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Did This Patient Have Cardiac Syncope?
The Rational Clinical Examination Systematic Review

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IMPORTANCE Syncope can result from a reduction in cardiac output from serious cardiac conditions, such as arrhythmias or structural heart disease (cardiac syncope), or other causes, such as vasovagal syncope or orthostatic hypotension.

OBJECTIVE To perform a systematic review of studies of the accuracy of the clinical examination for identifying patients with cardiac syncope.

STUDY SELECTION Studies of adults presenting to primary care, emergency departments, or referred to specialty clinics.

DATA EXTRACTION AND SYNTHESIS Relevant data were abstracted from articles in databases through April 9, 2019, and methodologic quality was assessed. Included studies had an independent comparison to a reference standard.

MAIN OUTCOMES AND MEASURES Sensitivity, specificity, and likelihood ratios (LRs).

RESULTS Eleven studies of cardiac syncope (N = 4317) were included. Age at first syncope of at least 35 years was associated with greater likelihood of cardiac syncope (n = 323; sensitivity, 91% [95% CI, 85%-97%]; specificity, 72% [95% CI, 66%-78%]; LR, 3.3 [95% CI, 2.6-4.1]), while age younger than 35 years was associated with a lower likelihood (LR, 0.13 [95% CI, 0.06-0.25]). A history of atrial fibrillation or flutter (n = 323; sensitivity, 13% [95% CI, 6%-20%]; specificity, 98% [95% CI, 96%-100%]; LR, 7.3 [95% CI, 2.4-22]), or known severe structural heart disease (n = 222; range of sensitivity, 35%-51%, range of specificity, 84%-93%; range of LR, 3.3-4.8; 2 studies) were associated with greater likelihood of cardiac syncope. Symptoms prior to syncope that were associated with lower likelihood of cardiac syncope were mood change or prodromal preoccupation with details (n = 323; sensitivity, 2% [95% CI, 0%-5%]; specificity, 76% [95% CI, 71%-81%]; LR, 0.09 [95% CI, 0.02-0.38]), feeling cold (n = 412; sensitivity, 2% [95% CI, 0%-5%]; specificity, 89% [95% CI, 85%-93%]; LR, 0.16 [95% CI, 0.06-0.64]), or headache (n = 323; sensitivity, 3% [95% CI, 0%-7%]; specificity, 80% [95% CI, 75%-85%]; LR, 0.17 [95% CI, 0.06-0.55]). Cyanosis witnessed during the episode was associated with higher likelihood of cardiac syncope (n = 323; sensitivity, 8% [95% CI, 2%-14%]; specificity, 99% [95% CI, 98%-100%]; LR, 6.2 [95% CI, 1.6-24]). Mood changes after syncope (n = 323; sensitivity, 3% [95% CI, 0%-7%]; specificity, 83% [95% CI, 78%-88%]; LR, 0.21 [95% CI, 0.06-0.65]) and inability to remember behavior prior to syncope (n = 323; sensitivity, 5% [95% CI, 0%-9%]; specificity, 82% [95% CI, 77%-87%]; LR, 0.25, [95% CI, 0.09-0.69]) were associated with lower likelihood of cardiac syncope. Two studies prospectively validated the accuracy of the multivariable Evaluation of Guidelines in Syncope Study (EGSYS) score, which is based on 6 clinical variables. An EGSYS score of less than 3 was associated with lower likelihood of cardiac syncope (n = 456; range of sensitivity, 89%-91%, range of specificity, 69%-73%; range of LR, 0.12-0.17; 2 studies). Cardiac biomarkers show promising diagnostic accuracy for cardiac syncope, but diagnostic thresholds require validation.

CONCLUSIONS AND RELEVANCE The clinical examination, including the electrocardiogram as part of multivariable scores, can accurately identify patients with and without cardiac syncope.

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Supplemental content

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Clinical Scenario

A 70-year-old woman presented to the clinic with her son for urgent assessment of her transient loss of consciousness. There was no history of episodes of loss of consciousness or cardiac or neurologic disease. Prior to the episode, she was sitting at the table eating breakfast. She felt nauseated and warm but did not experience chest pain, shortness of breath, palpitations, head turning, déjà vu, or jamais vu prior to the episode. She lost consciousness and her son lowered her to the ground. He observed generalized asymmetric limb twitching for less than 10 seconds. He did not see his mother turn blue during the loss of consciousness, which lasted for approximately 60 seconds. After the episode, the patient remembered feeling cold just prior to the loss of consciousness. She was not confused after the loss of consciousness and had normal mental status within 5 minutes. Her son persuaded her to be evaluated at the clinic the day after the episode. On examination, her heart rate was 70/min and regular and her blood pressure was 135/85 mm Hg in both arms while sitting and standing. There was no trauma to the tongue and the cardiac and neurologic examination findings were normal. A 12-lead electrocardiogram (ECG) showed normal sinus rhythm at 80/min, with normal PR interval, QRS duration and axis, and QT interval. Does this patient have cardiac syncope?

Box. Causes of Nontraumatic Transient Loss of Consciousness With Spontaneous Recovery[a]

Syncope
- Cardiac
- Orthostatic hypotension
- Reflex
  - Vasovagal
  - Situational
  - Carotid sinus hypersensitivity

Seizure
- Generalized onset
  - Motor
  - Nonmotor
- Focal onset with impaired awareness[b]
  - Motor
  - Nonmotor

Rare Causes
- Subclavian steal syndrome
- Vertebrobasilar transient ischemic attack
- Subarachnoid hemorrhage

[a] Adapted from Fisher et al[1] and Brignole et al.[2]

[b] Focal seizures may also progress to bilateral tonic-clonic seizures with impaired awareness.

Why Is This an Important Question to Answer With the Clinical Examination?

Syncope is transient loss of consciousness with spontaneous recovery due to a global reduction in cerebral perfusion. Syncope may be due to serious or benign causes, so accurate diagnosis is essential. The most common causes of syncope are cardiac syncope, reflex syncope, and orthostatic hypotension. Transient loss of consciousness with spontaneous recovery can also be due to seizures and rare causes (**Box**). This review focuses on the accuracy of the clinical examination for detecting cardiac syncope. Risk assessments of patients with unexplained syncope in the emergency department, which predict heterogeneous clinical events rather than identifying a specific diagnosis,[3] are not addressed.

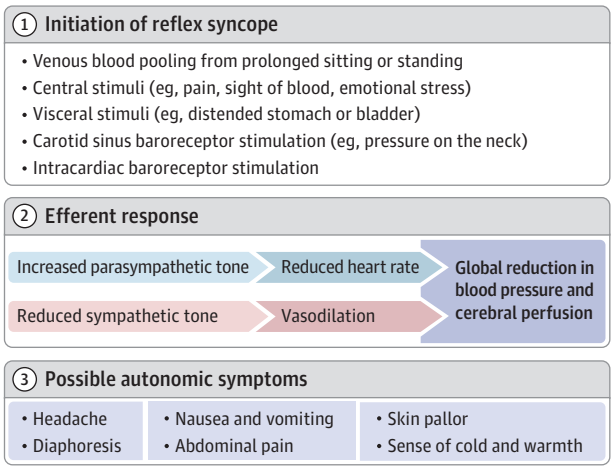
The Anatomic/Physiologic Origins of the Symptoms and Signs Used to Answer This Question

In cardiac syncope, the primary event is a marked reduction in cardiac output due to cardiopulmonary disease, such as arrhythmia, structural heart disease, or pulmonary embolism that leads to cerebral hypoperfusion. The event may occur at rest, in the supine position, or during effort when the patient is unable to increase the cardiac output to meet the increased demand. Cardiac syncope may be preceded by chest pain, shortness of breath, or palpitations. Patients may have witnessed cyanosis during unconsciousness. After awakening, patients may have persistent cardiac symptoms, abnormalities in heart rate or rhythm, abnormal cardiac physical examination findings, an abnormal electrocardiogram, or abnormal serum troponin or B-type natriuretic peptide levels.

Reflex syncope refers to a centrally mediated reflex reduction in heart rate, systemic vascular resistance, or both. Vasovagal syncope, the most common form of reflex syncope, is usually initiated by prolonged sitting or standing, which results in 500 to 800 mL of blood remaining in the distensible veins below the heart. Venous return, cardiac output, and blood pressure decrease during reflex syncope. These changes are detected by intracardiac and arterial baroreceptors, signaling the central nervous system to preserve cerebral perfusion through reduced vagal tone and increased sympathetic tone. In some patients, the reduction in vagal tone and increase in sympathetic tone are exaggerated, leading to excessive increases in heart rate and myocardial contractility against a relatively underfilled ventricle. Intracardiac baroreceptors become paradoxically overstimulated, leading to a second centrally mediated reflex characterized by an increased vagal tone and reduced sympathetic tone, reduced heart rate, reduced peripheral vascular resistance, and a global reduction in cerebral perfusion. Reflex syncope may also be precipitated by afferent central stimuli, such as pain or the sight of blood during venipuncture; afferent visceral stimuli, such as a distended stomach or bladder; or pressure on the carotid sinus baroreceptor, such as from a tight collared shirt while turning the neck. The efferent vagal component of the reflex leads to autonomic symptoms, such as headache, sweating, a sense of cold or warmth, nausea, vomiting, abdominal discomfort, or urge to defecate (**Figure 1**).

In syncope due to orthostatic hypotension, the primary disorder may be a reduction in venous return, due to conditions such as volume depletion or gastrointestinal bleeding or a reduction in systemic vascular resistance, caused by medications or disorders of

Figure 1. Stages of Reflex Syncope



the autonomic nervous system. Patients with orthostatic hypotension typically experience syncope within 5 minutes of sitting or standing. The patient may experience a warning of blurred vision or lightheadedness prior to loss of consciousness.

Transient loss of consciousness with spontaneous recovery may be due to seizures. Seizures are a constellation of symptoms that occur because of a transient episode of abnormal excessive or synchronous neuronal activity in the brain.[1] There are 2 main types of seizure onset, focal and generalized. In focal seizures, awareness may be preserved or lost. Focal seizures also may be associated with a variety of motor or nonmotor components. Motor features of focal seizures include automatisms or tonic, clonic, or hyperkinetic activity. Behavioral arrest and cognitive, autonomic, or emotional changes are nonmotor signs of focal seizures. Generalized seizures can also present with motor and nonmotor features. The motor features include tonic-clonic, myoclonic, or other types of motor activity. Nonmotor features of generalized seizures include staring spells, drop attacks, and eyelid myoclonus.[1] During the seizure, the patient may appear cyanotic because they are not breathing. The patient's relaxed tongue may be injured by the posterior teeth during tonic contraction of the jaw. Although patients with syncope or seizure may not recall symptoms just prior to the loss of consciousness, patients with syncope usually rapidly regain awareness in their environment, while patients with seizure may have prolonged confusion (ie, postictal confusion).

Witness accounts of the loss of consciousness are extremely valuable. Witnesses might report brief asymmetric or symmetric myoclonic or tonic-clonic movements at the time of loss of consciousness in patients with syncope. These movements should not be mistaken for a seizure.[4-6] The movements typically occur at the time of or within 10 seconds after the loss of consciousness, but not before. The duration of movements is usually less than 15 seconds. When eliciting the history of abnormal movements from a witness, the clinician may avoid diagnostic confusion with seizures by giving a timed physical demonstration of sustained tonic-clonic activity indicative of seizures. First responder reports can also provide important information, including vital signs, cardiac rhythm, and neurologic status shortly after the episode.

Prevalence

The incidence of syncope in adults is approximately 0.6% per year, increasing to 2% to 6% in elderly patients, and the prevalence of syncope in adults is 18% to 47%.[7,8] The cause of transient loss of consciousness for patients presenting to primary care or the emergency department is cardiac syncope in 5% to 21% of cases, vasovagal syncope in 21% to 48%, orthostatic hypotension in 4% to 24%, nonsyncopal syndromes (such as psychogenic nonepileptiform events or cataplexy) in 8% to 20%, and unexplained syncope in 17% to 37%.[2] Syncope is more common than seizures. The incidence of seizures is about 0.05% per year and the prevalence of seizures is about 0.3% to 1.7%.[9]

Methods

Search Strategy and Study Selection

The MEDLINE, Embase, CINAHL, and Cochrane databases were searched for articles published from the earliest possible date to April 9, 2019, using the following Medical Subject Heading terms and search strategy: "Physical examination or medical history taking or professional competence or sensitivity and specificity or reproducibility of results or observer variation or decision support techniques or Bayes theorem" and "syncope or consciousness or unconsciousness or seizures." The terms "consciousness," "unconsciousness," and "seizures" were added to identify potentially relevant articles that were not indexed with the term syncope. The Medical Subject Heading terms were replaced with the appropriate Emtree terms when Embase was searched, along with searching for key words related to each Medical Subject Heading term in the title and abstract. The searches were limited to articles published in English.

Pairs of investigators (O.T.A., R.J.R., S.S., or E.E.E.) independently reviewed all abstracts for English-language studies that included at least 10 human participants aged 12 years or older. An age of 12 years or older was included at this stage of review because studies can included a broad range of ages that span from adolescence to adulthood.

Studies with a valid reference standard,[10] such as cardiology consultation; noninvasive cardiac evaluation, such as echocardiography, Holter monitoring, loop monitoring, tilt table testing, or carotid sinus massage; or invasive cardiac evaluation, such as cardiac catheterization or electrophysiologic study, were included. Studies restricted to patients with recurrent unexplained syncope, a single defined cause of syncope, or who had completed invasive cardiac evaluation were excluded. The full text article of any abstract that was considered potentially relevant by either investigator was obtained. Pairs of investigators (O.T.A., R.J.R., S.S., or E.E.E.) independently reapplied the inclusion criteria to the full text articles. Additional articles were identified by searching the bibliographies of retrieved articles and position papers of professional organizations.

Assessment of Methodologic Quality and Data Abstraction

Two important methodologic issues could bias estimates of the accuracy of the clinical examination for detecting cardiac syncope. First, clinical findings alone are an accepted reference standard for

Table 1. Characteristics of Patients in Studies Included in a Review of the Accuracy of Clinical Examinations for Detecting Cardiac Syncope

Finding	No. of Patients (No. With Cardiac Syncope)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)[a]	LR− (95% CI)[a]
Patient Demographics					
Atrial fibrillation or flutter[17]	323 (88)	0.13 (0.06-0.20)	0.98 (0.96-1.0)	7.3 (2.4-22)	0.89 (0.82-0.97)
Severe structural heart disease[18,19b]	222 (98)	0.35-0.51	0.84-0.93	3.3-4.8	0.58-0.70
History of heart failure[18,27b]	1633 (299)	0.16-0.41	0.88-0.94	2.7-3.4	0.39-0.78
Age at first syncopal spell >35 y[17]	323 (88)	0.91 (0.85-0.97)	0.72 (0.66-0.78)	3.3 (2.6-4.1)	0.13 (0.06-0.25)
Precipitating or Predisposing Factors					
During effort[18,21b]	421 (122)	0.12-0.14	0.92-0.99	1.4-15	0.88-0.96
While supine[18,21b]	421 (122)	0.06-0.14	0.94-0.97	1.1-4.9	0.89-1.0
Prolonged sitting/standing[17]	323 (88)	0.38 (0.28-0.48)	0.31 (0.25-0.37)	0.54 (0.41-0.72)	2.0 (1.6-2.6)
On way to the toilet[17]	323 (88)	0.05 (0-0.09)	0.84 (0.79-0.89)	0.28 (0.10-0.76)	1.1 (1.1-1.2)
Stress[17]	323 (88)	0.08 (0.02-0.14)	0.68 (0.62-0.74)	0.25 (0.12-0.51)	1.4 (1.2-1.5)
Warm place[17]	323 (88)	0.09 (0.03-0.15)	0.45 (0.39-0.51)	0.17 (0.08-0.33)	2.0 (1.7-2.4)
Pain or medical procedure[17]	323 (88)	0.06 (0.01-0.11)	0.52 (0.46-0.58)	0.12 (0.05-0.28)	1.8 (1.5-2.1)
After using the toilet[17]	323 (88)	0 (0-0.03)	0.89 (0.85-0.93)	0.05 (0.003-0.85)	1.1 (1.1-1.2)
Symptoms Prior to the Episode					
Dyspnea[18,19,21,23]	699 (176)	0.18 (0.08-0.36)	0.95 (0.80-0.99)	3.5 (1.5-9.1)	0.87 (0.74-0.94)
Chest pain/angina[23,27b]	1680 (255)	0.06-0.19	0.95-0.98	3.4-3.8	0.71-0.79
Palpitations[17,18,21-23,27]	2836 (581)	0.13 (0.09-0.19)	0.93 (0.82-0.98)	1.9 (0.86-4.5)	0.94 (0.89-1.0)
Absence of prodromes[18,20-22]	1031 (353)	0.43 (0.35-0.51)	0.73 (0.55-0.86)	1.6 (1.0-2.6)	0.79 (0.69-0.96)
Pallor[17,23,27]	2003(343)	0.22 (0.08-0.48)	0.69 (0.34-0.90)	0.69 (0.58-0.82)	1.2 (1.0-1.4)
Blurred vision[17,20-23]	1401 (397)	0.16 (0.09-0.28)	0.71 (0.56-0.83)	0.55 (0.27-1.1)	1.2 (0.96-1.5)
Diaphoresis[21-23,27]	2352 (415)	0.15 (0.10-0.23)	0.69 (0.66-0.71)	0.49 (0.33-0.71)	1.2 (1.1-1.3)
Nausea[17,18,21-23,27]	2836 (581)	0.11 (0.07-0.18)	0.74 (0.65-0.81)	0.44 (0.31-0.62)	1.1 (1.1-1.3)
Awareness of being about to faint[22,23b]	620 (150)	0.12-0.38	0.64-0.66	0.35-1.0	0.97-1.3
Sweating or warm feeling[17]	323 (88)	0.24 (0.15-0.33)	0.38 (0.32-0.44)	0.38 (0.26-0.57)	2.0 (1.6-2.5)
Auditory distortion[17]	323 (88)	0.14 (0.07-0.21)	0.64 (0.58-0.7)	0.38 (0.22-0.66)	1.3 (1.2-1.5)
Lightheadedness[22]	412 (116)	0.08 (0.03-0.13)	0.8 (0.75-0.85)	0.38 (0.20-0.75)	1.2 (1.1-1.2)
Numbness or tingling[17]	323 (88)	0.09 (0.03-0.15)	0.72 (0.66-0.78)	0.33 (0.16-0.66)	1.3 (1.1-1.4)
Abdominal discomfort[17,23b]	531 (122)	0.029 -0.034	0.84-0.93	0.21-0.39	1.0-1.2
Headache[17]	323 (88)	0.03 (0-0.07)	0.8 (0.75-0.85)	0.17 (0.06-0.55)	1.2 (1.1-1.3)
Feeling cold[22]	412 (116)	0.02 (0-0.05)	0.89 (0.85-0.93)	0.16 (0.04-0.64)	1.1 (1.0-1.2)
Mood changes or prodromal preoccupation with details[17]	323 (88)	0.02 (0-0.05)	0.76 (0.71-0.81)	0.09 (0.02-0.38)	1.3 (1.2-1.4)
During and After the Episode					
Cyanotic during syncope[17]	323 (88)	0.08 (0.02-0.14)	0.99 (0.98-1.0)	6.2 (1.6-24)	0.93 (0.88-0.99)
Injury[19,27b]	1533 (241)	0.16-0.25	0.80-0.86	1.13-1.28	0.90-0.98
Numbness or tingling[17]	323 (88)	0.06 (0.01-0.11)	0.82 (0.77-0.87)	0.31 (0.13-0.76)	1.2 (1.1-1.2)
Nausea[17,22b]	735 (204)	0.06-0.10	0.65-0.84	0.29-0.38	1.1-1.4
Cannot remember behavior during syncope[17]	323 (88)	0.05 (0-0.09)	0.82 (0.77-0.87)	0.25 (0.09-0.69)	1.2 (1.1-1.2)
Mood changes[17]	323 (88)	0.03 (0-0.07)	0.83 (0.78-0.88)	0.21 (0.06-0.65)	1.2 (1.1-1.2)
Combinations of Findings					
Heart disease, abnormal ECG, or both[20]	198 (115)	0.88 (0.82-0.94)	0.61 (0.51-0.71)	2.3 (1.7-3.0)	0.20 (0.12-0.33)
EGSYS score ≥3[20,21b]	456 (150)	0.89-0.91	0.69-0.73	2.8-3.3	0.12-0.17
Vasovagal score<−2[17,25b]	703 (116)	0.32-0.91	0.81-0.89	1.7-8.6	0.10-0.84

Abbreviations: ECG, electrocardiogram; EGSYS, Evaluation of Guidelines in Syncope Study; LR, likelihood ratio.

[a] When a finding is present, as the LR+ becomes increasingly greater than 1, the likelihood of cardiac syncope increases. When a finding is absent, as the LR− becomes increasingly less than 1, the likelihood of cardiac syncope decreases. When a finding is present and the LR− becomes increasingly greater than 1, the likelihood of noncardiac syncope increases.

[b] Sensitivity, specificity, and LRs are reported as ranges.

vasovagal syncope,[2] orthostatic hypotension, and seizures. Clinical findings that define the reference standard will have high estimates of specificity. Second, the reference standard evaluation of syncope is guided by results of the clinical examination. Patients with a typical history for vasovagal syncope, normal cardiac examination findings, and a normal electrocardiogram, will generally not undergo further

Table 2. The Evaluation of Guidelines in Syncope Study (EGSYS) Scores[a,b]

Clinical Variable	Points
Palpitations	4
Abnormal ECG/heart disease[c,d]	3
Effort syncope	3
Syncope in supine position	2
Neurovegetative prodromes[e]	−1
Precipitating and predisposive factors[f]	−1

Abbreviation: ECG, electrocardiogram

[a] Adapted from Kariman et al[20] and Del Rosso et al.[21]

[b] A total score of 3 or more implies an increased risk of cardiac syncope.

[c] Abnormal ECG was defined as any of the following: bradycardia less than 40/min, repetitive sinoatrial blocks, sinus pauses greater than 3 seconds, ST changes >1 mm elevation or depression, QT prolongation ≥440 ms or more, ventricular tachycardia, atrioventricular block (mobitz 2, second or third degree atrioventricular block, alternating left and right bundle branch block, sick sinus syndrome, ventricular and rapid paroxysmal supraventricular arrhythmias, or sinus pauses and pacemaker malfunction.

[d] Heart disease was defined as congestive heart failure or any form of structural heart disease, including ischemic disease, valvular dysfunction, cardiomyopathy, and congenital heart disease.

[e] Neurovegetative prodromes: nausea, vomiting, abdominal discomfort, feeling of cold, sweating, aura, pain in neck or shoulders, blurred vision, and dizziness.

[f] Precipitating and predisposive factors: position (supine, sitting or standing); activity (rest, change in posture, during or after exercise, during or immediately after urination, defaecation, cough or swallowing); predisposing factors (eg, crowded or warm places, prolonged standing, postprandial period); and precipitating events (eg, fear, intense pain, neck movements).

testing. This raises the potential for misclassification bias,[11] which could lead to overestimates of sensitivity and specificity.

Pairs of investigators (O.T.A., R.J.R., S.S., or E.E.E.) independently completed qualitative methodological reviews using the Quality Assessment of Diagnostic Accuracy Studies tool[12] and resolved any disagreements by consensus. A third investigator (S.S. or E.E.E.) independently performed a qualitative methodologic review when consensus could not be reached. The level of evidence was assigned by adapting the grading system developed for the Rational Clinical Examination series.[13] Level 1 studies were prospective studies of at least 100 consecutive patients who underwent an independent comparison to a reference standard evaluation. Level 2 studies were similar to level 1 studies but with fewer than 100 patients. Level 3 studies were comparisons of patients to a reference standard that otherwise did not meet criteria for level 1 or 2 studies, such as retrospective studies, studies of nonconsecutive patients, or studies in which the independence between the test and reference standard could be inferred, but not confirmed, from the study methods. Studies below level 3 evidence were excluded. Pairs of investigators (O.T.A., R.J.R., S.S., or E.E.E.) independently abstracted data and resolved any disagreements about abstracted data through discussion. A third investigator (S.S., E.E.E., or D.S.) independently abstracted data when an agreement could not be reached. Authors of published studies were contacted for methodologic information or additional data when necessary.

Analysis

The sensitivity and specificity CIs were estimated using exact methods if cells had zero values.[14] If there were values of zero in the 2 × 2 matrix, 0.5 was added to each cell to calculate likelihood ratios. Findings evaluated in only 2 studies were summarized with the range. Findings evaluated in 3 studies were summarized with univariate random effects measures because bivariate methods may not work with few studies or small cell values.[15] Findings evaluated in at least 4 studies were analyzed using bivariate random effects measures, which accounts for the heterogeneity between studies.[16] We did not weigh for quality measures.

Results

After screening 11 460 abstracts and reviewing 552 full-text articles, 540 full-text articles were excluded because the study did not meet inclusion criteria after full-text review (n = 448), was below level 3 evidence (n = 75), did not evaluate any elements of the clinical examination (n = 13), or was a duplicate publication (n = 4) (eFigure in the Supplement). Of the remaining 12 studies, 11 addressed the question of cardiac syncope or other causes of syncope and 1 addressed the question of seizure or syncope.

Did This Patient Have Cardiac Syncope?

Among 11 studies that included 4317 total patients,[17-27] 6 studies enrolled patients with syncope presenting to emergency departments, 3 enrolled patients admitted to hospitals for evaluation of syncope, and 2 enrolled inpatients and outpatients referred for evaluation of syncope. In most studies, the clinical examination was completed by study personnel or trained expert physicians. In these studies, 9% to 58% of patients had a final diagnosis of cardiac syncope and 3% to 37% remained undiagnosed after extensive workup. Four studies were graded as level 1, 2 were graded level 2, and the remaining 5 were graded level 3. Nine studies were prospective, all of which enrolled consecutive participants. Seven studies explicitly described independence between the index clinical examination and the reference standard assessment. Most studies did not explicitly ensure that the index clinical examination was independent of the reference standard assessment (**Table 1** and **Table 2**; eTables 1-3 in the Supplement).

Patient Demographics

Age at first syncope of 35 years or older was associated with greater likelihood of cardiac syncope (n = 323; sensitivity, 91% [95% CI, 85%-97%]; specificity, 72% [95% CI, 66%-78%]; likelihood ratio [LR], 3.3 [95% CI, 2.6-4.1]), while age 35 years or younger was associated with lower likelihood of cardiac syncope (LR, 0.13 [95% CI, 0.06-0.25]). A history of atrial fibrillation or flutter (n = 323; sensitivity, 13% [95% CI, 6%-20%]; specificity, 98% [95% CI, 96%-100%]; LR, 7.3 [95% CI, 2.4-22]), heart failure (n = 1633; range of sensitivity, 16%-41%; range of specificity, 88%-94% ; range of LR, 2.7-3.4; 2 studies), or known severe structural heart disease (n = 222; range of sensitivity, 35%-51%; range of specificity, 84%-93%; range of LR, 3.3-4.8; 2 studies) were associated with greater likelihood of cardiac syncope (Table 1; eTable 4 in the Supplement).

Precipitating and Predisposing Factors

Predisposing and precipitating factors that were associated with lower likelihood of cardiac syncope were pain or medical procedure prior to syncope (n = 323; sensitivity, 6% [95% CI, 1%-11%]; specificity, 52% [95% CI, 46%-58%]; LR, 0.12 [95% CI, 0.05-0.28])

Table 3. Cardiac Biomarkers of Patients in Studies Included in a Review of the Accuracy of Clinical Examinations for Detecting Cardiac Syncope

Finding	No. With Cardiac Syncope	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR− (95% CI)
High-sensitivity cardiac troponin T >14 ng/L[24]	360 (80)	0.74 (0.64-0.84)	0.68 (0.63-0.73)	2.3 (1.9-2.9)	0.39 (0.26-0.56)
High-sensitivity cardiac troponin T [27]	1338 (221)	NA[b]	NA[b]		NA[b]
>42 pg/mL				5.1 (3.6-7.1)	
5-42 pg/mL				1.0 (0.91-1.1)	
<5 pg/mL				0.15 (0.08-0.31)	
High-sensitivity cardiac troponin I[27]	1338 (221)	NA[b]	NA[b]		NA[b]
>31.3 pg/mL				5.4 (3.9-7.6)	
2.2-31.3 pg/mL				0.96 (0.87-1.1)	
<2.2 pg/mL				0.18 (0.10-0.35)	
NT-proBNP above upper limit normal[18,19a]	222 (98)	0.90-0.90	0.49-0.52	1.8-1.9	0.20-0.21
NT-proBNP ≥210.5 pg/ml[26]	100 (50)	0.94 (0.9 -1.0)	0.98 (0.94-1.0)	47 (6.7-328)	0.06 (0.02-0.18)
NT-proBNP[27]	1338 (221)	NA[b]	NA[b]		NA[b]
>1966 pg/mL				5.8 (4.2-8.1)	
69-1966 pg/mL				1.1 (1.0-1.2)	
<69 pg/mL				0.16 (0.09-0.28)	
BNP[27]	1338 (221)	NA[b]	NA[b]		NA[b]
>302 pg/mL				6.3 (4.6-8.8)	
15-302 pg/mL				0.91 (0.82-1.0)	
<15 pg/mL				0.20 (0.11-0.40)	

Abbreviations: BNP, B-type natriuretic peptide; LR, likelihood ratio; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NA, not applicable.

[a] Upper limit of normal >156 pg/mL[18] and ≥164 pg/mL.[19] Sensitivity, specificity, and LRs are reported as ranges.

[b] For ordinal results with 3 or more levels, sensitivity and specificity no longer apply. The serial LRs are shown for each threshold.

or syncope in a warm place (n = 323; sensitivity, 9% [95% CI, 3%-15%]; specificity, 45% [95% CI, 39%-51%]; LR, 0.17 [95% CI, 0.08-0.33]). Syncope after using the toilet was associated with a lower likelihood of cardiac syncope, but the CIs were wide (LR, 0.05 [95% CI, 0.003-0.85]). There were inconsistent results for syncope during effort and syncope while supine (Table 1; eTable 5 in the Supplement).

Symptoms Prior to Syncope

Dyspnea prior to syncope (n = 699; sensitivity, 18% [95% CI, 8%-36%]; specificity, 95% [95% CI, 80%-99%]; LR, 3.5 [95% CI, 1.5-9.1]) and chest pain prior to syncope (n = 1680; range of sensitivity, 6%-19%; range of specificity, 95%-98%; range of LR, 3.4-3.8; 2 studies) were associated with higher likelihood of cardiac syncope. There were inconsistent results for palpitations prior to syncope. Symptoms prior to syncope that were associated with lower likelihood of cardiac syncope were mood change or prodromal preoccupation with details (n = 323; sensitivity, 2% [95% CI, 0%-5%]; specificity, 76% [95% CI, 71%-81%]; LR, 0.09 [95% CI, 0.02-0.38]), feeling cold (n = 412; sensitivity, 2% [95% CI, 0%-5%]; specificity, 89% [95% CI, 85%-93%]; LR, 0.16 [95% CI, 0.06-0.64]), headache (n = 323; sensitivity, 3% [95% CI, 0%-7%]; specificity, 80% [95% CI, 75%-85%], LR, 0.17 [95% CI, 0.06-0.55]), or abdominal discomfort (n = 531; range of sensitivity, 2.9%-3.4%; range of specificity, 84%-93%; range of LR, 0.21-0.39; 2 studies). Pallor and absent prodrome were not associated with higher or lower likelihood of cardiac syncope (Table 1; eTable 6 in the Supplement).

Symptoms and Signs During and After Syncope

Cyanosis witnessed during the episode was associated with higher likelihood of cardiac syncope (n = 323; sensitivity, 8% [95% CI, 2%-14%]; specificity, 99% [95% CI, 98%-100%]; LR, 6.2 [95% CI, 1.6-24]). Mood changes after syncope (n = 323; sensitivity, 3% [95% CI, 0%-7%]; specificity, 83% [95% CI, 78%-88%]; LR, 0.21 [95% CI, 0.06-0.65]) and inability to remember behavior prior to syncope (n = 323; sensitivity, 5% [95% CI, 0%-9%]; specificity, 82% [95% CI, 77%-87%]; LR, 0.25 [95% CI, 0.09-0.69]) were associated with lower likelihood of cardiac syncope (Table 1; eTables 7 and 8 in the Supplement). Injury after syncope was not associated with higher or lower likelihood of cardiac syncope.

Combinations of Findings

Cardiac syncope was less likely if there was no history of heart disease and a normal ECG (n = 198; sensitivity, 88% [95% CI, 82%-94%]; specificity, 61% [95% CI, 51%-71%]; LR, 0.20 [95% CI, 0.12-0.33]). Two studies prospectively validated the accuracy of the multivariable Evaluation of Guidelines in Syncope Study (EGSYS) score (range, −2 to 12; higher scores indicate higher likelihood of cardiac syncope), which is based on 6 clinical variables (Table 1 and Table 2; eTable 9 in the Supplement) An EGSYS score less than 3 was associated with lower likelihood of cardiac syncope (n = 456; range of sensitivity, 89%-91%; range of specificity, 69%-73%; range of LR, 0.12-0.17; 2 studies).

One level 3 study (n = 323) retrospectively validated the multivariable vasovagal score (Table 1). The vasovagal score assigns

Table 4. Distinguishing Seizure From Syncope[a]

	LR (95% CI)			
	When Finding Is Present		When Finding Is Absent	
Finding	Seizure	Syncope	Seizure	Syncope
Symptoms[28]				
Head turning	14 (8.2-23)	0.07 (0.04-0.12)	0.59 (0.50-0.70)	1.7 (1.4-2.0)
Unusual posturing	13 (7.6-24)	0.08 (0.04-0.13)	0.67 (0.58-0.77)	1.5 (1.3-1.7)
Bedwetting	6.7 (3.8-12)	0.15 (0.08-0.26)	0.79 (0.71-0.88)	1.3 (1.1-1.4)
Blue color observed by bystanders	5.8 (3.7-8.9)	0.17 (0.11-0.27)	0.72 (0.63-0.82)	1.4 (1.2-1.6)
Limb jerking noted by others	5.6 (4.3-7.2)	0.18 (0.14-0.23)	0.36 (0.27-0.48)	2.8 (2.1-3.7)
Prodromal trembling	4.9 (3.2-7.7)	0.2 (0.13-0.31)	0.75 (0.66-0.85)	1.3 (1.2-1.5)
Prodromal preoccupation	4.5 (1.8-11)	0.22 (0.09-0.56)	0.94 (0.89-0.99)	1.1 (1.0-1.1)
Prodromal hallucinations	4.5 (1.8-11)	0.22 (0.09-0.56)	0.94 (0.89-0.99)	1.1 (1.0-1.1)
Any presyncope	0.27 (0.19-0.39)	3.7 (2.6-5.3)	5.6 (4.4-7)	0.18 (0.14-0.23)
Warmth before a spell	0.23 (0.12-0.46)	4.3 (2.2-8.3)	1.4 (1.3-1.5)	0.71 (0.67-0.77)
Any chest pain	0.22 (0.12-0.39)	4.5 (2.6-8.3)	1.7 (1.5-1.8)	0.59 (0.56-0.67)
Nausea before a spell	0.21 (0.1-0.47)	4.8 (2.1-10)	1.3 (1.2-1.4)	0.77 (0.71-0.83)
Remembered loss of consciousness	0.21 (0.12-0.35)	4.8 (2.9-8.3)	2.1 (1.8-2.3)	0.48 (0.43-0.56)
Presyncope with prolonged sitting/standing	0.18 (0.08-0.4)	5.6 (2.5-13)	1.4 (1.3-1.5)	0.71 (0.67-0.77)
Diaphoresis before a spell	0.17 (0.08-0.37)	5.9 (2.7-13)	1.4 (1.3-1.6)	0.71 (0.63-0.77)
Chest pain before a spell	0.15 (0.04-0.61)	6.7 (1.6-25)	1.1 (1.1-1.2)	0.91 (0.83-0.91)
Palpitations before loss of consciousness	0.12 (0.04-0.31)	8.3 (3.2-25)	1.5 (1.4-1.6)	0.67 (0.63-0.71)
Dyspnea before loss of consciousness	0.08 (0.02-0.33)	13 (3.0-50)	1.3 (1.2-1.4)	0.77 (0.71-0.83)
Loss of consciousness with prolonged sitting/standing	0.05 (0.01-0.19)	20 (5.3-100)	1.6 (1.5-1.7)	0.63 (0.59-0.67)
Coronary heart disease	0.08 (0.02-0.31)	13 (3.2-50)	1.3 (1.2-1.4)	0.77 (0.71-0.83)
Signs[28]				
Cut tongue	17 (9.9-29)	0.06 (0.03-0.10)	0.56 (0.47-0.67)	1.8 (1.5-2.1)
Behaviors not recalled	4 (3-5.3)	0.25 (0.19-0.33)	0.54 (0.44-0.67)	1.8 (1.5-2.3)

Abbreviation: LR, likelihood ratio.

[a] Adapted from Sheldon et al.[28]

points to 7 clinical variables (score range, −14 to 6; a lower score indicates a higher likelihood of cardiac syncope): (1) history of bifascicular block, asystole, supraventricular tachycardia, and/or diabetes (−5 points); (2) blue in the face, as noted by bystanders (−4 points); (3) 35 years of age or older (−3 points); (4) memory of being unconscious (−2 points); (5) lightheaded spells or fainting with prolonged sitting or standing (+1 point); (6) sweating or feeling warm before fainting (+2 points); and (7) lightheaded spells or fainting with pain or in medical settings (+3 points). A vasovagal score less than −2 was associated with a lower likelihood of cardiac syncope (sensitivity, 91% [95% CI, 85%-97%]; specificity, 89% [95% CI, 85%-93%]; LR for a vasovagal score <−2, 8.6 [95% CI, 5.9-13]), whereas cardiac syncope was unlikely with a vasovagal score of at least −2 (LR for a vasovagal score ≥−2, 0.10 [95% CI, 0.05-0.20]). A subsequent level 3 study[25] of patients with vasovagal syncope and cardiac syncope found that a vasovagal score of less than −2 was associated with a slightly higher likelihood of cardiac syncope (n = 265; sensitivity, 32% [95% CI, 15%-49%]; specificity, 81% [95% CI, 77%-85%]; LR for a vasovagal score <−2, 1.7 [95% CI, 0.95-3.0]), whereas a vasovagal score of at least −2 was not associated with a difference in the likelihood of cardiac syncope (LR for a vasovagal score ≥−2, 0.84 [95% CI, 0.65-1.1]).

Biomarkers

A high-sensitivity cardiac troponin T (Roche assay) greater than or equal to 42 ng/L was required to achieve a predefined specificity of 95% for cardiac syncope (LR, 5.1 [95% CI, 3.6-7.1]), whereas a threshold of greater than or equal to 31.3 ng/L was required for the high-sensitivity cardiac troponin I (Abbott assay) to achieve a specificity of 95% (LR, 5.4 [95% CI, 3.9-7.6]).[27] A predefined sensitivity of 95% to rule out cardiac syncope was achieved with a high-sensitivity cardiac troponin T less than 5 ng/L (LR, 0.15 [95% CI, 0.08-0.31]) or a high-sensitivity cardiac troponin I less than 2.2 ng/L (LR, 0.18 [95% CI, 0.10-0.35]).[27] An N-terminal pro–B-type natriuretic peptide (NT-proBNP) level greater than 1966 pg/mL (LR, 5.8 [95% CI, 4.2-8.1]) was required to achieve a predefined specificity of 95% for ruling in cardiac syncope.[27] An elevated NT-proBNP (thresholds of >156 pg/mL[19]; ≥164 pg/mL[20]; and ≥210.5 pg/mL[26]) was associated with a higher likelihood of cardiac syncope, but with wide variations between studies (range of sensitivity, 90%-94%; range of specificity, 49%-98%; range of LR, 1.8-47). A predefined sensitivity of 95% to rule out cardiac syncope was achieved with an NT-proBNP less than 69 pg/L (LR, 0.16 [95% CI, 0.09-0.28]).[26] A normal NT-pro-BNP (thresholds of ≤156 pg/mL[19]; <164 pg/mL[20]; and <210.5 pg/mL[27]) was associated with a lower likelihood of cardiac

Table 5. Clinical Prediction Rule for Distinguishing Seizure vs Syncope[a,b]

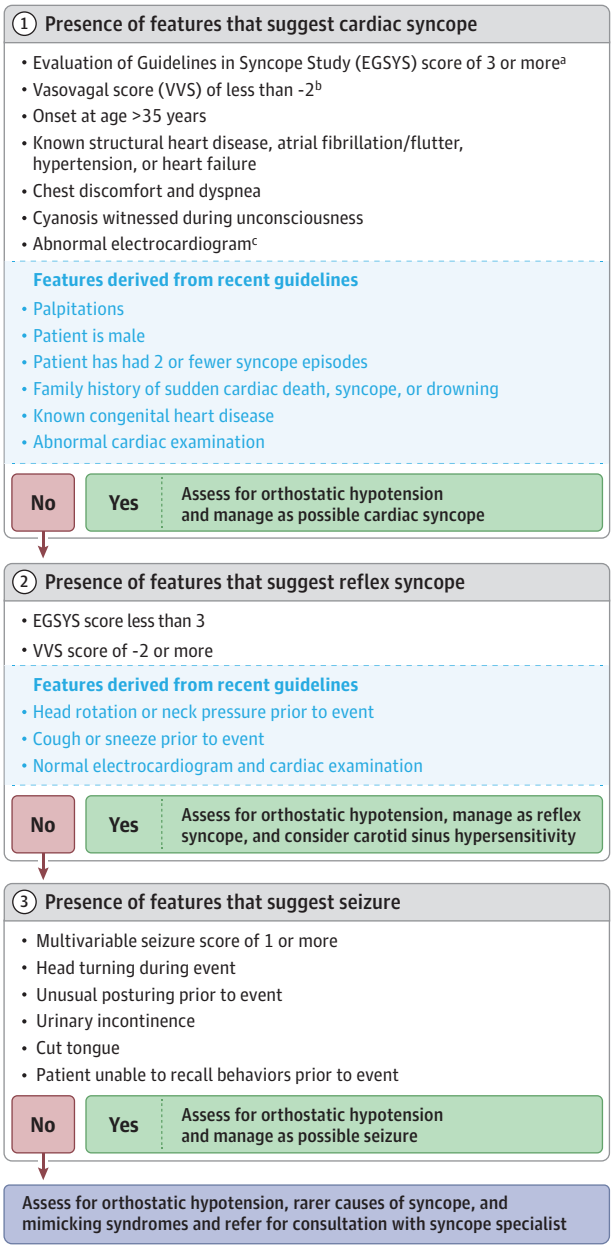
Symptom	Points
Waking with cut tongue	2
Abnormal behavior noted[c]	1
Loss of consciousness with emotional stress	1
Postictal confusion	1
Head turning to one side during loss of consciousness	1
Prodromal deja vu or jamais vu	1
Any presyncope	−2
Loss of consciousness with prolonged standing or sitting	−2
Diaphoresis before a spell	−2

[a] Adapted from Sheldon et al.[28]

[b] A score ≥1 suggests seizure and a score <1 suggests syncope.

[c] Witnessed amnesia, unresponsiveness, unusual posturing, and/or limb jerking.

Figure 2. Approach to Determining Whether a Patient Has Cardiac Syncope



This approach integrates the main findings of this review with the recommendations of the European Society of Cardiology and American College of Cardiology/American Heart Association guidelines.[2,29]
The approach outlined has not been evaluated or validated in rigorous studies.

[a] See Table 2 for an explanation of EGSYS.

[b] See Table 3 for an explanation of VVS.

[c] An abnormal electrocardiogram is defined in Table 2 and the Supplement.

syncope (range of LR, 0.06-0.21). About 36% of patients had a useful NT-proBNP result that was either above the predefined threshold for "ruling in" or below the predefined threshold for "ruling out" cardiac syncope (**Table 3**; eTable 10 in the Supplement).[27]

Differentiating Syncope From Seizure

One level 3 study[28] (prevalence of definite seizure, 15%; n = 671 patients) reported the diagnostic accuracy of symptoms and signs for differentiating seizure from syncope (**Table 4**). The most useful symptoms (reported by the patient or a witness) for identifying patients with seizures were head turning during the event (sensitivity for seizure, 43% [95% CI, 33%-53%]; specificity for seizure, 97% [95% CI, 95%-98%]; LR for seizure, 14 [95% CI, 8.2-23]), unusual posturing during the event (sensitivity for seizure, 35% [95% CI, 26%-45%]; specificity for seizure, 97% [95% CI, 96%-99%]; LR for seizure, 13 [95% CI, 7.6-24]), urinary incontinence (sensitivity for seizure, 24% [95% CI, 15%-32%]; specificity for seizure, 96% [95% CI, 95%-98%]; LR for seizure, 6.7 [95% CI, 3.8-12]), and the absence of presyncope (sensitivity for seizure, 77% [95% CI, 68%-85%]; specificity for seizure, 86% [95% CI, 83%-89%]; LR for seizure, 5.6 [95% CI, 4.4-7]). The most useful findings evaluated by the physician for identifying patients with seizures were the presence of a cut tongue (sensitivity for seizure, 45% [95% CI, 35%-55%]; specificity for seizure, 97% [95% CI, 96%-99%]; LR for seizure, 17 [95% CI, 9.9-29]) and the patient having no recall of unusual behaviors before the loss of consciousness (sensitivity for seizure, 53% [95% CI, 43%-63%]; specificity for seizure, 87% [95% CI, 84%-90%]; LR for seizure, 4.0 [95% CI, 3.0-5.3]).

The most useful symptoms (reported by the patient or a witness) for identifying patients with syncope were loss of consciousness with prolonged sitting or standing (sensitivity for syncope, 40% [95% CI, 36%-44%]; specificity for syncope, 98% [95% CI, 95%-100%]; LR for syncope, 20 [95% CI, 5.3-100]), dyspnea before loss of consciousness (sensitivity for syncope, 24% [95% CI, 20%-27%]; specificity for syncope, 98% [95% CI, 95%-100%]; LR for syncope, 13 [95% CI, 3.0-50]), and palpitations before loss of consciousness (sensitivity for syncope, 34% [95% CI, 30%-38%]; specificity for syncope, 96% [95% CI, 92%-100%]; LR for syncope, 8.3 [95% CI, 3.2-25]). The presence of coronary heart disease was associated with a higher likelihood of cardiac syncope (sensitivity for syncope, 25% [95% CI, 22%-29%]; specificity for syncope, 98% [95% CI, 95%-100%]; LR for syncope, 13 [95% CI, 3.2-50]) (**Table 5**).

Combinations of Findings for Seizures vs Syncope

In the same level 3 study,[28] the authors developed and tested a clinical prediction rule in a population of patients referred to a specialty clinic; 102 patients (15%) had seizures and 437 patients (65%) had

syncope with an established cause. The remaining 132 patients (20%) with syncope of uncertain cause were not included in the clinical prediction rule development and testing. The patients with seizures were limited to patients with electroencephalographic evidence that supported the diagnosis of seizures. In this study, some patients with seizures and normal interictal electroencephalograms would have been misclassified as having syncope, which may lead to an underestimate of accuracy of the clinical prediction rule, especially the positive likelihood ratio for ruling in seizure. The authors used logistic regression to identify 9 independently useful findings for detecting patients with seizures, and developed a simplified scoring system (range, −6 to 7; a lower score indicates a higher likelihood of cardiac syncope) (Table 5). With a score of at least 1, the model was 94% sensitive and 94% specific (LR for score ≥1 for seizures, 16; LR for score <1 for syncope, 16; CIs cannot be derived from modeled data). The study population in which the model was developed showed a 15% prevalence of seizure, meaning that a score of at least 1 had a positive predictive value of 74% for seizure; with a 65% prevalence of established syncope, a score less than 1 had a positive predictive value of 97% for syncope.

Discussion

This review of 11 studies involving patients with suspected cardiac syncope suggests that the clinical examination can accurately identify patients with cardiac syncope. Multivariable clinical prediction rules are an attractive option because no single variable will accurately diagnose syncope (or seizure). Two level 3 studies involving a total of 456 patients evaluated the multivariable EGSYS score and showed some promise for excluding the diagnosis of cardiac syncope. Misclassification bias and other methodologic limitations could bias toward overly optimistic negative likelihood ratios, so clinicians should not use these clinical predictions alone to rule out cardiac syncope. The vasovagal score (Calgary score) showed promise in its initial study,[17] but was not validated in a subsequent independent level 3 study.[26] Some classically taught findings lack accuracy (despite the methodologic limitations that would inflate accuracy), such as palpitations, diaphoresis, absence of prodromes, blurred vision or pallor prior to syncope, and injury after syncope.

The main findings of this review are consistent with existing European Society of Cardiology and American College of Cardiology/American Heart Association guidelines.[2,29] **Figure 2** integrates the main findings of this review with the recommendations of these 2 guidelines, leaving out biomarkers until the data are replicated and validated. Both guidelines indicate that cardiac markers, such as NT-proBNP and troponin, should not be routinely used but may be useful in select patients. Clinicians may be asked to evaluate patients after syncope in the emergency department, where biomarkers are obtained as part of patient assessment. These markers can have thresholds set so that they accurately identify patients with and without cardiac syncope, although about 65% of patients will have nondiagnostic intermediate values.[27] Application of the sensitivity and specificity of biomarkers for cardiac syncope requires an understanding of the assay used by each laboratory and prospectively collected data from additional populations of patients with syncope. However, the approach outlined in Figure 2 has not been evaluated or validated in rigorous studies.

This review has several limitations. Misclassification bias may have increased the estimates of sensitivity and specificity in some of the studies. Patients with unexplained syncope were excluded from some of the studies, which may have increased the sensitivity and specificity estimates. Most of the studies used structured questionnaires, trained researchers, or expert clinicians for the clinical examination, so diagnostic accuracy by less-trained clinicians is not known. About 13% of patients in the studies reviewed had a final diagnosis of unexplained syncope, highlighting the clinical challenge of establishing a final diagnosis of transient loss of consciousness when ECG findings and other critical data are not always available.

Scenario Resolution

The patient's clinical assessment revealed no features that raised the likelihood of cardiac syncope and many features that suggested that reflex syncope was more likely. In addition, her EGSYS score was −1 (range of LR, 0.12-0.17) and her vasovagal score was −1 (range of LR, 0.10-0.84), both of which made cardiac syncope less likely. The patient's multivariable score for seizure was −4, making syncope more likely (LR for score <1 for syncope, 16). There was no evidence of orthostatic hypotension, so reflex syncope was the most likely diagnosis. The physician advised the patient that if she had future similar events with warning symptoms, she should immediately lie down, elevate her legs in an effort to avoid loss of consciousness, and seek medical attention.

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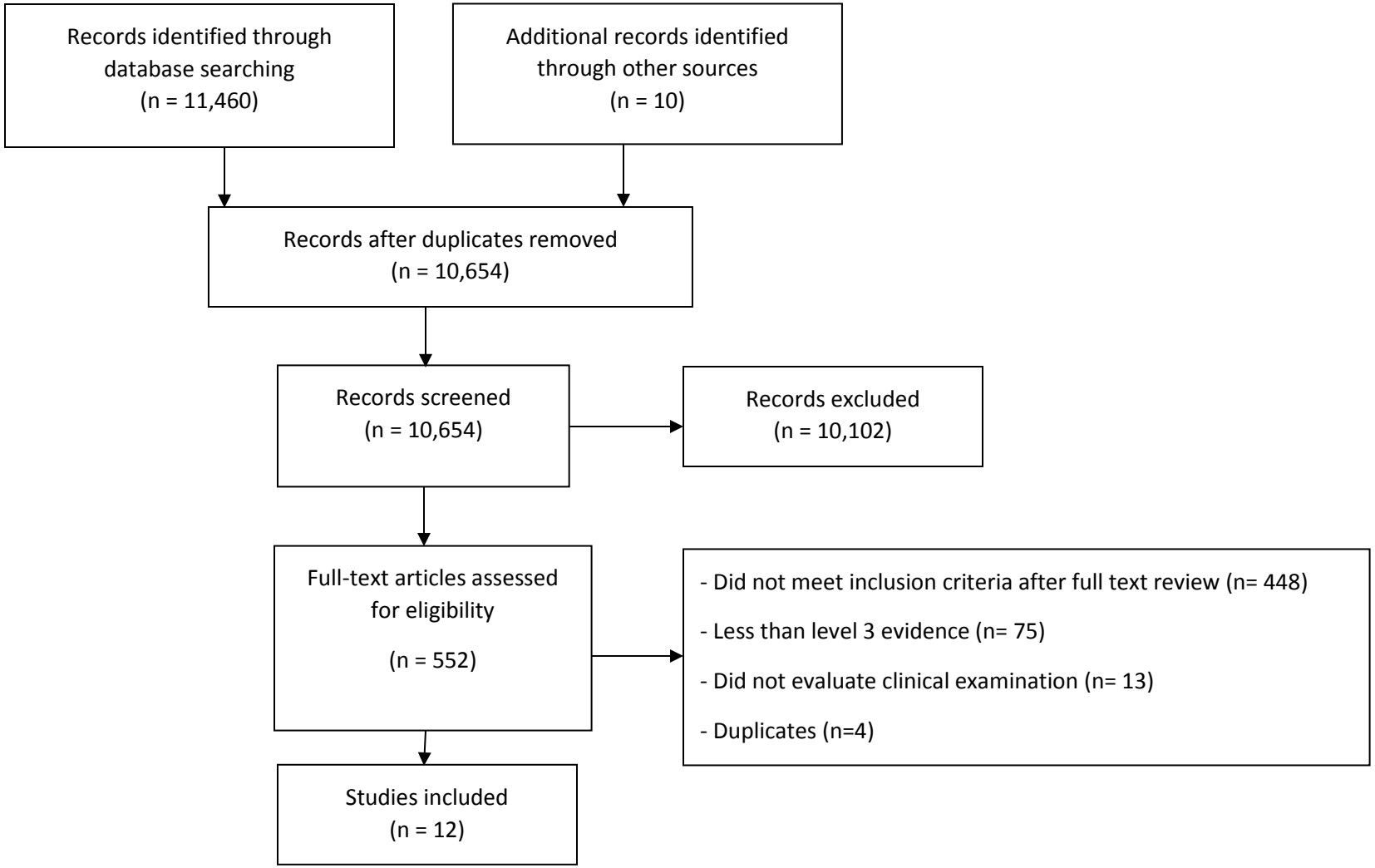
Supplementary Online Content

Albassam OT, Redelmeier RJ, Shadowitz SS, Husain AM, Simel DL, Etchells E. Did this patient have cardiac syncope? the rational clinical examination systematic review. *JAMA*. doi:10.1001/jama.2019.8001

This supplementary material has been provided by the authors to give readers additional information about their work.

efigure1. PRISMA Flow Diagram



eTable1. Description of Included Studies

Study	LOE	Prospective	Consecutive	N	Patients and Setting	Index Test	Reference Standard	Reference Standard Diagnoses
Sheldon 2006[1]	3	Yes	Yes	418	Patients with one or more loss of consciousness referred to specialty clinics and hospital cardiology wards in Canada and Wales	Syncope symptom questionnaire completed by patients and double checked for completion by study coordinators	Documented arrhythmia at time of syncope or shortly afterwards, or during electrophysiologic study Documented structural heart disease (aortic stenosis or pulmonary embolism) Tilt Table Test diagnostic of vasovagal syncope or orthostatic hypotension	21% 'secondary syncope" mostly due to documented arrhythmia; this category included 2% with cough syncope, autonomic failure, or hypersensitive carotid sinus syndrome 56% had positive tilt tablet test diagnostic of reflex/vasovagal syncope 23% unknown excluded from analysis
Pfister 2012[2]	1	Yes	Yes	161	Patients with main diagnosis of syncope admitted to a cardiology service in Cologne Germany	NT-pro-BNP	Specific testing was initiated by the treating physician guided by the recent recommendation of the European Society of Cardiology for the evaluation of syncope. Cause of syncope was defined by two independent cardiologists.	48% cardiac syncope 15% reflex syncope 10% orthostatic hypotension 17% unknown 9% non syncopal event
Pfister 2009[3]	2	Yes	Yes	61	Patients with main diagnosis of syncope admitted to an internal medicine service in Cologne Germany	NT-pro-BNP	Specific testing was initiated by the treating physician guided by the recent recommendation of the European Society of Cardiology for the evaluation of syncope. Cause of syncope was defined on the basis of all test results by two independent cardiologists.	33% cardiac syncope 26% reflex syncope 15% orthostatic hypotension 18% unknown 5% non syncopal event 3% cerebrovascular
Karaman 2015[4]	1	Yes	Yes	206	Patients with syncope referred within 24 hour of symptom initiation in three emergency departments in Iran	Clinical exam by a single emergency medicine resident. EKGs	Final decision on the cause of syncope was made based on the results of echocardiography, stress testing, prolonged Holter ECG monitoring, and electrophysiological study.	56% cardiac syncope 40% non-cardiac 4% unknown; excluded from analysis

						interpreted by an independent cardiologist.	In cases of normal cardiac evaluations, probable neurologic causes were ruled out using tilt testing, brain imaging, and carotid massage	
Del Rosso 2008[5]	3	Yes	Yes	516	Patients presenting to an emergency department with transient loss of consciousness within 24 hours of the episode to 14 emergency departments in Italy	Trained physician using decision-making software based on the European Society of Cardiology guidelines. EKG evaluated by emergency physician and study cardiologist	Diagnostic criteria as per the, European Society of Cardiology 2004.	15% cardiac 67% reflex (neurally mediated) 10% orthostatic hypotension 2.5% unexplained
Del Rosso 2005[6]	3	Uncl ear	Yes	485	Patients referred for evaluation of unexplained syncope within the previous 2 months to 4 syncope units in Italy	Standardized clinical assessment by study personnel.	mechanical cardiac syncope in the presence of severe valvular stenosis or other outflow obstruction; arrhythmic syncope diagnosed by electrocardiographic findings or ambulatory electrocardiographic recording electrophysiologic study	24% cardiac 61% reflex (neurally mediated) 2% orthostatic hypotension 15% unexplained excluded from the analysis
Galizia 2009[7]	3	No	Yes	242	Patients 65 years or older admitted for syncope to six hospitals in Italy	Structured clinical history, physical exam and EKG by study personnel at specialized syncope units	all suspected episodes of cardiac syncope were evaluated following a standardized cardiovascular assessment.	14% cardiac 72% non cardiac 10% unknown; excluded 5% non syncopal excluded
Christ 2015[8]	1	Yes	Yes	360	Patients with syncope or presyncope	high sensitivity	Cardiac cause of syncope including dysrhythmia or structural	22% cardiac 40% reflex 20% orthostatic hypotension

					presenting to an emergency room in Germany.	cardiac troponin T	disease of the heart based on published diagnostic criteria	17% unexplained; included in analysis
Romme 2009[9]	3	Yes	Yes	430	Patients with transient loss of consciousness presenting to any department at an Academic medical center, excluded 73 patients with known cardiomyopathy, MI or seizures	Calgary vasovagal score variables obtained by attending physicians	Selected testing as per European Society of Cardiology guidelines, plus all patients received 2 year follow up review by study personnel, with selected expert review of uncertain cases (19% of initial cohort) at 2 years	7% cardiac 55% vasovagal syncope 10% other reflex syncope 12% unknown cause - excluded 6% psychogenic pseudosyncope 1% neurologic/ metabolic causes
Stryjewski 2018[10]	2	Yes	Yes	100	Patients admitted to emergency room because of syncope	NT-pro-BNP	All patients had a history, physical, EKG, 24 hour EKG, tilt table test and echocardiogram.	50% cardiac 50% reflex syncope
Du Fay de Lavallez[11]	1	Yes	Yes	1338	Patients aged 40 years or older, and presenting to emergency with syncope within the last twelve hours,	EGSYS BNP NT pro BNP hs cTnT hs TnI	Excluded patients who did not have biomarkers measured (n=205) and patients where a final diagnosis could not be ascertained (n=134). Reference standard blinded to BNP but not troponin levels.	reflex (n=588, 39.9%), orthostatic (n=403, 27.3%), other non-cardiac (n=126, 8.6%) and syncope of unknown etiology (n=134, 9.1%).
Sheldon 2002[12]	3	Yes	Yes	671 (539 analyzed)	Patients with loss of consciousness recruited from specialty clinics and cardiology wards, 132 patients with unknown cause were excluded from analysis.	All patients completed a structured 118 item questionnaire	Documented arrhythmia at time of syncope or shortly afterwards, or during electrophysiologic study Documented structural heart disease (aortic stenosis or pulmonary embolism) Tilt Table Test diagnostic of vasovagal syncope or orthostatic hypotension. Seizure was only diagnosed if there was a diagnostic EEG.	25% cardiac 40% reflex syncope 20% syncope, unknown cause – excluded 15% seizure

LOE- level of evidence. Level 1 studies were prospective studies of at least 100 consecutive patients who underwent an independent comparison to a reference standard evaluation. Level 2 studies were similar to level 1 studies but with fewer than 100 patients. Level 3 studies were comparisons of patients to a reference standard that otherwise did not meet criteria for level 1-2 studies, such as retrospective studies, studies of non-consecutive patients, or studies where the independence between the test and reference standard could be inferred, but not confirmed, from the study methods.

eTable 2. QUADAS Assessments

Study	1.	2.	3.	4.	5.	If incomplete, state	6.	7.	8.	9.	10.	11.	12.	13.	14.	14a.	14b.	Level of Evidence
Sheldon 2006[1]	+	+	+	+/-	+/-	Only included patients with a verified diagnosis	+/-[a]	+/-	+	+	+/-	+/-	+	+	+	+	+/-	3
Pfister 2012[2]	+	+/-	+	+	+		+/-	+/-	+	+	+	+	+	+	+	+	+/-	1
Pfister 2009[3]	+	+/-	+	+/-	+		+/-	+	+	+	+	+	+	+	+	+	-	2
Kariman 2015[4]	+	+	+	+	+/-	198/206	+/-	+/-	+	+/-	+	+	+	+	+	+	-	1
Del Rosso 2008[5]	+	+	+	+	+/-	516/541	+	-	+	+	+/-	+/-	+	+/-	+	+	+/-	3
Del Rosso 2005[6]	+	+/-	+	+/-	+/-	Only report patients who had test and reference standard completed	+	+/-	+	+	+/-	+/-	+	-	-	+	+/-	3
Galizia 2009[7]	+/-	+/-	+/-	+	+		-	+/-	+	+	+/-	+	+	+	+	+	-	3
Christ 2015[8]	+	+	+	+	+/-	360/397	+	+/-	+	+	+	+	+	+	+	+	+/-	1
Romme 2009[9]	+	+	+	+	-	380/430	+	-	+	+	+	+/-	+	-	+	+	-	3
Stryjewski 2018[10]	+	+/-	+	+	+		+	+	+	+	+	+	+	+/-	+	+	+	2
Du Fay de Lavallez 2019[11]	+	+	+	+/-	+		+	+	+	+	+	+	+	+	+	+	-	1
Sheldon 2002[12]	+	+/-	+	+/-	-	Only included patients with a verified diagnosis	+/-	+/-	+	+	+	-	+	-	-	+	+/-	3

eTable 3 Legend

QUADAS Questions, *with clarifications/adaptations for our study in italics*

1. Was the spectrum of patients representative of the patients who will receive the test in practice?
    a. + = "The spectrum of patients included in this study was representative of those in whom the test will be used in practice. The judgement should be based on both the method of recruitment and the characteristics of those recruited."
    b. - = "Studies which recruit a group of healthy controls and a group known to have the target disorder" or "the population studied does not fit into what you specified as acceptable" *or studies which only examine patients with a specific type of syncope*
    c. +/- = "Insufficient information available to make a judgement"
2. Were selection criteria clearly described?
    a. + = "all relevant information regarding how participants were selected for inclusion in the study has been provided"
    b. - = "study selection criteria are not clearly reported"
    c. +/- = "not enough information to score this item as +"
3. Is the reference standard likely to correctly classify the target condition?
    a. + = "reference standard is likely to correctly classify the target condition or is the best method available"
        i. *Cardiac evaluation including (but not limited to) carotid sinus massage, holter monitor, loop recorder, tilt table testing, electrophysiologic testing, expert cardiology consultation*
        ii. *Neurologic evaluation including electroencephalography (EEG), sleep deprived EEG, neuroimaging (Ct scan or MRI of brain), expert neurologic consultation*
    b. - = "the reference standard was not likely to have correctly classified the target condition"
    c. +/- = "insufficient information to make a judgement"
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
    a. + = *Less than or equal to 30 days between reference standard and index test*
    b. - = "the time period between the performance of the index test and the reference standard was sufficiently long that disease status may have changed between the performance of the two tests" *>= 30 days*
    c. +/- = "insufficient information is provided"
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
    a. + = "all patients, or a random selection of patients, who received the index test went on to receive verification of their disease status using a reference standard"
        i. *100%*
    b. - = "some of the patients who received the index test did not receive verification of their true disease state, and the selection of patients to receive the reference standard was not random"
    c. +/- = "information is not reported by the study"
6. Did patients receive the same reference standard regardless of the index test result?
    a. + = "it is clear patients received verification of their true disease status using the same reference standard"
    b. - = "some patients received verification using a different reference standard"
    c. +/- = "information is not reported by the study"

7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?
    a. + = “it is clear from the study that the index test did not form part of the reference standard then this item”
    b. - = “appears the index test formed part of the reference standard”
    c. +/- = “information is not reported by the study”
8. Was the execution of the index test described in sufficient detail to permit replication of the test?
    a. + = “sufficient details or citations to permit replication of the index test”
    b. - = “other cases”
    c. +/- = “details of test performance are partially reported and you feel that you don’t have enough information to score this item”
9. Was the execution of the reference standard described in sufficient detail to permit its replication?
    a. + = “sufficient details or citations to permit replication of the reference standard”
    b. - = “other cases”
    c. +/- = “details of test performance are partially reported and you feel that you do not have enough information to score this item”
10. Were the index test results interpreted without knowledge of the results of the reference standard?
    a. + = “study clearly states that the test results (index or reference standard) were interpreted blind to the results of the other test”
    b. - = “this does not appear to be the case”
    c. +/- = “this information is not reported by the study”
11. Were the reference standard results interpreted without knowledge of the results of the index test?
    a. + = “study clearly states that the test results (index or reference standard) were interpreted blind to the results of the other test”
    b. - = “this does not appear to be the case”
    c. +/- = “this information is not reported by the study”
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
    a. + = “clinical data would normally be available when the test is interpreted in practice and similar data were available when interpreting the index test in the study” or vice versa
    b. - = “this is not the case”
    c. +/- = “information is not reported by the study”
13. Were uninterpretable/ intermediate test results reported?
    a. + = “it is clear that all test results, including uninterpretable/ indeterminate/intermediate are reported”
    b. - = “you think that such results occurred but have not been reported”
    c. +/- = “it is not clear whether all study results have been reported”
14. Were withdrawals from the study explained?
    a. + = “If it is clear what happened to all patients who entered the study, for example if a flow diagram of study participants is reported”
    b. - = “it appears that some of the participants who entered the study did not complete the study, i.e. did not receive both the index test and reference standard, and these patients were not accounted for”
    c. +/- = “Not clear whether all patients who entered the study were accounted for”
15. Did the study provide a clear definition of what was considered to be a ‘positive’ result?
    a. + = *Any citation or clinically sensible description of a ‘positive’ result*
    b. - = *no explanation of a ‘positive’ result*
    c. +/- = *Explanation of a ‘positive’ result lacks sufficient detail or is incomplete*

d. *Any citation or clinically sensible description = +, no requirement for kappa*

16. Was treatment withheld until both the index test and reference standard were performed?
    a. *This will generally by unsure for syncope studies. Accepting that up to 30 days may pass, we may not know what happens in those 30 days*
    b. *If there is definite evidence of cardiac surgery, electrophysiologic treatments, anti-rhythmic treatments, anti-seizure treatments or medication changes = -*

eTable 4 **. Patient Demographics**

Finding	Level of Evidence	N (with cardiac syncope)	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI
Age at first syncopal spell >35 yrs [1]	3	323 (88)	80	65	8	170	0.91 (0.85-0.97)	0.72 (0.66-0.78)
Atrial fibrillation or flutter[1]	3	323 (88)	11	4	77	231	0.13 (0.06-0.20)	0.98 (0.96-1.0)
History of heart failure[2]	1	161 (78)	32	10	46	73	0.41 (0.3-0.52)	0.88 (0.81-0.95)
Chronic heart failure (NYHA II-IV)[11]	1	1472 (221)	35	73	186	1178	0.16 (0.11-0.21)	0.94 (0.93-0.95)
Heart failure (combined)		1633 (299)					0.16-0.41	0.88-0.94
Hypertension[1]	3	323 (88)	32	26	56	209	0.36 (0.26-0.46)	0.89 (0.85-0.93)
Hypertension[11]	1	1472 (221)	153	728	68	523	0.69 (0.63-0.75)	0.42 (0.39-0.45)
Hypertension (combined)		1795 (309)					0.36-0.69	0.42-0.89
Severe structural heart disease[3]	2	61 (20)	7	3	13	38	0.35 (0.14-0.56)	0.93 (0.85-1.01)
Severe structural heart disease[2]	1	161 (78)	40	13	38	70	0.51 (0.4-0.62)	0.84 (0.76-0.92)
Severe structural heart disease (combined)		222 (98)					0.35-0.51	0.84-0.93

eTable 5 **Precipitating or predisposing factors**

Finding	Level of Evidence	N (with cardiac syncope)	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI
After using the toilet [1]	3	323 (88)	0	25	88	210	0 (0-0.03)	0.89 (0.85-0.93)
Headaches[1]	3	323 (88)	4	71	84	164	0.05 (0-0.09)	0.7 (0.64-0.76)
On the way to the toilet[1]	3	323 (88)	4	38	84	197	0.05 (0-0.09)	0.84 (0.79-0.89)
Pain or medical procedure[1]	3	323 (88)	5	113	83	122	0.06 (0.01-0.11)	0.52 (0.46-0.58)
Prolonged sitting/standing[1]	3	323 (88)	33	163	55	72	0.38 (0.28-0.48)	0.31 (0.25-0.37)
Stress[1]	3	323 (88)	7	76	81	159	0.08 (0.02-0.14)	0.68 (0.62-0.74)
Warm place[1]	3	323 (88)	8	129	80	106	0.09 (0.03-0.15)	0.45 (0.39-0.51)
During effort[2]	1	161 (78)	9	7	69	76	0.12 (0.05-0.19)	0.92 (0.86-0.98)
During effort[5]	3	260 (44)	6	2	38	214	0.14 (0.04-0.24)	0.99 (0.98-1.0)
During effort (combined)		421 (122)					0.12-0.14	0.92-0.99
While supine[2]	1	161 (78)	5	5	73	78	0.06 (0.01-0.11)	0.94 (0.89-0.99)
While supine[5]	3	260 (44)	6	6	38	210	0.14 (0.04-0.24)	0.97 (0.95-0.99)
While supine (combined)		421 (122)					0.06-0.14	0.94-0.97

eTable 6. Symptoms prior to syncope

Finding	Level of Evidence	N (with cardiac syncope)	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI
Chest pain[7]	3	208 (34)	2	3	32	171	0.06 (0-0.14)	0.98 (0.96-1)
Angina[11]	1	1472 (221)	23	62	98	1189	0.19 (0.12-0.26)	0.95 (0.94-0.96)
Chest pain/angina combined		1680 (255)					0.06-0.19	0.95-0.98
Dyspnea[7]	3	208 (34)	3	3	31	171	0.09 (0-0.19)	0.98 (0.96-1)
Dyspnea[2]	1	161 (78)	27	15	51	68	0.35 (0.24-0.46)	0.82 (0.74-0.9)
Dyspnea[3]	2	61 (20)	6	9	14	32	0.3 (0.1-0.5)	0.78 (0.65-0.91)
Dyspnea[5]	3	269 (44)	4	2	40	214	0.09 (0.01-0.17)	0.99 (0.98-1)
Dyspnea (combined)		699 (176)					0.18 (0.08-0.36)	0.95 (0.80-0.99)
Palpitations[2]	1	161 (78)	9	4	69	79	0.12 (0.05-0.19)	0.95 (0.9-1)
Palpitations[7]	3	208 (34)	1	6	33	168	0.03 (0-0.09)	0.97 (0.94-1)
Palpitations[1]	3	323 (88)	21	107	67	128	0.24 (0.15-0.33)	0.54 (0.48-0.6)
Palpitations[5]	3	260 (44)	4	2	40	214	0.09 (0.01-0.17)	0.99 (0.98-1)

Palpitations[6]	3	412 (116)	13	38	103	258	0.11 (0.05-0.17)	0.87 (0.83-0.91)
Palpitations[11]	1	1472 (221)	22	78	99	1173	0.18 (0.11-0.25)	0.94 (0.92-0.95)
Palpitations (combined)		2836 (581)					0.13 (0.09-0.19)	0.93 (0.82-0.98)
Abdominal discomfort[7]	3	208 (34)	1	13	33	161	0.03 (0-0.09)	0.93 (0.89-0.97)
Awareness of being about to faint[7]	3	208 (34)	4	59	30	115	0.12 (0.01-0.23)	0.66 (0.59-0.73)
Awareness of being about to faint[6]	3	412 (116)	44	106	72	190	0.38 (0.29-0.47)	0.64 (0.59-0.69)
Awareness of being about to faint (combined)		620 (150)					0.12-0.38	0.64-0.66
Abdominal discomfort[1]	3	323 (88)	3	38	85	197	0.03 (0-0.07)	0.84 (0.79-0.89)
Absence of prodromes[4]	1	198 (115)	37	9	78	74	0.32 (0.23-0.41)	0.89 (0.82-0.96)
Absence of prodromes[2]	1	161 (78)	37	45	41	38	0.47 (0.36-0.58)	0.46 (0.35-0.57)
Absence of prodromes[5]	3	260 (44)	23	56	21	160	0.52 (0.37-0.67)	0.74 (0.68-0.80)
Absence of prodromes[6]	3	412 (116)	52	86	64	210	0.45 (0.36-0.54)	0.71 (0.66-0.76)
Absence of prodromes (combined)		1031 (353)					0.43 (0.35-0.51)	0.73 (0.55-0.86)
Auditory distortion[1]	3	323 (88)	12	84	76	151	0.14 (0.07-0.21)	0.64 (0.58-0.70)

Blurred vision[1]	3	323 (88)	27	126	61	109	0.31 (0.21-0.41)	0.46 (0.4-0.52)
Blurred vision[4]	1	198 (115)	11	29	104	54	0.1 (0.05-0.15)	0.65 (0.55-0.75)
Blurred vision[7]	3	208 (34)	1	45	33	129	0.03 (0-0.09)	0.74 (0.67-0.81)
Blurred vision[6]	3	412 (116)	30	31	86	265	0.26 (0.18-0.34)	0.9 (0.87-0.93)
Blurred vision[5]	3	260 (44)	8	68	36	148	0.18 (0.07-0.29)	0.69 (0.63-0.75)
Blurred vision (combined)		1401 (397)					0.16 (0.09-0.28)	0.71 (0.56-0.83)
Diaphoresis[7]	3	208 (34)	2	50	32	124	0.06 (0-0.14)	0.71 (0.64-0.78)
Diaphoresis[6]	3	412 (116)	16	83	100	213	0.14 (0.08-0.2)	0.72 (0.67-0.77)
Diaphoresis[5]	3	260 (44)	6	80	38	136	0.14 (0.04-0.24)	0.63 (0.57-0.69)
Diaphoresis[11]	1	1472 (221)	47	405	174	846	0.21 (0.16-0.27)	0.68 (0.65-0.70)
Diaphoresis (combined)		2352 (415)					0.18 (0.09-0.35)	0.63 (0.47-0.77)
Feeling cold[6]	3	412 (116)	2	33	114	263	0.02 (0-0.05)	0.89 (0.85-0.93)
Headache[1]	3	323 (88)	3	46	85	189	0.03 (0-0.07)	0.8 (0.75-0.85)
Less than 5 s warning[1]	3	323 (88)	58	91	30	144	0.66 (0.56-0.76)	0.61 (0.55-0.67)
Duration of prodromes less than or equal to 10 seconds[6]	3	412 (116)	93	200	23	96	0.8 (0.73-0.87)	0.32 (0.27-0.37)

Lightheadedness[6]	3	412 (116)	9	60	107	236	0.08 (0.03-0.13)	0.8 (0.75-0.85)
Mood changes or prodromal pre-occupation with details [1]	3	323 (88))	2	57	86	178	0.02 (0-0.05)	0.76 (0.71-0.81)
Nausea[6]	3	412 (116)	7	45	109	251	0.06 (0.02-0.1)	0.85 (0.81-0.89)
Nausea[7]	3	208 (34)	2	37	32	137	0.06 (0-0.14)	0.79 (0.73-0.85)
Nausea or vomiting[2]	1	161 (78)	7	15	71	68	0.09 (0.03-0.15)	0.82 (0.74-0.9)
Nausea or vomiting[1]	3	323 (88)	17	102	71	133	0.19 (0.11-0.27)	0.57 (0.51-0.63)
Nausea or vomiting[5]	3	260 (44)	3	76	41	140	0.07 (0-0.15)	0.65 (0.59-0.71)
Nausea or vomiting[11]	1	1472(221)	42	384	179	867	0.19 (0.14-0.24)	0.69 (0.67-0.72)
Nausea (combined)		2836 (581)					0.11 (0.07-0.18)	0.74 (0.65-0.81)
Numbness or tingling[1]	3	323 (88)	8	65	80	170	0.09 (0.03-0.15)	0.72 (0.66-0.78)
Pallor[1]	3	323 (88)	42	166	46	69	0.48 (0.38-0.58)	0.29 (0.23-0.35)
Pallor[7]	3	208 (34)	1	15	33	159	0.03 (0-0.09)	0.91 (0.87-0.95)
Pallor[11]	1	1472 (221)	45	356	176	895	0.20 (0.15-0.26)	0.72 (0.69-0.74)
Pallor (combined)		2003 (343)					0.22 (0.08-0.48)	0.69 (0.34-0.90)

Sweating or warm feeling[1]	3	323 (88)	21	146	67	89	0.24 (0.15-0.33)	0.38 (0.32-0.44)

eTable 7. **Witnessed During The Episode**

Finding	Level of Evidence	N	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Myoclonic movements	3	412 (116)	10	20	106	276	0.09 (0.04-0.14)	0.93 (0.9-0.96)
(Evaluated in presence of witness)[6]								
Cyanotic during syncope[1]	3	323 (88)	7	3	81	232	0.08 (0.02-0.14)	0.99 (0.98-1.0)

eTable 8. **After The Syncope**

Finding	Level of Evidence	N	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI
Injury[3]	2	61 (20)	5	8	15	33	0.25 (0.06-0.44)	0.80 (0.68-0.92)
Caused Injury[11]	1	1472 (221)	35	176	186	1075	0.16 (0.11-0.21)	0.86 (0.84-0.88)
Caused injury (combined)		1533 (241)					0.16-0.25	0.80-0.86
Mood changes[1]	3	323 (88)	3	39	85	196	0.03 (0-0.07)	0.83 (0.78-0.88)
Numbness or tingling[1]	3	323 (88)	5	43	83	192	0.06 (0.01-0.11)	0.82 (0.77-0.87)
Cannot remember behaviour during syncope[1]	3	323 (88)	4	42	84	193	0.05 (0-0.09)	0.82 (0.77-0.87)
Nausea[6]	3	412 (116)	7	47	109	249	0.06 (0.02-0.10)	0.84 (0.8-0.88)
Nausea or vomiting[1]	3	323 (88)	9	83	79	152	0.10 (0.04-0.16)	0.65 (0.59-0.71)
Nausea (combined)		735 (204)					0.06-0.10	0.65-0.84
Abnormal ECG[2]	1	161 (78)	54	24	24	59	0.69 (0.59-0.79)	0.71 (0.61-0.81)
Abnormal ECG [3,]	2	61 (20)	8	12	12	29	0.40 (0.19-0.61)	0.71 (0.57-0.85)
Abnormal ECG (combined)							0.40-0.69	0.71-0.71

Abnormal EKG: intraventricular conduction block (QRS duration >/= 0.12 sec), Mobitz second or third degree AV block, asymptomatic bradycardia, sinoatrial block or sinus pause (./= 3 seconds), Q waves suggesting prior myocardial infarction, signs of myocardial hypertrophy, atrial fibrillation/flutter, pre-excited QRS complexes, and short or long Qt interval.[2,,3]

eTable 9. **Combinations of Findings**

	Level of Evidence	N	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI
any of: bifascicular block, asystole, diabetes, supraventricular tachycardia[1]	3	323 (88)	56	8	32	227	0.64 (0.54-0.74)	0.97 (0.95-0.99)
Heart disease, or abnormal ECG , or both[4]	1	198 (115)	101	32	14	51	0.88 (0.82-0.94)	0.61 (0.51-0.71)
EGSYS >=3[4]	1	198 (115)	105	20	10	53	0.91 (0.86-0.96)	0.73 (0.63-0.83)
EGSYS >=3[5]	3	258 (35)	31	70	4	153	0.89 (0.79-0.99)	0.69 (0.63-0.75)
EGSYS >=3 (combined)		456 (150)					0.89-0.91	0.69-0.73
Vasovagal score less than -2[1]	3	323 (88)	80	25	8	210	0.91 (0.85-0.97)	0.89 (0.85-0.93)
Vasovagal score less than -2[9]	3	380 (28)	9	67	19	285	0.32 (0.15-0.49)	0.81 (0.77-0.85)
Vasovagal score less than -2 (combined)		703 (116)					0.32-0.91	0.81-0.89

[4]Abnormal EKG defined as: bradycardia <40 beat/minute, , St changes (>1 mm elevation or depression), QT prolongation (440 ms), ventricular tachycardia, atrioventricular block (second or third degree), sick sinus syndrome, ventricular and rapid paroxysmal supraventricular arrhythmias, sinus pauses, and pace malfunction.

eTable 10. **Biomarkers**

	Level of Evidence	N	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI
Elecsys proBNP assay, Roche Diagnostics, NT-pro-BNP (> 156pg/ml)[2]	1	161 (78)	70	40	8	43	0.90 (0.83-0.97)	0.52 (0.41-0.63)
Elecsys proBNP assay, Roche Diagnostics, NT-pro-BNP ≥164 pg/ml[3]	2	61 (20)	18	21	2	20	0.90 (0.77-1.0)	0.49 (0.34-0.64)
Roche, NT-pro-BNP (>/= 210.5 pg/ml)[10]	2	100 (50)	47	1	3	49	0.94 (0.87 -1.0)	0.98 (0.94-1.0)
Elecsys proBNP (Roche Diagnostics)[11]	1							
> 1966pg/ml		1338 (221)	62	54			LR 5.8 (4.2-8.1) [a]	
>/= 69- </=1966pg/ml			148	708			1.1 (1.0-1.2)	
< 69pg/ml			11	355			0.16 (0.09-0.28)	
Architect BNP assay BNP[11]	1							
>302pg/ml		1338 (221)	69	55			LR 6.3 (4.6-8.8)[a]	
>/= 15 - </= 302pg/ml			141	785			0.91 (0.82-1.0)	
< 15pg/ml			11	277			0.20 (0.11-0.40)	
hs-cTnT Roche assay > 14 ng/L[8]	1	360 (80)	59	89	21	191	0.74 (0.64-0.84)	0.68 (0.63-0.73)
hs-cTnT Roche assay[11]	1							
>42 pg/ml		1338 (221)	55	55			LR 5.1 (3.6-7.1)	
>/= 5 - </= 42pg/ml			158	798			1.0 (0.91-1.1)	
< 5pg/ml			8	264			0.15 (0.08-0.31)	
ARCHITECT High Sensitive STAT Troponin I assay (Abbott Laboratories)[11]	1							
> 31.3pg/ml		1338 (221)	59	55			LR 5.4 (3.9-7.6) [a]	
>/=2.2 - </=31.3pg/ml			153	810			0.96 (0.87-1.1)	
< 2.2pg/ml			9	252			0.18 (0.10-0.35)	

[a] For ordinal results with 3 or more levels, sensitivity and specificity no longer apply. The serial LR are shown for each threshold level.

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