0–1.6). 96 (7.7%) had a drop of ≥20 mmHg systolic and 66 (5.4%) had a drop of ≥10 mmHg diastolic	• Prevalence of OH in elderly pts with hypertension was 12%
Blake AJ, et al. 1988, 3266440 (339)	**Aim:** To assess falls and their associated causes **Study type:** Descriptive cross sectional survey **Size:** n=356 pts	**Inclusion**: Community survey (Activity and Ageing survey conducted between 5/1985 and 9/1985 of individuals age ≥65 y of age who reported ≥ 1 fall in preceding y **Exclusion**: Mental incompetence, dementia, acute organic brain syndrome	**1° endpoint:** Prevalence of and factors associated with falls in the elderly **Results:** Women were more likely to report falls than men (p<0.001). Older respondents were more likely to report falls (p<0.05). Increasing number of prescribed drugs correlated increased prevalence of falls (p<0.001). There was no significant difference in antihypertensives (p=NS) or diuretics (p=NS). Hypnotics (p<0.05) and antidepressants (p<0.01) were more associated falls	• Decreasing handgrip strength, arthritis, and foot difficulties were strongest predictors of falls. Hypnotics and antidepressants (tricyclic antidepressants) were the medication classes associated with falls.
Burke V, et al. 1992 1484937 (340)	**Aim:** To assess relation of drug treatment to postural fall in BP in elderly, **Study type:** Descriptive, cross-sectional survey **Size:** n=843 pts	**Inclusion**: Independent elderly volunteers (pts >60 y of age) in Perth, Australia; **Exclusion**: N/A	**1° endpoint:** Factors associated with postural fall in SBP **Results:** Postural fall in SBP was related to alcohol intake >20 mL/day, sleeping tablet use, higher anxiety level, and lower body mass index. Postural fall in SBP was not related to HTN, age, gender, diabetes, or cardiac medications [verapamil (p=0.092), BB (p=0.728),	• There was no relation of anti-hypertensive medication to postural fall, but sleeping aid use was associated. • Postural fall in SBP defined as ≥ 20 mmHg decrease when changing from sitting to standing

			diuretics (p=0.356), or vasodilators (p=0.199)].	
Craig GM, et al. 1994 7971628 (341)	**Aim:** Presentation of OH in elderly **Study type:** Descriptive retrospective chart review **Size:** n=50 pts	**Inclusion**: Elderly pts with OH (defined as ≥ 20 mmHg fall in SBP) **Exclusion**: N/A	**1° endpoint:** Factors associated with orthostatic fall in SBP ≥ 20 mmHg **Results:** Presenting features of OH: Falls 64%, poor mobility 44%, unsteadiness 38%, confusion 22%. Medication usage in OH pts: • Diuretic 56%, benzodiazepine 26%, anti-depressant 24%, anti-parkinsonian therapy 22%, phenothiazine 18%, BB 12%, hydralazine 10%, calcium antagonist 8%, nitrates 6%.	• Medication was primarily responsible for OH in 66%, and implicated in 80% of cases.
Fotherby MD, et al. 1994 7870633 (342)	**Aim:** Assess prevalence of OH in elderly HTN pts whether anti-HTN therapy was continued or not, **Study type:** Analytical, observational, prospective cohort **Size:** n=47 pts	**Inclusion**: Pts ≥ 65 y of age, BP <175/100 mmHg on pharmacological treatment >1. **Exclusion**: 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 • Following treatment withdrawal, pts whose SBP was ≥175 mmHg and/or whose DBP >100 mmHg on 2 occasions were withdrawn from the study and deemed unsuitable for anti-HTN withdrawal	**1° endpoint:** Prevalence of OH **Intervention:** Anti-HTN medication withdrawal, BP measured at 1, 3, 6, 9, and 12 mo of anti-HTN therapy withdrawal **Comparator:** Continuing on anti-HTN had BP measure at 6 and 12 mo. **Results:** For pts stopping anti-HTN medication, the number of OH fell from 11 (23%) on anti-HTN treatment to 4 (11%, p<0.05) off treatment. • The pts continuing anti-HTN medication showed no significant change in prevalence of OH, 5 (38% at baseline, and 4 (31%) at 12 mo. • 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)	• 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 • 13 of the 47 pts did not meet criteria for anti-hypertensive withdrawal • OH defined as mean SBP fall ≥ 20 mmHg on standing from supine
Jansen RW, et al. 1996 8636581 (343)	**Aim:** To assess post-prandial hypotension and relation to chronic use of CV medications **Study type:** Analytical, observational, prospective	**Inclusion**: Nursing home residents, sinus rhythm, be able to stand from supine position within 30 s and remain standing for 10 min	**Comparator:** Standing test, then **Intervention:** repeat standing test after eating meal. Same protocol repeated in 3 to 14 days. **1° endpoint:** BP and heart rate before and after postural change;	• 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

	cohort **Size:** n=22 pts	**Exclusion**: Presence of pacemaker, insulin-dependent DM	BP and heart rate before and after meals **Results:** Mean SBP, mean DBP, and MAP all declined 45 min after the meal (p<0.001 for each). • Mean SBP declined 16+/-4 mmHg (p<0.001) at 45 min and by 12+/-4 mmHg (p<0.01) during second test with no difference between the 2 tests. MAP similarly declined in each test after means (p<0.001). • Postprandial hypotension occurred in 10 pts in first test and 1 additional pts in second test. Administration of CV medications did not affect significantly subsequent BP response after meals but did affect SBP after standing.	response may be distinct from postprandial hypotension • Post-prandial hypotension defined as SBP decline of ≥20 mmHg within 90 min study period • OH defined as SBP decline ≥ during first and/or third min after standing
Jodaitis L, et al. 2015 26135806 (344)	**Aim:** Association of OH with use of drugs with psychotropic, CV, or diuretic effect **Study type:** Prospective observational, multicenter, **Size:** n=285 pts	**Inclusion**: Older (pts ≥75 y of age) in pts screened for OH (defined as reduction of ≥20 mmHg in SBP or ≥10 mmHg in DBP within 3 min of standing **Exclusion**: N/A	**1° endpoint:** Prevalence of OH **Results:** 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<0.001) and syncope (29% vs. 4%, p<0.001). There was no difference in proportions of pts receiving drugs or drug potentially associated with falls and/or OH.	• There was no association of any medication with OH or falls, but many pts in this study had frailty which could affect response to medication
Kamaruzzaman S, et al. 2010 19897539 (345)	**Aim:** Association of OH and medication use in British Women's Heart and Health Study Cross-sectional analysis **Study type:** Retrospective, observational cross-sectional cohort **Size:** n=3,775 pts	**Inclusion**: British Women's Heart and Healthy Study cohort, OH (defined as SBP ≥ 20 mmHg and/or diastolic BP ≥ 10 mmHg). **Exclusion**: N/A	**1° endpoint:** Prevalence of OH **Results:** Higher prevalence of OH in women with HTN than without HTN (79% vs. 64%, p<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<0.01). Women on multiple antihypertensive drugs (≥ 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<0.001)	• OH was associated with increasing age, HTN, and death. Use of BB and use of 3 or more antihypertensive medications were associated with OH. Polypharmacy in of itself was not associated with OH.
McLachlan CY, et al. 2014 24750276	**Aim:** To assess frequency, nature, and causality of ADE resulting in acute admissions	**Inclusion**: All admissions at single center in New Zealand between 10/1/2011	**1° endpoint:** Prevalence of ADE **Results:**	• ADE comprises a significant amount of admissions at this single center, with the syncope being the

(346)	**Study type:** Analytical, observational, prospective cohort **Size:** n=96 pts	to 11/11/2011 and 12/24/2011 to 4/4/2012. **Exclusion**: N/A	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%)	most frequent effect. Vasodilators and diuretics comprise 39% of ADE-related admissions
Ooi WL, et al. 1997 9109468 (347)	**Aim:** To assess for clinical correlates for orthostatic BP change, **Study type:** Analytical, prospective observational cohort **Size:** n=911 pts	**Inclusion**: Nursing home residents ≥ 60 y of age, life expectancy >3 mo, able to stand at least 1 min **Exclusion**: N/A	**1° endpoint:** supine BP, 1-min standing BP, 3-min standing BP, and heart rate **Results:** After multivariate analysis, significantly associated ($p<0.05$) 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.	• Antihypertensive medication use was not associated with OH, but lower body mass index and Parkinson disease medications were.
Panayiotou B, et al. 2002 11824858 (348)	**Aim:** To assess antihypertensive medications in acute stroke for OH **Study type:** Analytical, prospective, observational cohort. **Size:** n=80 pts	**Inclusion**: Pts ≥ 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) **Exclusion**: 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 >10 mmol/L, hemoglobin <10 g/dL, antibiotic requirement, serious illness,	**1° endpoint:** 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 **Results:** Between d 1 and wk 1, supine BP fell significantly in treated group (165 +/-24/87+/-14 mmHg to 155 +/-24/83+/-14 mmHg, p=0.003 for SBP and p=0.03 for diastolic BP, but no significant difference in untreated group. On day 1, OH was observed within 5 min in 11 treated and 5 untreated pts, p=0.09. At wk 1, OH occurred in 5 treated and 8 untreated pts, p=0.36. Only cardiac dysfunsion was associated with OH on multivariate analysis (OR: 3.5, 95% CI: 1.0–13.1, p=0.05) independent of age, HTN stroke score, and anti-HTN treatment. Anti-HTN medication was not associated with OH, p=0.48	• 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.	**1° 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 x^2=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	**1° 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)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)

Moya, et al. 2009 19713422 (351)	**Study type:** Practice guideline consensus (European Society of Cardiology) **Size**: N/A	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** 1. Frequent attacks, often many times a d 2. Eyes closed 3. Prolonged episodes, often many mins in duration 4. No apparent trigger for attack 5. Prone to being 'suggestible' which favors triggering attacks in clinic/laboratory	• Summarizes the key clinically useful markers to aid recognition of PPS/PNES
Tannamaat, et al. 2013 23873974 (126)	**Study type:** Tilt-test induction of PPS/PNES examined retrospectively to assess clinical features **Size:** n=43 pts with PPS/PNES vs. 69 pts with vasovagal syncope	**Inclusion criteria:** Diagnosis of PPS/PNES by Tilt-test and video EEG **Exclusion criteria:** N/A	**1° endpoint:** Pseudosyncope **Results** PPS/PNES can be diagnosed and differentiated from vasovagal syncope by use of a tilt-test.	• Provides a quantitative assessment of clinical features distinguishing PPS/PNES from vasovagal syncope
McKenzie PS, et al. 2010 21421771 (352)	**Study type:** Retrospective observational study of PNES pts diagnosed by inpatient or outpatient EEG or video-EEG **Size:** n=187 pts	**Inclusion criteria:** Diagnosed PPS/ PNES **Exclusion criteria:** N/A	**1° endpoint:** New onset of medically unexplained symptoms (MUS) in pts diagnosed with PPS/PNES. **Results:** Approx. 25% of PNES pts develop new medically unexplained symptoms after initial diagnosis	• 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.
Iglesias, et al. 2009 19250095 (353)	**Study type:** Single center prospective syncope evaluation **Size:** n=131 PPS/PNES cases out of 939 pts undergoing TLOC evaluation	**Inclusion criteria:** Presentation of TLOC or apparent TLOC **Exclusion criteria:** N/A	**1° endpoint:** Frequency of PPS/PNES in a TLOC population **Results:** 14% of all pts were considered PPS/PNES. Approx. 60% are young woman with multiple pre-syncope and syncope	• 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.

Elliot JO, et al. 2014 25262500 (354)	**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	• Psychosocial issues (e.g., anxiety, physical/sexual abuse) as well as co-morbidities (e.g., prior head injury, GERD) are important features of PPS/PNES pts.
Mayor, et al. 2012 23168089 (355)	**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 20561022 (356)	**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 18061753 (357)	**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.

LaFrance Jr WC, et al. 2010 20739647 (358)	**Study type:** Prospective double-blind RCT of sertraline in PPS/PNES **Size:** 38 enrollees; n=26 completed study	**Inclusion criteria:** Diagnosed PPS/PNES **Exclusion criteria:** N/A	**1° endpoint:** Symptom frequency sertraline vs. placebo **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	• 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.
Santos, et al. 2014 25650860 (359)	**Study type:** Observational effects of psychoanalytic therapy; no controls **Size:** n=37 pts	**Inclusion criteria:** PNES diagnosed by video-EEG **Exclusion criteria:** N/A	**1° endpoint:** Symptom recurrence frequency during follow-up **Results:** During 1 y follow-up, 30% had cessation of symptoms, and 51% had reduced number of attacks.	• Individual psychoanalytic therapy proved beneficial in this uncontrolled study

Data Supplement 39. RCTs for Pseduosyncope – (Section 8)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Goldstein LH, et al. 2010 20548043 (360)	**Study type:** RCT **Size:** n=36 pts randomized to standard therapy vs. CBT psychotherapy	**Inclusion criteria:** Diagnosis of PPS/PNES **Exclusion criteria:** N/A	**Intervention:** CBT in addition to standard therapy **Comparator:** Standard therapy alone	**1° endpoint:** Symptom recurrence frequency **Result** With short-term application of CBT, the CBT group tended to have a better 3-mo event freedom (OR: 3.125, p<0.086) **Safety endpoint (if relevant):** N/A	• CBT tended to improve short-term outcomes but larger controlled studies are needed.

Data Supplement 40. Nonrandomized Trials, Observational Studies, and/or Registries of Pediatrics – (Section 10.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type*; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Include Absolute Event Rates, P value; OR or RR; and 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events; Summary
Zhang Q, et al. 2009 19183119 (361)	**Aim:** Aimed to measure the diagnostic value of a protocol on the management of children and adolescents with syncope. **Study type:** Multi center, prospective consecutive pts <18 y of age with syncope. **Size:** n=474 consecutive pts presenting with syncope. (20 mo period)	**Inclusion criteria:** <18 y of age with syncope as defined as TLOC and postural tone caused by cerebral hypo-perfusion **Exclusion criteria:** Pts with symptoms compatible with seizures, vertigo, or shock were excluded.	**Intervention:** **1st Step:** H&P, and ECG **2nd Step:** Echo, Holter, CT, Psych evaluation. 2nd Step diagnostic maneuvers were only performed if 1st step did not yield a definitive diagnosis. HUTT was only used if unexplained syncope. **Comparator:** None	**1° endpoint:** Initial diagnostic work-up (H&P & ECG) gave a definitive diagnosis in 59 (12.4%). 2nd 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&P).	• HUTT can help with the diagnosis. An extensive neurological work-up is not indicated unless the H&P is suspicious for a neuro condition (i.e. vertigo seizure) **Summary**: HUTT can help make the diagnosis of VVS. An extensive neurological work-up should be reserved for pts whose H&P is concerning for a neuro condition.
Miyake, et al. 2015 26277987 (362)	**Aim:** Aimed to evaluate the incidence of cardiac disorders among children with mid-exertional syncope. **Study type:** Single center, retrospective evaluation of children who presented for cardiac evaluation with exertional syncope (1999-2012) **Size:** n=60 pts	**Inclusion criteria:** ≤18 y of age with mid-exertional syncope an EKG and ECHO and at least one of the following: TTT, EST, EPS **Exclusion criteria:** Pts with known structural heart defects or known arrhythmia disorders	**Intervention:** None, Clinical Evaluation Only **Comparator:** None	**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.	• Reported symptoms before and after a mid-exertional syncopal event may not distinguish between a benign noncardiac condition and a cardiac condition. **Summary**: Mid-exertional syncope in children carries a high-risk of being diagnosed with a cardiac condition.

Zhang, et al. 2013 22417947 (363)	**Aim:** Value of Hx taking in identifying children with cardiac syncope **Study type:** Multicenter prospective consecutive series of pts in the Pediatric Syncope Unit **Size:** n=275 pts <18 y of age	**Inclusion criteria:** ≤18 y of age with suspected syncope admitted to the Pediatric Syncope Unit of 5 hospitals in China **Exclusion criteria:** Pts with known CHD or known arrhythmia disorders	**Intervention:** Clinical history, physical exam, BP measurements and ECG. All pts complete 118 item questionnaire **Comparator:** None	**1° endpoint:** Clinical diagnosis made	**Results** Cardiac 31 (11%) Autonomic mediated 214 (78%) Unexplained 15 (5%) **Summary**: Multivariate analysis showed the history of exercise-triggered syncope or ECG abnormalities were independent predictors of cardiac syncope.
Qingyou, et al. 2004 14727100 (364)	**Aim:** To determine usefulness in children with unexplained syncope. **Study type:** Single center prospective study of pts with unexplained syncope. **Size:** n=47 pts divided into a positive response group (I) and a negative tilt response group (II)	**Inclusion criteria:** ≤18 y of age with unexplained syncope. **Exclusion criteria:** Pts with known structural heart defects or known arrhythmia disorders	**Intervention:** All syncopal pts (all unexplained) had a normal exam, EKG, Echo, and head CT). **Comparator:** Positive tilt vs. Negative tilt groups	**1° endpoint:** Clinical diagnosis made	**Results** HUTT positive results more common in 12–16 y of age than younger children. Prodrome of syncope had an odds ratio of 17 in predicting positive TTT results. **Summary**: Clinical history of a prodrome prior to syncope in conjunction with a positive HUTT supports diagnosis of vasovagal syncope.
Udani, et al. 2004 15269465 (365)	**Aim:** Aimed to measure the diagnostic value of a HUTT **Study type:** Single center, prospective consecutive pts <18 y of age with syncope. **Size:** n=18 pts	**Inclusion criteria:** <18 y of age with strong clinical suspicion of neurocardiogenic syncope **Exclusion criteria:** N/A	**Intervention:** HUTT following Hx and clinical examination **Comparator:** None	**1° endpoint:** Recurrent syncope	• 16/18 (90%) with clinical suspicion of vasodepressor syncope had a positive tilt test **Summary**: HUTT can help make the diagnosis of neurocardiogenic syncope.
Fouad, et al. 1993 7681189 (366)	**Aim:** Measure the diagnostic value of a HUTT in pts with syncope compared to healthy controls w/o syncope **Study type:** Single center, retrospective study of syncopal pts and prospective	**Inclusion criteria:** <18 y of age with strong clinical suspicion of neurocardiogenic syncope **Exclusion criteria:** N/A	**Intervention:** HUTT following Hx and clinical examination **Comparator:** Healthy controls	**1° endpoint:** Syncope on tilt test	• 25/44 (58%) of symptomatic pts ha a positive tilt • 3/18 (17%) normal volunteers had a positive tilt • Sensitivity of a positive tilt 57% and specificity 83% **Summary**: HUTT has a high specificity in

	study of healthy controls **Size:** n=44 syncope pts (16±3 y vs. 18 healthy controls (16±2 y)				diagnosing vasodepressor syncope.
Lerman-Sagie, et al. 1991 2019920 (367)	**Aim:** Measure the diagnostic value of a HUTT in pts with syncope compared to healthy controls w/o syncope **Study type:** Single center, prospective study **Size:** n=15 syncope pts (10–18 y of age vs. n=10 healthy controls (11–18 y of age)	**Inclusion criteria:** <18 y of age with strong clinical suspicion of neurocardiogenic syncope. **Exclusion criteria:** Healthy controls without syncope.	**Intervention:** HUTT following Hx and clinical examination **Comparator:** Healthy controls	**1° endpoint:** Syncope on tilt test	• 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.
Al Dhahri, et al. 2009 19694968 (368)	**Aim:** Measure the usefulness of ILR in children with unexplained syncope. **Study type:** Retrospective study of pts with unexplained syncope after initial evaluation identified cause of syncope. **Size:** 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).	**Inclusion criteria:** Pts with unexplained syncope undergoing ILR after conventional diagnostic testing failed to provide a definitive diagnosis. **Exclusion criteria:** None	**Intervention:** ILR implantation **Comparator:** None	**1° endpoint:** Identification of a substrate on ILR interrogation to explain causal syncope.	Among the 21 pts who presented with syncope, 14 of 21 (67%) were diagnosed with reflex-mediated syncope, 2 of 21 (9%) with seizures, and 2 of 21 (9%) with arrhythmias, while in 3 of 21 (15%) other causes were found, but we were able to rule out arrhythmias as a possible etiology. **Summary**: ILR may be beneficial in children with syncope of unknown etiology to rule-out arrhythmias as a cause of syncope. The risk of infection and need for device removal is rare.

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 presyncope. 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 presyncope 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.

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 syncopal pts (11.3±2.9 y of age)	**Inclusion criteria:** Syncope diagnosis **Exclusion criteria:** None	**Intervention:** None **Comparator:** None	**1° 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	**1° 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	**1° 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.

Salim, et al. 2005 15708690 (238)	**Aim:** Effectiveness of salt and fludocrotisone in prevention of VVS in children **Study type:** Randomized (pediatric) **Size:** n=32; florinef 0.1mg/day and salt 1g/d n=18; control n=14	**Inclusion criteria**: >1 syncope or presyncope; +HUTT; <18 y of age; no prior therapy for syncope **Exclusion criteria**: No structural heart disease	**Intervention:** Florinef 0.1mg/day and salt 1g/d **Comparator:** Placebo	**1° endpoint:** Syncope or pre-syncope recurrence **1° Safety endpoint** (if relevant):	• Follow up 176+117d ; recurrence 36% in controls and 55% active arm (p<0.04). **Summary:** Symptoms were more frequent in the placebo group.
Massin MM, et al. 2004 15289772 (375)	**Aim:** Analyzed the etiology of consecutive cases of syncope presenting to a pediatric emergency room. **Study type:** Prospective cohort study **Size:** n=252 presentations of syncope in 226 pts (mean age 10.8 ± 3.6 y of age)	**Inclusion criteria:** Primary complaint of syncope (witnessed and unwitnessed) upon presentation to the emergency department. **Exclusion criteria:** None	**Intervention:** None **Comparator:** None	**1° endpoint:** Clinical diagnosis **Safety endpoint:** None	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<. 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. **Limitation:** ECG were not obtained in 58% of the pts and as such the utility of an ECG cannot be measured in this study.
Chen L, et al. 2011 21629199 (376)	**Aim:** Analyze the spectrum of underlying diseases in children presenting with syncope. **Study type:** Multicenter retrospective chart review **Size:** n=888 children (median age 12.0 ± 3.0 y of age)	**Inclusion criteria:** Presentation with syncope **Exclusion criteria:** None	**Intervention:** All pts underwent H&P, orthostatic vital sign measurements and an ECG. **Comparator:** None	**1° endpoint:** Clinical diagnosis **Safety endpoint:** None	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.

Colman N, et al. 2009 19482852 (377)	**Aim:** 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. **Study type:** Retrospective study comparing 2 populations. The control cohort was evaluated as part of a Dutch Fainting Assessment Trial **Size:** n=32 LQTS pts, n=113 pts in ED with syncope, and n=69 known vasovagal syncope pts.	**Inclusion criteria:** All LQT pts confirmed genotype positive. **Exclusion criteria:** >40 y of age.	**Intervention:** Clinical assessment with detailed Hx and detailed family Hx. **Comparator:** LQT pts compared to a consecutive heterogeneous group of patients with syncope presenting to the emergency department	**1° endpoint:** Clinical comparison **Safety endpoint:** None	**Results:** 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% ($p<0.001$). Syncope while supine and syncope with exercise were significantly more common in the LQTS cohort compared to the ED cohort. **Summary:** A family Hx or syncope and sudden cardiac death are important questions that should be asked when evaluating a young group of pts with syncope.
Tretter JT, et al. 2013. 23992679 (378)	**Aim:** To identify characteristics that distinguishes VVS from cardiac syncope. **Study type:** Retrospective review of pts presenting a vasovagal syncope vs. cardiac syncope. **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.	**Inclusion criteria:** All pts (newborn to 18 y of age) presenting to the outpatient faculty with diagnosis of syncope) **Exclusion criteria:** None	**Intervention:** None **Comparator:** Vasovagal Symptoms vs. Cardiac Syncope Symptoms (identified from the ICD database and the cardiac stress lab database)	**1° endpoint:** Syncope at follow-up and comparison between 2 groups of etiology **Safety endpoint:** None	**Results**: 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. **Summary**: 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.

Ritter S, et al. 2000. 10799622. (379)	**Aim:** Understand the clinical symptoms in pts with syncope. **Size:** n=480 pts (1.5 to 18 y of age)	**Inclusion criteria:** Syncope diagnosis **Exclusion criteria:** Pts with previously known cardiac disease (cardiomyopathies, arrhythmias, or CHD)	**Intervention:** None **Comparator:** None	**1° endpoint:** Use of H&P, and ECG in identifying pts with cardiac syncope. **Safety endpoint:** None	**Results**: 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.
MacCormick JM, et al. 2011 21616715 (380)	**Aim:** Understand the signs and symptoms before the cardiac syncope and before the patient was diagnosed with a channelopathy. **Study type:** Retrospective review of consecutive gene positive probands and symptoms before syncope. **Size:** n=35 pts (8-19) with unexplained syncope	**Inclusion criteria:** Syncope diagnosis amongst consecutive gene positive probands. **Exclusion criteria:** Pts with syncope and LQT that was not genetically confirmed.	**Intervention:** None **Comparator:** Comparison was done on a historical and literature based control not in the same time period or by same authors.	**1° endpoint:** Clinical presentation of syncope. **Safety endpoint:** None	**Results**: 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 64% of cases. **Summary:** 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.
Grubb BP, et al. 1992 1382276 (381)	**Aim:** Understand the utility of HUTT testing in the evaluation of recurrent syncope of unknown etiology in children and adolescents. **Study type:** Prospective study **Size:** 30 pts (15 males and 15 females; mean age: 14 ± 6 y of age)	**Inclusion criteria:** A minimum of 3 episodes of syncope in the preceding 6 mo with the cause of syncope unknown by H&P, ECG, echocardiogram, and exercise stress test. **Exclusion criteria:** None	**Intervention:** Baseline HUTT (30 mins) with or without isoproterenol. **Comparator:** None	**1° endpoint:** Clinical outcomes following HUTT results. **Safety endpoint:** None	**Results:** 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 asses the utility of the HUTT itself.
Numan M, et al. 2015. 25087055 (382)	**Aim:** To report experience with pts with cardiac asystole during HUTT	**Inclusion criteria:** Cardiac asystole (defined as absence of ventricular activity of >3 s)	**Intervention:** No uniform treatment strategy follow-up of cardiac asystole. All pts received education of	**1° endpoint:** Clinical recurrent syncope **Safety endpoint:** None	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

	Study type: Retrospective study, no placebo group. **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	**Exclusion criteria:** None	symptom awareness, fluids and salt and additional treatment. **Comparator:** None This study did not compare medical management vs. pacemaker therapy.		but one responded to medical management. Only 1 patient required a pacemaker for failing numerous pharmacologic strategies. **Summary:** Children and young adults (<25 y of age) with cardiac asystole at time of HUTT can be managed with pharmacologic agents and do not necessarily need a pacemaker immediately.
Yilmaz S, et al. 2012. 22459868 (383)	**Aim:** Define predictors of recurrence of vasovagal syncope. **Study type:** Retrospective observational study **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)	**Inclusion criteria:** 8–18 y of age with clinical VVS. **Exclusion criteria:** Excluded CHD, LQT, Brugada, or medications that affect the heart rate.	**Intervention:** VVS pts follow after HUTT. **Comparator:** Compare Recurrent syncope group (n=40) and Non-recurrent syncope group (n=110). Average Follow up: 3.8±4.7 y	**1° endpoint:** Syncope recurrence **Safety endpoint:** None	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. **Summary**: Number of prior syncopal episodes and family Hx of syncope predict clinical recurrence of VVS. Result HUTT does not predict recurrence.
Liu JF, et al. 2011 21329841 (197)	**Aim:** Identify risk factors for recurrent syncope in children and adolescents with LQT syndrome. **Study type:** Retrospective review of data from the International Long QT Registry. **Size:** n=1,648 pts <20 y of age with LQT (genotype or genotype and phenotype)	**Inclusion criteria:** QTc ≥450 msec, or a known pathogenic QT mutation, and syncope. **Exclusion criteria:** QTc ≤450 ms without pathogenic mutation.	**Intervention:** Registry follow-up **Comparator:** Different LQT genotypes and BB utilization with recurrent syncope.	**1° endpoint:** Occurrence of recurrent syncopal episodes. **Safety endpoint:** Aborted cardiac arrest and LQT related sudden cardiac death as a defined endpoint.	**Results:** 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 & LQT 2 pts significantly (>70%) reduced subsequent syncopal events.

Younoszai AK, et al. 1998 9491043 (384)	**Aim:** Assessment of oral fluid therapy in children with vasodepressor syncope on clinical recurrence. **Study type:** Retrospective, non comparison study **Size:** 58 pts (8.7–27.6 y)	**Inclusion criteria:** Clinical diagnosis of VDS and positive TTT **Exclusion criteria:** Tilt positive with isoproterenol.	**Intervention:** Following a positive TTT pts were prescribed oral fluid therapy (64 oz/daily) and encouragement to drink more fluid and avoid caffeine. **Comparator:** None	**1° endpoint:** 90% had resolution of syncope **Safety endpoint:** Tolerance of fluid bolus.	**Results:** • Treatment of neurally-mediated syncope with oral rehydration reduced the number of syncopal events. • No control and not randomized, cannot account for placebo effect.
Chu W, et al. 1998 25577227 (385)	**Aim:** Whether oral rehydration salts is effective in treatment of children with VVS **Study type:** Single center, randomized; placebo-controlled. 6 mo-f/u **Size:** Group I (n=87) conventional therapy (health education, tilt training, and oral rehydration salts) vs. Group II (n=79) conventional therapy.	**Inclusion criteria:** At least 2 episodes of syncope in prior 6 mo. Positive HUTT with clinical diagnosis of VVS. (Children 7-17) **Exclusion criteria:** Other disease ruled-out by ECG, EEG, and head imaging.	**Intervention:** Conventional therapy +/- oral rehydration salts (oral rehydration salts: glucose, NaCl, KCl, dissolved in 500 ml H2O) for 6 mo **Comparator:** Placebo plus conventional therapy (education – symptom awareness)	**1° endpoint:** Clinical symptoms **Safety endpoint:**	**Results:** • Group I (oral rehydration salts): No recurrence (56%), Decrease in syncope (39%) and No change in syncope (5%). • Group II (Placebo): No recurrence (39%), Decrease in syncope (47%) and No change in syncope (14%). p<0.05 **Summary**: • Oral Rehydration Salts significantly reduced the recurrence rate of syncope in children 7–17 y of age.
Strieper MJ, et al. 1993. 8101533 (386)	**Aim:** Whether alpha-adrenergic agonist prevents syncope **Study type:** Single center, prospective study **Size:** n=16 pts (mean 13 y of age)	**Inclusion criteria:** Recurrent syncope and a positive HUTT **Exclusion criteria:** Free of any other cardiac medication.	**Intervention:** Following HUTT discharged on pseudoephedrine 60 mg PO BID **Comparator:** None	**1° endpoint:** Clinical symptoms **Safety endpoint:** Tolerance of alpha-adrenergic medication.	Results: Follow up: 11.6 mo; 15/16 (94%) pts reported control of clinical symptoms. **Summary**: Pseudoephedrine alleviates syncope in children without significant side effects.
Qingyou Z, et al. 2006. 17137891 (243)	**Aim:** Efficacy of midodrine in preventing VVS in children. **Study type:** Single center, randomized control trial between 2003-2004. Not	**Inclusion criteria:** At least 3 episodes of syncope in prior 12 mo and "positive" tilt with clinical diagnosis of VVS. **Exclusion criteria:** At least 3	**Intervention:** Conventional therapy + midodrine (Group I) or sole conventional therapy without midodrine (Group II).	**1° endpoint:** Syncope recurrence (AIM 1) and repeat HUTT (AIM 2) **Safety endpoint:**	**Results:** • Group I (Midodrine): Effective rate of repeat HUTT evaluation 75%. Recurrence rate of clinical syncope: 22%. • Group II (Conventional): Effective rate of repeat HUTT evaluation 20%. Recurrence

	blinded, no placebo. **Size:** Group I (n=13) midodrine & conventional therapy (health education, tilt training, and salt) vs. Group II (n=13) conventional therapy only. 6 mo follow-up plus repeat HUTT.	episodes of syncope in prior 12 mo AND "positive" tilt with clinical diagnosis of VVS.	**Comparator:** Midodrine vs. no additional pharmacotherapy 6 mo follow-up. Not blinded, no placebo, no control.		rate of clinical syncope 80% (p<0.05) **Summary**: • Midodrine is effective in reducing clinical recurrence of syncope. • No significant adverse side effects of midodrine.
Zhang Q, et al. 2008. 18376348 (387)	**Aim:** Efficacy of BB in conjunction with conventional treatment in reducing VVS in children. **Study type:** Single center, prospective randomized. (2001-2003) **Size:** n=28 pts; Age 12.3±3 y of age with 22±10 mo. Group I (n=14 pts) Metoprolol and Group II (n=14 pts) control	**Inclusion criteria:** At least 3 episodes of syncope in prior 12 mo along with a positive tilt. **Exclusion criteria:** Other causes of CV or systemic causes of syncope.	**Intervention:** Conventional therapy + metoprolol (Group I) or sole conventional therapy without metoprolol (Group II). **Comparator:** Metoprolol vs. conventional therapy.	**1° endpoint:** Recurrence of syncope in 2 wk after beginning therapy. Presyncope symptoms were not considered a failure of therapy. **Safety endpoint:** None	Results: Group I (Metoprolol): Syncope recurrence 6/14 (43%) • Group II (Conventional): Syncope recurrence 4/14 (29%) **Summary**: In a prospective randomized study Metoprolol was not effective in reducing VVS in children.
Scott WA, et al. 1995 7639169 (388)	**Aim:** Comparison of Atenolol vs. Florinef in treatment of neurally mediated syncope **Study type:** Prospective randomized **Size:** n=58 pts	**Inclusion criteria:** ≥2 episodes of syncope in preceding 6 mo and a positive TTT (BL or Isuprel). All pts had a normal H&P, ECP, and echocardiogram. **Exclusion criteria:** None	**Intervention:** Following a positive TTT randomized to Atenolol (25 or 50 mg) or Florinef (0.1 mg) followed 6 mo **Comparator:** Atenolol (N=29 pts) vs. Florinef (N=29 pts) No placebo group	**1° endpoint:** 48/58 (82%) cured or improved. No difference was observed between the 2 groups. **Safety endpoint:** No	**Secondary Comment:** 11/29 (38%) o Atenolol had an adverse event. (depression, suicide ideation, headaches) **Summary**: Oral treatment of neurally mediated syncope with Florinef or Atenolol is safe and efficacious. • However, a major limitation of this paper is the absence of a placebo group.
Balaji S, et al. 1994. 7906701	**Aim:** Outcomes of children with neurocardiogenic syncope. **Study type:** Single center	**Inclusion criteria:** Age <20 y of age with ≥3 episode of syncope in preceding 12 mo. Structurally normal heart, normal ECG (normal QT)	**Intervention:** Of 100 pts positive orthostatic response, 84 were treated with fludrocortisone and NaCl.	**1° endpoint:** Response to medical management. Syncope present, absent, improved over a 12 mo period	**Results:** Of the 100 orthostatic positive responders, 84 treated with fludrocortisone and NaCl. Of these 65% complete resolution and 17% some improvement Of the 11 nonresponders 10 were treated BB

(389)	study comparing pts with positive autonomic maneuver vs. negative autonomic response. **Size:** n=162 pts with syncope (12.8 y of age) compared 100 positive orthostatic response to 62 negative orthostatic response	**Exclusion criteria:** Other disease ruled-out by ECG, EEG, and head imaging.	**Comparator:** Orthostatic (autonomic abnormal) response compared to orthostatic negative response	**Safety endpoint:** No	and 4 responded. **Summary**: Benefit to combination salt and Fludrocortisone in pts with orthostatic intolerance. • Cannot exclude placebo effect
McLeod KA, et al. 1999 10573501 (390)	**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 This study did not compare medical management vs. pacemaker therapy.	**1° 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 11533339 (391)	**Aim:** Determine resolution of significant bradycardia related pallid-breatholding 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	**1° 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)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Khairy P, et al. 2004 15051640 (392)	**Study type:** Retrospective Cohort Multicenter (6) **Size:** n=252 pts	**Inclusion criteria:** Programmed ventricular stimulation between 1985 and 2002 **Exclusion criteria:** Unrepaired TOF, pulmonary atresia, AV canal	**1° endpoint:** Composite of sustained VT or SCD **Results:** Age at EPS ≥18 y, palpitations, prior palliative surgery, Modified Lown ≥2, cardiothoracic ratio ≥0.6	• Programmed ventricular stimulation is of diagnostic and prognostic value in risk stratifying pts with repaired TOF.
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	**1° endpoint:** Risk factors for shocks **Results:** Annual rates of appropriate shocks were 0.5% and 6.0% in primary and secondary prevention, respectively (p=0.0366)	• 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.

Data Supplement 42. Nonrandomized Trials, Observational Studies, and/or Registries of Geriatrics – (Section 10.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
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:** Proxpective 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

	Size: n=200 pts	consciousness		
Richardson DA, et al. 1997 9080518 (398)	**Aim:** to assess for CSS-mediated syncope in pts with falls **Study type:** Prospective, observational **Size:** n=279 pts	**Inclusion:** Unexplained fallers age ≥50 y **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	**1° endpoint:** diagnosis of CSS with cardiac inhibition	**Summary:** 65/279 had cardioinhibitory carotid hypersensitivity, raising question of pacing.
GIS Ungar A, et al. 2006 17038070 (399)	**Aim:** Older adults (≥65 referred to ER) (mean age 79±7), 160 ≥75 **Study type:** Observational **Size:** n=231 pts	**Inclusion criteria:** 65 and older with transient LOC **Exclusion criteria:** Presyncope or cognitive impairment	**1° endpoint:** Diagnosis **1° Safety endpoint (if relevant):** N/A	**Summary**: Definite diagnosis in 40.1%, suspected in 57.9%

GIS Ungar A, et al. 2011 21908471 (400)	**Aim:** To study 2 y f/u of guideline algorithm on outcomes in older adults (age ≥60, mean 78.7±6.8) **Study type:** Controlled, 2 y f/u **Size:** n=242 pts	**Inclusion criteria:** Pts assessed using GIS diagnostic algorithm Pts referred to clinic for syncope/falls or dizziness **Exclusion criteria:** Exclusion criteria were symptoms limited to pre-syncope, severe cognitive impairment , active (<5 y) malignancies and disability in more than 4 activities of daily living	**1° endpoint:** Recurrent syncope and mortality **1° Safety endpoint (if relevant):** N/A	**Summary**: 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
O'Mahony, et al. 1998 9823747 (401)	**Aim:** Diagnostic sensitivity of algorithm in pts 61–91 y of age **Study type:** Observational **Size:** n=54 pts	**Inclusion criteria:** Pts with unexplained syncope, falls, or dizziness were referred for assessment **Exclusion criteria:** N/A	**1° endpoint:** Diagnostic sensitivity and specificity **1° Safety endpoint (if relevant):**	**Summary**: High aggregate sensitivity of clinical thought process. Utility of TT esp in context of syncopal amnesia.
Aging Clin Exp Res Ungar, et al. 2015 25820493 (53)	**Aim:** To assess w/u of protocol in pts with dementia **Study type:** Observational **Size:** n=296 pts	**Inclusion criteria:** Pts ≥65 with dementia (83±6 yo) with falls or syncope. (52% falls, 45% syncope and 3% overlap); 60% did not remember episode **Exclusion criteria:** Absence of informed consent	**1° endpoint:** Diagnosis **1° Safety endpoint (if relevant):** N/A	**Summary**: Pts with dementia and high comorbidity, still with successful w/ workup

Data Supplement 43. Nonrandomized Trials, Observational Studies, and/or Registries of Syncope in Athletes – (Section 10.5)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
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	**1° 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	**1° 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	**1° 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	**1° 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.

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