APPENDIX D1 - CHARACTERISTICS OF INCLUDED STUDIES

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1.2 Decision rules for diagnosis review

1.3 Initial symptoms for risk stratification (death) review

1.4 Initial symptoms for risk stratification review

1.5 Decision rules for risk stratification (death) review

1.6 Decision rules for risk stratification review

1.7 Decision rules for recurrence of TLoC review

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1 Initial Assessment – included studies table

1.1 Initial symptoms for diagnosis review

<table>
<thead>
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<th>Study</th>
<th>Participants</th>
<th>Diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alboni 2001 prospective cohort study; study held in Italy.</td>
<td>TLoC population: unclear/not stated. Prior tests: Unclear or Not stated. Consecutive patients with a syncopal episode in the previous 2 months; unclear who referred to syncope unit. Definition of TLoC: Brief, self limited loss of consciousness with the inability to maintain postural tone.</td>
<td>Index test: initial evaluation questionnaire (46 items); history taking; physical and neurological examinations; bp in supine and standing positions; 12 lead ECG; time: within 2 months of episode (n=356)</td>
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<td>Inclusion criteria: Age 18 and over; TLoC referred to Syncope unit.</td>
<td>Reference standard: initial evaluation + other test results (ECG, echo, exercise test, CSM, tilt test, Electrophysiologic study, pulmonary scintigraphy, EEG, ATP test - given according to suspected cause); time: unclear time (n=341)</td>
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<td>Other details: referrals from ED, inpatients and outpatients.</td>
<td>for Target Condition/Outcome: cardiac or NM syncope cause</td>
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<td>Other study comments: Unexplained cause 60/341 (18%)</td>
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<tr>
<td>del Rosso 2008 cross sectional study index 1st; study held in Italy.</td>
<td>TLoC population: unselected patients. Prior tests: Unclear or Not stated. Consecutive patients admitted. Definition of TLoC: stated to be syncope (other causes excluded).</td>
<td>Index test: Signs and symptoms from standardised assessment (palpitations preceding syncpe, heart disease/abnormal ECG, syncope during effort, syncope while supine, precipitating factors, autonomic prodromes (N &amp; V); time: initial (n=256)</td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria: not stated.</td>
<td>Reference standard: initial ECG + ECG monitoring or 24h Holter or during electrophysiologic study; time not stated (n=256)</td>
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<td></td>
<td>Other details: Patients aged less than 18 years and those referred more than 24h after their episode. Patients with a non-syncopal cause of LoC (as seizures, drop attacks, transient ischaemic attacks).</td>
<td>for Target Condition/Outcome: Mechanical: severe valvar stenosis or other flow obstruction, or acute myocardial ischaemia. Arrhythmias: bradycardia &lt;40bpm/repetitive sinoatrial blocks/sinus pause &gt;3s. 2nd or 3rd AV block; SVT or VT, etc.</td>
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<td>Other study comments: Validation cohort. Prospective</td>
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Transient loss of consciousness: full guideline DRAFT (January 2010)
<table>
<thead>
<tr>
<th><strong>Study</strong></th>
<th><strong>Participants</strong></th>
<th><strong>Diagnostic tests</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Graf 2008</strong>&lt;br&gt;cross sectional&lt;br&gt;study index 1st; study held in Switzerland.</td>
<td>TLoC population: selected patients with unexplained syncope or presyncope. Prior tests: All patients had at least 1 prior test. consecutive outpatients referred to syncope clinic. Definition of TLoC: brief, self-limited loss of consciousness with the inability to maintain postural tone. Presyncope was a near syncopal event. tilt test, supine &amp; upright CSM, continuous.</td>
<td>Index test: initial symptoms determined from patient history, physical exam, 12-lead ECG; time: initial (n=175) Reference standard: 12-lead ECG, positive bp, adenosine triphosphate &amp; dinitrate isosorbide, hyperventilation test, psychiatrist evaluation, stress test, echo, coronary angiography, electrophysiology; time (n=317) for Target Condition/Outcome: Different causes of TLoC: arrhythmias (including bradyarrhythmias (AV block, cardioinhibitory CSS) and tachyarrhythmias (SVT and VT); vasovagal (tilt induced) syncope &amp; psychogenic pseudosyncope; orthostatic hypotension and vasodilative CSS.</td>
</tr>
<tr>
<td><strong>Sarasin 2003</strong>&lt;br&gt;cross sectional&lt;br&gt;study index 1st; study held in Switzerland.</td>
<td>TLoC population: selected patients with partly unexplained cause after initial stage. Prior tests: All patients had at least 1 prior test. patients with syncope as chief complaint, for whom there was no clear suspicion of the cause of syncope from initial tests (history, physical examination, bp measurements, 12-lead ECG). Identified by investigator from daily visits.</td>
<td>Index test: initial symptoms derived from age &gt;65y, history of congestive heart failure, abnormal ECG; time: initially (n=175) Reference standard: Diagnostic tests performed and interpreted by cardiologists: echocardiography, ambulatory ECG (24h Holter or event recorder) and electrophysiological studies to detect arrhythmias in presence of syncope or near syncope; time not stated (n=175) for Target Condition/Outcome: Arrhythmias, incl: AF, sinus pause ≥2 &amp; &lt;3s; bradycardia &gt;55bpm &amp; ≤45; conduction disorders; signs of old MI or VH; multiple premature ventricular beats; prolonged corrected sinus node recovery time (≥250ms); prolonged H-T interval (≥100ms); SVT 180bpm.</td>
</tr>
</tbody>
</table>
Study  | Participants  | Diagnostic tests
---|---|---
Sheldon 2002 prospectively conducted study; study held in Canada.  
Setting: Hospital several departments. university and private practice neurology and cardiology clinics; pacemaker, arrhythmia and syncope clinics; and hospital cardiology wards (i.e tertiary referral and acute care facilities only).  
Funding: Grants from Medtronic; validation by same group that developed decision rule  
TLoC population: selected patients with TLoC of mixed known causes. Prior tests: All patients had 1 prior test. Diagnosis established: not if had >1 plausible cause of TLoC; sample randomly divided to allow validation  
Definition of TLoC: Loss of consciousness and loss of control of posture.  
Inclusion criteria: loss of consciousness and diagnosis established according to preset criteria.  
Exclusion criteria: patients with more than 1 plausible cause of syncope; people with pseudosyncope.  
Patient characteristics: age: seizure pts 35 (SD 12 years) syncope 53 (SD20) p<0.001; sex: seizure pts 44% men; syncope 55% p=0.062; some patients with existing heart disease (146/671 structural heart disease); history of TLoC: some patients; some had >30 Comorbidities: not stated. Other details: overall sample: 267/671 vasovagal; 90 VT; 40 complete heart block; 22 SVT; 4 sick sinus; 4 hypertensive carotid sinus syndrome; 3 aortic stenosis; etc  
Other study comments: Seizure patients only included if had diagnostic EEG may have created bias. Patients required to recall symptoms (unclear over what time period). Tertiary referral clinics and acute care facilities only.  
Index test: initial symptoms and patient history; time: initially (n=268)  
Reference standard: positive tilt test for vasovagal and orthostatic hypotension; ECG/electrophysiology for arrhythmias/heart block (diagnosis also included palpitations pre-syncope); EEG; time unclear (n=268)  
Comparator test: initial evaluation symptoms + history: as above but no. of spells and length of history of LoC and lightheaded spells also included; time: initially (n=268).  
for Target Condition/Outcome: Seizure diagnosis if patients had diagnostically positive EEGs
1.2 Decision rules for diagnosis review

Diagnostic Test: ACEP guidelines

**Study**
Elseber 2005 retrospective cohort study; study held in USA.

**Participants**
TLoC population: unselected patients. Prior tests: Unclear or Not stated.

Retrospective records of all patients presenting to ED with a diagnosis of mental status change, light headedness, spells, syncope, presyncope or LoC were screened. Only syncope included Definition of TLoC: Sudden and temporary loss of consciousness and postural tone with spontaneous recovery.

Inclusion criteria: 18 years or older having had syncope.

Exclusion criteria: Patients requiring chemical or electrical cardioversion.

Patients who had light-headedness, dizziness, vertigo, presyncope, coma, shock, spells, fall, typical seizure presentation or recurrence of known seizure or other states of altered mentation.

Other study comments: 180/200 (90%) had an ECG. Actual admission rate 57.5%; level B rate: 28.5%; level B + C rate: 71.0%

**Diagnostic tests**
Index test: ACEP guidelines for admission, higher risk group - from records (history; physical examination; ECG findings); time: initially (n=200; but 180 with ECG)

Reference standard: cardiac tests including initial ECG, plus Holter monitoring or event recording or electrophysiological testing, or cardiac catheterisation or echocardiography; time at the ED, the hospital or an outpatient clinic; follow up 4.9 years (SD 1.9) (n=200)

Comparator test: ACEP guidelines for admission, medium risk group - from records (history; physical examination; ECG findings); time: initially (n=200).

Other comparator tests: 3) ED physicians admission criteria.

for Target Condition/Outcome:
Bradyarrhythmias (rate < 40 bpm; pauses > 3s; high degree AV block); sinus node dysfunction (corrected recovery time >550ms). VTs (prolonged, non-sustained or sustained), SVTs (symptomatic, AF or flutter) and aortic stenosis

Diagnostic Test: EGYS score

**Study**
Del Rosso 2008 cross sectional study index 1st; study held in Italy.

**Participants**
TLoC population: unselected patients. Prior tests: Unclear or Not stated.

Consecutive patients admitted to the ED

Definition of TLoC: stated to be syncope (other causes excluded).

Inclusion criteria: not stated.

Exclusion criteria: Patients aged less than 18 years and those referred more than 24h after their episode. Patients with a non-syncope cause of LoC (as seizures, drop attacks, transient ischaemic attacks).

Patient characteristics: age: mean 63 years (SD 22); sex: 121/256 male (47%); some patients with existing heart disease (29% structural heart disease); history of TLoC: 24% with history of pre-syncope. Mean no. of syncopal episodes: 3 (SD 5)

Comorbidities: not stated. Other details: Final diagnosis: 14% cardiac syncope; 70% neurally mediated syncope; 10% orthostatic hypotension; 4% non-syncope attacks; 3% unexplained

Other study comments: Validation cohort. Prospective

**Diagnostic tests**
Index test: EGYS symptom score based on ESC: standardised assessment (palpitations preceding syncope, heart disease/abnormal ECG, syncope during effort, syncope while supine, precipitating factors, autonomic prodomes (N & V); time: initial (n=256)

Reference standard: initial ECG + ECG monitoring or 24h Holter or during electrophysiological study; time not stated (n=195)

for Target Condition/Outcome:
Mechanical: severe valvular stenosis or other flow obstruction, or acute myocardial ischaemia. Arrhythmias: bradycardia <40bpms/repetitive sinoatrial blocks/sinus pause >3s, 2nd or 3rd AV block, SVT or VT, etc.
# Diagnostic Test: ESC guidelines

**Study**

<table>
<thead>
<tr>
<th>van Dijk 2008</th>
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<tbody>
<tr>
<td>prospective cohort study; study held in The Netherlands.</td>
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</table>

**Participants**

TLoC population: unselected patients. Prior tests: Some patients had 1 prior test.

consecutive adult patients presenting with TLoC to any department of University hospital

Definition of TLoC: Self limited TLoC not due to head trauma.

**Setting**: Hospital several departments.

**Comorbidities**:

Patient characteristics: age: mean 53 years (SD 19); sex: 56% male; some patients with existing heart disease (10% previous MI; 3% heart failure; 13% rhythm disturbances; 22% hypertension (may be in >1 category)); history of TLoC: median 3 (IQR 1-8) previous episodes; 2 (1-3) in year before presentation

Comorbidities: 10% previous MI; 3% heart failure; 13% rhythm disturbances; 22% hypertension; 7% cerebrovascular accident; 7% diabetes (may be in >1 category). Other details: 64% had had previous consultations with: GP (30%); cardiologist (31%); internist (7%); neurologist (26%); psychiatrist (1%); other (6%) and many were referred from GP or other hospitals; many ED pts were acute

Other study comments: 33% had trauma due to syncopal episode; initial evaluation led to 'certain' and 'highly likely' diagnoses; 35% had recurrences during follow up; 40 died and 5 lost to follow up

**Diagnostic tests**

Index test: initial evaluation based on ESC guidelines: standardised history taking (ESC); physical exam (pulse; bp supine & after 3min upright; cardiac auscultation) in 97% pts; 12 lead ECG (84% pts); time: initially (n=503; 424 got all 3)

Reference standard: questionnaire after 1y & at least 2 y on recurrence & additional tests/treatment then review of records re subsequent evaluations, hospital admissions & other events. Final diagnosis using these & ESC criteria + expert panel if disagree (95 pts); time 2 year follow up (mean 31.6 months) (n=458)

for Target Condition/Outcome: all causes; diagnosis obtained from follow up outcomes and additional diagnostic tests; cardiac syncpe (arrhythmias + structural cardiopulmonary conditions; reflex syncope; orthostatic hypotension; neurological diagnosis (epilepsy, brain tumour, stroke, vascular steal; psychiatric diagnosis

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# Diagnostic Test: Initial symptoms decision rule

**Study**

<table>
<thead>
<tr>
<th>Graf 2008</th>
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<tbody>
<tr>
<td>cross sectional study index 1st; study held in Switzerland.</td>
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</tbody>
</table>

**Participants**

TLoC population: selected patients with unexplained syncpe or presyncope.

Prior tests: All patients had at least 1 prior test.

consecutive outpatients referred to syncpe clinic

Definition of TLoC: brief, self-limited loss of consciousness with the inability to maintain postural tone. Presyncope was a near syncopal event.

Inclusion criteria: patients with unexplained syncope or presyncope.

Exclusion criteria: patients with symptoms compatible with: seizure disorders, vertigo, dizziness or coma

Patient characteristics: age: not stated; sex: not stated; some patients with existing heart disease (17% coronary artery disease); history of TLoC: Not stated

Comorbidities: not stated. Other details: Final diagnosis: 9% cardiac arrhythmias (7% tachyarrhythmia, 2% AV block); 48% neurally mediated syncope; 3% orthostatic hypotension; 2% miscellaneous; 21% unexplained

Other study comments: Validation cohort

**Diagnostic tests**

Index test: initial symptoms determined from patient history, physical exam, 12-lead ECG; Arrhythmia rule; time: initial (n=65)

Reference standard: 12-lead ECG, positive tilt test, supine & upright CSM, continuous bp, adenosine triphosphate & dinitrate isosorbide, hyperventilation test, psychiatrist evaluation, stress test, echo, coronary angiography, electrophysiology; (n=65)

for Target Condition/Outcome: Different causes of TLoC: arrhythmias (including bradyarrhythmias (AV block, cardioinhibitory CSS) and tachyarrhythmias (SVT and VT); vasovagal (tilt induced) syncope & psychogenic pseudosyncope; orthostatic hypotension and vasodilative CSS
## Diagnostic Test: Initial symptoms decision rule

### Study

<table>
<thead>
<tr>
<th>Study</th>
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<th>Diagnostic tests</th>
</tr>
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<tbody>
<tr>
<td>Sarasin 2003</td>
<td>TLoC population: selected patients with partly unexplained cause after initial stage. Prior tests: All patients had at least 1 prior test. Patients with syncope as chief complaint, for whom there was no clear suspicion of the cause of syncope from initial tests (history, physical examination, bp measurements, 12-lead ECG). Identified by investigator from daily visits.</td>
<td>Index test: risk score derived from age &gt;65y, history of congestive heart failure, abnormal ECG; time: initially (n=267)</td>
</tr>
<tr>
<td>Setting: Emergency Department. ED in primary and tertiary care main teaching hospital between 1989 and 1991.</td>
<td>Definition of TLoC: Sudden transient loss of consciousness with an inability to maintain postural tone and with spontaneous recovery.</td>
<td>Reference standard: Diagnostic tests performed and interpreted by cardiologists: echocardiography, ambulatory ECG (24h Holter or event recorder) and electrophysiological studies to detect arrhythmias in presence of syncope or near syncope; time not stated (n=267)</td>
</tr>
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<td>Sheldon 2002</td>
<td>TLoC population: selected patients with TLoC of mixed known causes. Prior tests: All patients had 1 prior test. Diagnosis established; not if had &gt;1 plausible cause of TLoC; sample randomly divided to allow validation</td>
<td>Index test: Decision rule based on symptoms alone with positive and negative scoring items; pts classified as having seizures if points score ≥1; time: initially (n=268)</td>
</tr>
<tr>
<td>prospective cohort study; study held in Canada.</td>
<td>Definition of TLoC: Loss of consciousness and loss of control of posture.</td>
<td>Reference standard: positive tilt test for vasovagal and orthostatic hypotension; ECG/electrophysiology for arrhythmias/heart block (diagnosis also included palpitations pre-syncope); EEG; time unclear (n=268)</td>
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<td>Setting: Hospital several departments. University and private practice neurology and cardiology clinics; pacemaker, arrhythmia and syncope clinics; and hospital cardiology wards (i.e. tertiary referral and acute care facilities only).</td>
<td>Inclusion criteria: loss of consciousness and diagnosis established according to preset criteria. Exclusion criteria: patients with more than 1 plausible cause of syncope; people with pseudosyncope.</td>
<td>Comparator test: initial evaluation symptoms + history: as above but no. of spells and length of history of LoC and lightheaded spells also included; time: initially (n=268).</td>
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<td>Funding: Grants from Medtronic; validation by same group that developed decision rule</td>
<td>Patient characteristics: age; seizure pts 35 (SD 12 years) syncpe 53 (SD20) p&lt;0.001; sex; seizure pts 44% men; syncpe 55% p=0.062; some patients with existing heart disease (146/671 structural heart disease); history of TLoC: some patients; some had &gt;30</td>
<td>for Target Condition/Outcome: Seizure diagnosis if patients had diagnostically positive EEGs</td>
</tr>
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</table>

### Participants

#### Study

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<td>Sarasin 2003</td>
<td>TLoC population: selected patients with partly unexplained cause after initial stage. Prior tests: All patients had at least 1 prior test. Patients with syncope as chief complaint, for whom there was no clear suspicion of the cause of syncope from initial tests (history, physical examination, bp measurements, 12-lead ECG). Identified by investigator from daily visits.</td>
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<td>Sheldon 2002</td>
<td>TLoC population: selected patients with TLoC of mixed known causes. Prior tests: All patients had 1 prior test. Diagnosis established; not if had &gt;1 plausible cause of TLoC; sample randomly divided to allow validation</td>
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### Diagnostic tests

#### Study

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<tr>
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<td>TLoC population: selected patients with TLoC of mixed known causes. Prior tests: All patients had 1 prior test. Diagnosis established; not if had &gt;1 plausible cause of TLoC; sample randomly divided to allow validation</td>
<td>Index test: risk score derived from age &gt;65y, history of congestive heart failure, abnormal ECG; time: initially (n=267)</td>
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<tr>
<td>Setting: Emergency Department. ED in primary and tertiary care main teaching hospital between 1989 and 1991.</td>
<td>Definition of TLoC: Sudden transient loss of consciousness with an inability to maintain postural tone and with spontaneous recovery.</td>
<td>Reference standard: Diagnostic tests performed and interpreted by cardiologists: echocardiography, ambulatory ECG (24h Holter or event recorder) and electrophysiological studies to detect arrhythmias in presence of syncope or near syncope; time not stated (n=267)</td>
</tr>
<tr>
<td>Setting: Hospital several departments. University and private practice neurology and cardiology clinics; pacemaker, arrhythmia and syncope clinics; and hospital cardiology wards (i.e. tertiary referral and acute care facilities only).</td>
<td>Inclusion criteria: loss of consciousness and diagnosis established according to preset criteria. Exclusion criteria: patients with more than 1 plausible cause of syncope; people with pseudosyncope.</td>
<td>Index test: Decision rule based on symptoms alone with positive and negative scoring items; pts classified as having seizures if points score ≥1; time: initially (n=268)</td>
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<tr>
<td>Funding: Grants from Medtronic; validation by same group that developed decision rule</td>
<td>Patient characteristics: age; seizure pts 35 (SD 12 years) syncpe 53 (SD20) p&lt;0.001; sex; seizure pts 44% men; syncpe 55% p=0.062; some patients with existing heart disease (146/671 structural heart disease); history of TLoC: some patients; some had &gt;30</td>
<td>Reference standard: positive tilt test for vasovagal and orthostatic hypotension; ECG/electrophysiology for arrhythmias/heart block (diagnosis also included palpitations pre-syncope); EEG; time unclear (n=268)</td>
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<td>Comorbidities: not stated. Other details: overall sample: 267/671 vasovagal; 90 VT; 40 complete heart block; 22 SVT; 4 sick sinus; 4 hypertensive carotid sinus syndrome; 3 aortic stenosis; etc</td>
<td>Comparator test: initial evaluation symptoms + history: as above but no. of spells and length of history of LoC and lightheaded spells also included; time: initially (n=268).</td>
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<td>Other study comments: Seizure patients only included if had diagnostic EEG (may have created bias). Patients required to recall symptoms (unclear over what time period). Tertiary referral clinics and acute care facilities only.</td>
<td>for Target Condition/Outcome: Seizure diagnosis if patients had diagnostically positive EEGs</td>
</tr>
</tbody>
</table>
1.3 Initial symptoms for risk stratification (death) review

Diagnostic Test: Initial symptoms

**Study**
Colivicchi 2003 prospective cohort study; study held in Italy.

**Participants**
TLoC population: unselected patients. Prior tests: Unclear or Not stated. Consecutive patients older than 12 years presenting with TLoC to ED; no more details on enrolment

**Diagnostic tests**
Index test: initial symptoms determined from patient history, physical exam, 12-lead ECG, haemoglobin count, blood glucose: score based on age >65 y, clin history of cardiovascular disease, syncope without prodromal symptoms, abnormal ECG; time: initially (n=270)

**Setting**
Emergency Department. EDs of 6 general community hospitals in 1 region [Nov 1997-Jan 1998].

**Inclusion criteria:** Patients presenting with syncope aged 12 years and older. Exclusion criteria: patients with an already known seizure disorder presenting a typical recurrence, with prolonged post-ictal phase; patients with presyncope only or dizziness or vertigo only.

**Patient characteristics:** age: mean 59.5 y (SD 24.3; range 14-88 years); i.e some children; sex: 46.3% male; some patients with existing heart disease (29% had a history of CV disease); history of TLoC: 32% had previous syncopal spells.

**Comorbidities:** 34% hypertension; 29% CV disease; 12% diabetes mellitus. Other details: 15% had syncope-related traumatic injuries; 35% syncope without prodromes; 30% abnormal ECG

**Other study comments:** Diagnostic accuracy results only possible for derivation cohort (numbers with different risk scores given) so likely bias introduced. 31/239 deaths
### 1.4 Initial symptoms for risk stratification review

#### Diagnostic Test: Initial symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
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<tr>
<td>Birnbaum 2008</td>
<td>TLoC population: unselected patients. Prior tests: Unclear or Not stated. ED patients with acute syncope or near syncope as reason for presentation; surveillance of ED tracking system to identify all possible patients; seizures and drug related TLoC excluded. Definition of TLoC: transient loss of consciousness (acute syncope) or sensation of impending but not actual loss of consciousness (near syncope). Did not specifically require return to nonlocal neurologic function.</td>
</tr>
<tr>
<td>Setting: Emergency Department. ED of large urban, academic center (80,000 visits per year). Funding: None that would create a conflict of interest</td>
<td>Inclusion criteria: adult patients 21 years and older with complaint of acute syncope or near syncope as reason for ED visit. Exclusion criteria: patients with head trauma-caused or alcohol or drug-related LoC; patients with a definite seizure; patients with an altered mental status. Patient characteristics: age: mean 61 years (21-101); 17% 21-40y, 30% 41-60y, 37% 61-80y, 16% 81-101y; sex: 38% male; some patients with existing heart disease (8% had history of CHF; 31% abnormal ECG); history of TLoC: not stated. Comorbidities: not stated. Other details: 39% Hispanic; 17% white, 38% black, 6% other. Other study comments: ECG assessors blinded to data on presence or absence of other predictors. Serious outcomes not indicated by rule were 1 death, 8 arrhythmias, 3 strokes, 1 SAH, 1 blood transfusion, 2 returned to ED within 7 days.</td>
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</table>

| Grossman 2007 | TLoC population: unselected patients. Prior tests: No patients had a prior test. Consecutive patients presenting 24h / 7 days for 8 months; only syncope; seizures excluded. Definition of TLoC: sudden and transient (< 5 min) loss of consciousness, producing a brief period of unresponsiveness and loss of postural tone, ultimately resulting in spontaneous recovery requiring no resuscitation. Inclusion criteria: 18 years or older who met definition of syncope; at least 1 episode of syncope. Exclusion criteria: near syncope; persistent altered mental status; alcohol or illicit drug related LoC; seizure; coma; hypoglycaemia; TLoC caused by head injury. Patient characteristics: age: mean 57.8 years (SD 24.2); sex: 42% male; some patients with existing heart disease (35% had history of heart disease); history of TLoC all had at least 1 episode of syncope; 20% had recurrent syncope. Comorbidities: Other details: 2% family history of sudden death. Other study comments: Rule is combination of ACEP, San Francisco SR and expert opinion. If a patient had a risk factor then admitted to hospital otherwise sent home; overall 69% admitted. 94% included in study. Validation study. Univariate analysis also. |
| Setting: Emergency Department. large urban teaching hospital ED; consecutive patients with syncope. Funding: None reported | Index test: symptoms: questionnaire on history of congestive heart failure; haemocrit < 30%; patient complaint of shortness of breath; triage systolic bp < 90 mm Hg, abnormal ECG (any non-sinus rhythm or any new changes) determined separately; time: in ED (n=730). Reference standard: Follow up determined by research associates by phone using structured data collection instrument; outcomes reviewed by study investigators and disagreements resolved through discussion; time 7 days (n=713). Comparator test: Decision to admit patient by ED physician independently of the decision rule; time: ED (n=738). Other comparator tests: 3. Individual patient history characteristics. |

**Diagnostic tests**

- Index test: signs/symptoms of acute coronary syndrome; worrisome cardiac history; family history of sudden death; valvular heart disease; signs of conduction disease; volume depletion; persistent (>15 min) abnormal vital signs; primary CNS event; time: in ED (n=362)
- Reference standard: Follow up with structured form, by phone and using medical record; time 30 days and subsequent med records (n=293)
- for Target Condition/Outcome: patients with (1) an adverse outcome (incl. death, PE; stroke; ventricular or atrial dysrhythmia; intracranial bleed; MI) or (2) critical intervention (incl. pacemaker, percutaneous coronary intervention, surgery) within 30 d of initial visit
### Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Diagnostic tests</th>
</tr>
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<tbody>
<tr>
<td>Hing 2005</td>
<td>TLoC population: unselected patients. Prior tests: Unclear or Not stated. Adult patients presenting with TLoC to ED; identified by ED staff. Patients enrolled only if investigators present and if their serum troponin level was measured at least 4h after syncope were included (113/508 with triage diagnosis of syncope) Definition of TLoC: Syncope: syncopal event with spontaneous recovery with no neurological sequelae.</td>
<td>Index test: Initial symptoms from patient history, ECG; time: initially (n=100) Reference standard: review of discharge medical records to determine the diagnosis; patients contacted by phone to determine adverse events, return to normal premorbid function and GP confirmation where necessary; time 3-6 months (n=100) Comparator test: Serum troponin T measured at least 4 hours after syncope; time: initially (n=100). for Target Condition/Outcome: Serious o/c: cardiac death, and adverse cardiac outcomes: diagnosis or ongoing episodes of ischaemic heart disease requiring further investigation, incl medication changes, admission to hospital, angiogram; significant arrhythmia requiring treatment; death as a result of presumed cardiac causes</td>
</tr>
<tr>
<td>Quinn 2004</td>
<td>TLoC population: unselected patients. Prior tests: Unclear or Not stated. ED patients with acute syncope or near syncope; 73% as primary complaint; prospective screening and review of patient logs to identify all possible patients; seizures and drug related TLoC excluded Definition of TLoC: syncope is a transient loss of consciousness with return to pre-existing neurologic function; near syncope not defined.</td>
<td>Index test: Signs and symptoms from San Francisco Syncope Rule validation: abnormal ECG result (any non-sinus rhythm or any new changes); time: in ED (n=684) Reference standard: Follow up determined by study nurse; includes ED and non-ED outcomes; 49/79 outcomes occurred after ED visit; time 7 days (n=684) Comparator test: Attending physicians &amp; house staff carried out normal assessment &amp; disposition of each patient, then completed standardised form (SFSR). Physicians estimated if 2% or less chance of serious outcome with in 7 days, based on their clinical assessment; time: ED (n=684). Other comparator tests: 3. Physician decision to admit patient (n=684) 4. Initial symptoms (n=684). for Target Condition/Outcome: Short term serious o/c: death, MI, arrhythmia, PE, stroke, SAH, signif hemorrhage; any condn causing return to ED and hospitalisation for related event</td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria: Patients presenting with syncope aged 18 years and older. Enrolled only if investigators or informed member of staff present. Exclusion criteria: patients presenting with seizures, coma, dizziness, vertigo or pre-syncope without LoC. Patient characteristics: age: 9% &lt;39y; 11% 40-49y; 8% 50-59y; 13% 60-69y; 28% 70-79y; 30% 80-89y; 1% 90-99y; sex: 47% male; some patients with existing heart disease (some had history of IHD, congestive cardiac failure); history of TLoC: not stated Comorbidities: 51% hypertension; 9% diabetes. Other details: Discharge diagnoses: 27% NM syncope; 21% orthostatic hypotension; 2% neurological; 3% cardiac organic; 16% cardiac arrhythmias</td>
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<tr>
<td>Funding:</td>
<td>none declared</td>
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<td></td>
<td>Emergency Department. ED of tertiary referral urban hospital (42,000 emergency presentations per annum) (Apr 2002–Apr 2003).</td>
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<td></td>
<td>Emergency Department. ED of large university teaching hospital (Jun 2000-Feb 2002).</td>
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<tr>
<td></td>
<td>Funding: 1st author received a NIH grant. Same authors developed SFSR - some potential for conflict of interest.</td>
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</tbody>
</table>

**Due to the length of the document, the full text is not provided.**
Study: Reed 2007 (ROSE pilot) prospective cohort study; study held in UK.

Participants: TLoC population: unselected patients. Prior tests: No patients had a prior test. Consecutive adult patients presenting with TLoC to ED; identified by ED staff, then checked patient records; previously recruited patients excluded. Only 38% eligible patients enrolled.

Definition of TLoC: Syncope: a transient loss of consciousness with an inability to maintain postural tone followed by spontaneous recovery.

Inclusion criteria: Patients presenting with syncope aged 16 years and older. Exclusion criteria: patients younger than 16 years; those previously recruited; those with a history of seizure with prolonged post-ictal phase; patients unable to give either written or verbal informed consent.

Other study comments: Pilot for ROSE study; recruitment doctors trained for 15 min to identify syncope; 62% patients missed (younger); study gp skewed towards more serious risk. Admission = >12 h in ED. Scores for SFSR & OESIL determined by study team from data forms.

Study: Sun 2007 prospective cohort study; study held in USA.

Participants: TLoC population: unselected patients. Prior tests: Unclear or Not stated. Adult ED patients with syncope or near syncope admitted 8am-10pm 7/7 days; review of ED intake log showed 76% eligible patients identified and screened; seizures and people with confusion excluded. Definition of TLoC: Sudden transient loss of consciousness (=syncope); sensation of imminent loss of consciousness (=near syncope).

Inclusion criteria: adult patients with complaint of acute syncope or near syncope. Exclusion criteria: head trauma-associated LoC; intoxication; patients with a witnessed seizure; ongoing confusion (incl. baseline cognitive impairment /dementia); age < 18 y; inability to speak English or Spanish; do-not-resus/DN intubate status; no follow-up contact info.

Other study comments: 51% admitted, 7% transferred to another hospital, 40% discharged, 2% left against medical advice. Attending physicians trained in completion of data forms. Inter-rater reliability also checked in convenience sample (subgroup).

Diagnostic tests: Index test: symptoms: questionnaire on history of congestive heart failure/haemocrit < 30%; abnormal ECG result (any non-sinus rhythm not new changes (no old ECG); patient complaint of shortness of breath; triage systolic bp < 90 mm Hg; time: in ED (n=477).

Reference standard: Follow up: phone interview by research nurse; then 2 independent emergency physicians reviewed ED documentation, inpatient records and telephone forms; records for all with potentially serious outcome reviewed by a panel of 3 ED physicians; time 7 days (n=463). Comparator test: Treating physician’s decision to hospitalise the patient; time: in ED (n=477).

for Target Condition/Outcome: death, MI, arrhythmia, PE, stroke, TIA, SAH/nontrauma hemorrhage, aortic dissection, new SHD, sig hemorrh/anemia needing transfusion; procedure to treat syncope cause; readmission for related event.
1.5 Decision rules for risk stratification (death) review

Diagnostic Test: ACP guidelines

**Study**

- **Crane 2002** retrospective cohort study; study held in UK.
- **Setting**: Emergency Department. ED of Leeds general infirmary; large urban department with 96000 patients in 1998.

**Participants**

- Definition of TLoC: Temporary LoC but recovered spontaneously.
- Inclusion criteria: age 16 and above with clear history of TLoC.
- Exclusion criteria: Focal neurological signs or a GCS < 15 when examined by doctor, clear seizure in a known epileptic, intoxication with alcohol/other drugs, patient ‘found on the floor’.

**Funding**: None

**Patient characteristics**: age: mean 54.7 years (SD 25); bimodal age distribution with peaks at 25-34 years and 75-84 years; sex: men 39%; women 61%; some patients with existing heart disease (18% known organic heart disease); history of TLoC: Not stated; but 2 patients presented twice in the 8 week period

**Comorbidities**: not stated. Other details: 33% on cardiovascular or psychotropic drugs

**Diagnostic tests**

- Index test: ACP guidelines for admission, high risk group - from records (history of CAD, CCF, VT; chest pain; physical symptoms of CCF, significant valve disease, stroke, focal neurology; ECG findings of ischaemia, arrhythmia, long QT, bundle branch); time: initially (n=208)

- Reference standard: Contact with general practice or health authority of patients plus registrar for deaths as to the cause of death; time 1 year (n=189)

- Comparator test: ACP guidelines for admission, moderate risk group - from records (TLoC with injury, rapid heart action, exertion; frequent episodes; suspicion of CHD or arrhythmia; moderate/severe postural hypotension; age over 70 years); time: initially (n=208)

- Other comparator tests: 3) ACP guidelines for admission, low risk group (none of above conditions) - safe to discharge with or without outpatient follow up..

- for Target Condition/Outcome: all-cause DEATH ONLY within 12 months of initial evaluation; 13% had died within 1 year

Diagnostic Test: EGSYS score

**Study**

- **del Rosso 2008** cross sectional study index 1st; study held in Italy.
- **Setting**: Emergency Department. ED of 14 general hospitals in Italy from Oct 2004 to Nov 2004.

**Participants**

- TLoC population: unselected patients. Prior tests: Unclear or Not stated. Consecutive patients admitted
- Definition of TLoC: stated to be syncope (other causes excluded).
- Inclusion criteria: not stated.
- Exclusion criteria: Patients aged less than 18 years and those referred more than 24h after their episode. Patients with a non-syncope cause of LoC as seizures, drug attacks, transient ischaemic attacks.

**Patient characteristics**: age: mean 63 years (SD 22); sex: 121/256 male (47%); some patients with existing heart disease (29% structural heart disease); history of TLoC: 24% with history of pre-syncope. Mean no. of syncope episodes: 3 (SD 5)

**Comorbidities**: not stated. Other details: Final diagnosis: 14% cardiac syncope; 70% neurally mediated syncope; 10% orthostatic hypotension; 4% non-syncope attacks; 3% unexplained

**Other study comments**: Validation cohort. Prospective

**Diagnostic tests**

- Index test: EGSYS symptom score based on ESC: standardised assessment (palpitations preceding syncope, heart disease/abnormal ECG, syncope during effort, syncope while supine, precipitating factors, autonomic prodromes (N & V); time: initial (n=256)

- Reference standard: Follow up data from family doctor or through phone call or outpatient visits; time 21-24 months (mean 614 days) (n=195)

- for Target Condition/Outcome: Death from any cause
## Diagnostic Test: OESIL score

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Diagnostic tests</th>
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</table>
| Colivicchi 2003        | TLoC population: unselected patients. Prior tests: Unclear or Not stated. ED patients with acute syncope or near syncope; use of electronic tracking system to identify all possible patients with appropriate tag terms.  
Definition of TLoC: syncope is a transient loss of consciousness with return to pre-existing neurologic function; near syncope not defined.  
Inclusion criteria: Patients presenting with syncope aged 12 years and older.  
Exclusion criteria: Patients with an already known seizure disorder presenting a typical recurrence, with prolonged post-ictal phase; patients with syncope only or dizziness or vertigo only.  
Patient characteristics: age: mean 59.5 years (SD 24.3; range 14-88 years); i.e some children; sex: 46.3% male; some patients with existing heart disease (29%) had a history of CV disease; history of TLoC: 32% had previous syncope spells.  
Comorbidities: 34% hypertension; 29% CV disease; 12% diabetes mellitus.  
Other details: 15% had syncope-related traumatic injuries; 35% syncope without prodromes; 30% abnormal ECG.  
Other study comments: Diagnostic accuracy results only possible for derivation cohort (numbers with different risk scores given) so likely bias introduced. 31/239 deaths. | Index test: OESIL score determined from patient history, physical exam, 12-lead ECG, haemoglobin count, blood glucose: score based on age >65 y, clin history of cardiovascular disease, syncope without prodromal symptoms, abnormal ECG; time: initially (n=270)  
Reference standard: contact with family physicians or through telephone follow up and outpatient visitation; not stated who did this; time 12 months (n=270) for Target Condition/Outcome: all-cause DEATH ONLY within 12 months of initial evaluation. |

## Diagnostic Test: San Francisco Syncope Rule

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Diagnostic tests</th>
</tr>
</thead>
</table>
| Quinn 2008             | TLoC population: unselected patients. Prior tests: Unclear or Not stated.  
Definition of TLoC: syncope is a transient loss of consciousness with return to pre-existing neurologic function; near syncope not defined.  
Inclusion criteria: acute syncope or near syncope.  
Exclusion criteria: patients with trauma-associated or alcohol or illicit drug-related LoC; patients with a definite seizure; patients with LoC associated with an altered level of consciousness or persistent new neurologic defects.  
Patient characteristics: age: mean 56 to 69 years; sex: 47-64% female; Unclear/not stated with existing heart disease (); history of TLoC: not stated.  
Comorbidities: not stated. Other details: cause of syncope reported to be: cardiac 11%, neurologic 3%, orthostasis 12%, vasovagal 21%, medications 5%, psychiatric 1%, unclear 47%. | Index test: San Francisco Syncope Rule: questionnaire on history of congestive heart failure/haemocrit < 30%; abnormal ECG result (any non-sinus rhythm or any new changes); patient complaint of shortness of breath; triage systolic bp < 90 mm Hg; time: in ED (n=1418, with 1474 visits)  
Reference standard: Follow up and interpretation by 2 physicians to decide if the death was related to TLoC. Online social security death index (checked in sample by direct follow up); confirmed by death certificate. No follow up for alive patients.; time 12 months (n=1418) for Target Condition/Outcome: Death that was possibly related to TLoC; 6 and 12 months reported. |

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**Transient loss of consciousness: full guideline DRAFT (January 2010)**
1.6 Decision rules for risk stratification review

### Diagnostic Test: Boston Syncope Criteria

**Study**
Grossman 2007

**Participants**
TLoC population: unselected patients. Prior tests: No patients had a prior test. Consecutive patients presenting 24h / 7 days for 8 months; only syncope; seizures excluded.

Definition of TLoC: sudden and transient (< 5 min) loss of consciousness, producing a brief period of unresponsiveness and loss of postural tone, ultimately resulting in spontaneous recovery requiring no resuscitation.

Inclusion criteria: 18 years or older who met definition of syncope; at least 1 episode of syncope.

Exclusion criteria: near syncope; persistent altered mental status; alcohol or illicit drug related LoC; seizure; coma; hypoglycaemia; TLoC caused by head injury.

Patient characteristics: age: mean 57.8 years (SD 24.2); sex: 42% male; some patients with existing heart disease (35% had history of heart disease); history of TLoC; all had at least 1 episode of syncope; 20% had recurrent syncope.

Comorbidities: Other details: 2% family history of sudden death.

Other study comments: Rule is combination of ACEP, San Francisco SR and expert opinion. If a patient had a risk factor then admitted to hospital otherwise sent home; overall 69% admitted. 94% included in study. Validation study. Univariate analysis also.

### Diagnostic tests

Index test: Boston Syncope Criteria: signs/symptoms of acute coronary syndrome; worrying cardiac history; family history of sudden death; valvular heart disease; conduction disease signs; volume depletion; persistent (>15min) abnormal vital signs; primary CNS event; time: in ED (n=362)

Reference standard: Follow up with structured form, by phone and using medical record; time 30 days and subsequent med records (n=293)

For Target Condition/Outcome: patients with (1) an adverse outcome (incl. death, PE, stroke; ventricular or atrial dysrhythmia; intracranial bleed; MI) or (2) critical intervention (incl. pacemaker, percutaneous coronary intervention, surgery) within 30 d of initial visit.

### Diagnostic Test: OESIL score

**Study**
Hing 2005

**Participants**
TLoC population: unselected patients. Prior tests: Unclear or Not stated. Adult patients presenting with TLoC to ED; identified by ED staff. Patients enrolled only if investigators present and if their serum troponin level was measured at least 4h after syncope were included (113/508 with triage diagnosis of syncope).

Definition of TLoC: Syncope: syncopal event with spontaneous recovery with no neurological sequelae.

Inclusion criteria: Patients presenting with syncope aged 18 years and older. Enrolled only if investigators or informed member of staff present.

Exclusion criteria: patients presenting with seizures, coma, dizziness, vertigo or pre-syncope without LoC.

Patient characteristics: age: 9% <39y, 11% 40-49y; 8% 50-59y; 13% 60-69y; 28% 70-79y; 30% 80-89y; 1% 90-99y; sex: 47% male; some patients with existing heart disease (some had history of IHD, congestive cardiac failure); history of TLoC: not stated.

Comorbidities: 51% hypertension; 9% diabetes. Other details: Discharge diagnoses: 27% NM syncope; 21% orthostatic hypotension; 2% neurological; 3% cardiac organic; 16% cardiac arrhythmias.

### Diagnostic tests

Index test: OESIL score determined from data collection by study team: based on age >65 y, clin history of cardiovascular disease, syncope without prodromal symptoms, abnormal ECG; time: initially (n=100)

Reference standard: review of discharge medical records to determine the diagnosis; patients contacted by phone to determine adverse events, return to normal premorbid function and GP confirmation where necessary; time 3-6 months (n=100)

Comparator test: Serum troponin T measured at least 4 hours after syncope; time: initially (n=100).

For Target Condition/Outcome: Serious o/c: cardiac death, and adverse cardiac outcomes: diagnosis or ongoing episodes of ischaemic heart disease requiring further investigation, incl medication changes, admission to hospital, angiogram; significant arrhythmia requiring treatment; death as a result of presumed cardiac causes.
DRAFT FOR CONSULTATION

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pilot) prospective cohort study; study held in UK.
Setting: Emergency Department. ED of large urban hospital (85,000 adult attendances per annum) [Nov 2005-Feb 2006].

Inclusion criteria: Patients presenting with syncope aged 16 years and older. Exclusion criteria: patients younger than 16 years; those previously recruited; those with a history of seizure with prolonged post-ictal phase; patients unable to give either written or verbal informed consent.

Patient characteristics: age: median 71 years (IQR 47-81); missed group median 62.5 years (IQR 29-78); p=0.047; sex: 48% male; some patients with existing heart disease (no details); history of TLoC: not stated
Comorbidities: not stated. Other details: Distribution of risk groups skewed towards more serious end => possible exclusion of younger patients with vasovagal syncope.

Other study comments: Pilot for ROSE study; recruitment doctors trained for 15 min to identify syncope: 62% patients missed (younger); study gp skewed towards more serious risk. Admission = >12 h in ED. Scores for SFSR & OESIL determined by study team from data forms.

Data collection by study team: based on age >65 y, clin history of cardiovascular disease, syncope without prodromal symptoms, abnormal ECG; time: initially (n=99)

Reference standard: review of local hospital records re inpatients and outpatients; death register and primary care records; not stated who did this; time 3 months (n=99)

Comparator test: San Fransisco Syncope Rule; time: initially (n=99).

Other comparator tests: 3)initial assessment based on ESC, AAP & ACEP g/ts: standardised assessment with 75 variables (11 clinical features, 9 med history, 11 current meds; 28 exam; 26 ECG) (n=99).

for Target Condition/Outcome: Serious o/c: all-cause death, acute MI, life threatening arrhythmia, PE, stroke, cerebrovasc accident/SAH, signif hemorrhage needing blood transfusion; acute surgical procedure/endoscopic interv. 5 died and 6 had serious outcome by 3 mo.
Diagnostic Test: San Francisco Syncope Rule

**Study**

Birnbaum 2008 prospective cohort study; study held in USA.

Cosgriff 2007 prospective cohort study; study held in Australia.

**Participants**

TLoC population: unselected patients. Prior tests: Unclear or Not stated. ED patients with acute syncope or near syncope as reason for presentation; surveillance of ED tracking system to identify all possible patients; seizures and drug related TLoC excluded

Definition of TLoC: transient loss of consciousness (acute syncope) or sensation of impending but not actual loss of consciousness (near syncope).

Did not specifically require return to nonfocal neurologic function.

Inclusion criteria: adult patients 21years and older with complaint of acute syncope or near syncope as reason for ED visit.

Exclusion criteria: patients with head trauma-caused or alcohol or drug-related LoC; patients with a definite seizure; patients with an altered mental status.

Patient characteristics: age: mean 61 years (21-101); 17% 21-40y, 30% 41-60y, 37% 61-80y, 16% 81-101y; sex: 38% male; some patients with existing heart disease (8% had history of CHF; 31% abnormal ECG); history of TLoC: not stated

Comorbidities: not stated. Other details: 39% Hispanic; 17% white, 38% black, 6% other

Other study comments: ECG assessors blinded to data on presence or absence of other predictors. Serious outcomes not indicated by rule were 1 death, 8 arrhythmias, 3 strokes, 1 SAH, 1 blood transfusion, 2 returned to ED within 7 days

TLoC population: unselected patients. Prior tests: Unclear or Not stated. Non-consecutive ED pts with acute syncope or near syncope: 2 groups: (1) 87% identified during ED presentation (2) surveillance of ED clinical database to identify other possible patients (med records for indicators); seizures & drug related TLoC excl

Definition of TLoC: full loss of consciousness (acute syncope) or near loss of consciousness (near syncope) with a return to pre-existing neurologic function..

Inclusion criteria: patients with syncope or near syncope.

Exclusion criteria: patients unable to communicate in English and an interpreter not available; those with head trauma-caused or alcohol or drug-related LoC; patients with a definite seizure; patients with a persistent altered mental or neurologic status.

Patient characteristics: age: follow up sample: median 74 years (range 20-93y); sex: follow up sample: 37:52 male:female (42% M); some patients with existing heart disease (8% had history of CHF; 21% abnormal ECG); history of TLoC: not stated

Comorbidities: not stated. Other details: race not stated

Other study comments: ECG assessors were 2 researchers experienced in ECG interpretn. Diagnosis at ED discharge incl: vasovagal 16%, dehydration 10%, and hypotension 10%, unknown 32%. Serious outcomes not indicated by rule: 1 sick sinus syndrome who needed pacemaker insertion

**Diagnostic tests**

Index test: San Francisco Syncope Rule: questionnaire on history of congestive heart failure;haemocrit < 30%; patient complaint of shortness of breath; triage systolic bp < 90 mm Hg, abnormal ECG (any non-sinus rhythm or any new changes) determined separately; time: in ED (n=730)

Reference standard: Follow up determined by research associates by phone using structured data collection instrument; outcomes reviewed by study investigators and disagreements resolved through discussion; time 7 days (n=713)

Comparator test: Decision to admit patient by ED physician independently of the decision rule; time: ED (n=738).

Other comparator tests: 3. Individual patient history characteristics.

for Target Condition/Outcome: Short term serious o/c: death, MI, arrhythmia, PE, stroke, SAH, sig hemorrhage needing transfusion; procedural intervention to treat syncope cause; any condn likely to/ causing return to ED; hospitalisation for related event

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Transient loss of consciousness: full guideline DRAFT (January 2010)

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Study
Quinn 2005
prospective cohort study; study held in USA.
Setting: Emergency Department. ED of large university teaching hospital (Jun 2000-Feb 2002).
Funding: 1st author received an NIH grant. Same authors developed SFSR - some potential for conflict of interest.

Participants
TLoC population: unselected patients. Prior tests: Unclear or Not stated. ED patients with acute syncope or near syncope; 73% as primary complaint; prospective screening and review of patient logs to identify all possible patients; seizures and drug related TLoC excluded
Definition of TLoC: syncope is a transient loss of consciousness with return to pre-existing neurologic function; near syncope not defined.
Inclusion criteria: acute syncope or near syncope as a reason for their presentation in ED.
Exclusion criteria: patients with head trauma-caused or alcohol or illicit drug-related LoC; patients with a definite seizure; patients with LoC associated with an altered mental status.
Patient characteristics: age: mean 62.1 years; sex: 41% male; some patients with existing heart disease (4.9% had MI; 4.4% had arrhythmia; 0.7% structural HD; 0.7% PE); history of TLoC: not stated although some had more than 1 episode
Comorbidities: not stated. Other details: race not stated
Other study comments: Validation study; 55% admitted; all had some form of follow up (96% directly and the rest through checks with death register and local hospitals)

Quinn 2006
prospective cohort study; study held in USA.
Setting: Emergency Department. ED of large university teaching hospital (Jul 2002-Aug 2004).
Funding: 1st author received an NIH grant. Same authors developed SFSR - some potential for conflict of interest.

Participants
TLoC population: unselected patients. Prior tests: Unclear or Not stated. consecutive ED patients with acute syncope or near syncope; electronic tracking system to identify all possible patients; seizures and drug related TLoC excluded
Definition of TLoC: transient loss of consciousness with return to baseline neurologic function.
Inclusion criteria: acute syncope or near syncope.
Exclusion criteria: patients with trauma-associated or alcohol or drug-related LoC; patients with a definite seizure; patients with LoC associated with an altered level of consciousness or persisting new neurological deficits.
Patient characteristics: age: mean 61 years (6-99); i.e includes children too; sex: 46% male; Unclear/not stated with existing heart disease (); history of TLoC: not stated although some had more than 1 episode
Comorbidities: not stated. Other details:
Other study comments: Validation study; patients also asked whether serious outcome had already been diagnosed and was present during ED presentation or evaluation. Data forms checked by study investigators.

Diagnostic tests
Index test: San Francisco Syncope Rule: questionnaire on history of congestive heart failure; haemocrit < 30%; abnormal ECG result (any non-sinus rhythm or any new changes); patient complaint of shortness of breath; triage systolic bp < 90 mm Hg; time: in ED (n=684)
Reference standard: Follow up determined by study nurse; includes ED and non-ED outcomes; 49/79 outcomes occurred after ED visit; time 7 days (n=684)
Comparator test: Attending physicians & house staff carried out normal assessment & disposition of each patient, then completed standardised form (SFSR). Physicians estimated if 2% or less chance of serious outcome within 7 days, based on their clinical assessment; time: ED (n=684).
Other comparator tests: Physician decision to admit patient (n=684).

for Target Condition/Outcome: Short term serious o/c: death, MI, arrhythmia, PE, stroke, SAH, signif hemorrhage; any condn causing return to ED and hospitalisation for related event

Index test: San Francisco Syncope Rule: questionnaire on history of congestive heart failure; haemocrit < 30%; abnormal ECG result (any non-sinus rhythm or any new changes); patient complaint of shortness of breath; triage systolic bp < 90 mm Hg; time: in ED (n=767 visits for same pts)
Reference standard: Follow up determined by trained research nurse and study
review of records, discussions with primary physicians or patient & family members; 54/108 outcomes in ED; time 30 days (n=725 visits followed up)

for Target Condition/Outcome: Short term serious o/c NOT diagn/presnt in ED: death, MI, arrhythmia, PE, stroke, SAH, sig hemorrhage/anaemia needing transfusion; procedural intervention to treat syncope cause; any condn likely to/ causing return to ED; hospitalisation for related event
Schladenhaufen  
Retrospective cohort study; study held in USA.

Study setting: Emergency Department. ED of community teaching hospital and level II trauma centre, with 61,000 patients from Jan 2000 to Aug 2001.

Funding: None stated.

Study participants: TLoC population: patients with syncope or near syncope. Prior tests: Unclear or Not stated.

Inclusion criteria: Aged at least 65 years.

Exclusion criteria: patients with head trauma, seizure, altered mental status, intoxication. Out of state residents. Patients with incomplete data (75/639=12%).

Patient characteristics: age: mean 78.8 years; 65 years and older; sex: 54.5% female; Unclear/not stated with existing heart disease (); history of TLoC: not stated

Comorbidities: not stated. Other details: Few details. 64% had arrhythmias, 17% returned to hospital, 11% had MI, 5% died, 2% had a pulmonary embolism, 2% had cerebrovascular accident

Diagnostic tests
Index test: retrospective determined SFSR items (ECG in comparison with previous ECG); time: (n=517)

Reference standard: death by documentation in medical record, discharge summary notes if hospital stay >7 days; subsequent inpatient and outpatient visits reports if <7days (if no subsequent visits then included); time 7 days (n=517)

for Target Condition/Outcome: Short term serious o/c: death, MI, arrhythmia that could cause TLoC, PE, stroke, SAH, sig hemorrhage needing blood transfusion; any condn likely to/ causing return to ED; hospitalisation for related event.
Study
Sun 2007 prospective cohort study; study held in USA.

Setting: Emergency Department. ED of urban, academic, Level I trauma centre.

Funding: university funding and American Geriatrics Society award (1st author)

Participants
TLoC population: unselected patients. Prior tests: Unclear or Not stated. adult ED patients with syncope or near syncope admitted 8am-10pm 7/7 days; review of ED intake log showed 76% eligible patients identified and screened; seizures and people with confusion excluded

Definition of TLoC: sudden transient loss of consciousness (≈syncope); sensation of imminent loss of consciousness (near syncope).

Inclusion criteria: adult patients with complaint of acute syncope or near syncope.

Exclusion criteria: head trauma-associated LoC; intoxication; patients with a witnessed seizure; ongoing confusion (incl. baseline cognitive impairment /dementia); age < 18 y; inability to speak English or Spanish; do-not-resus/DN intubate status; no follow-up contact info..

Patient characteristics: age: median 58 years (IQR 35-79); 30% <40y, 23% 40-59y; 24% 60-79y; 21% >80y; sex: 44% male; some patients with existing heart disease (8% had history of CHF); history of TLoC: not stated

Comorbidities: not stated. Other details: 10% Hispanic; 77% white; 9% black; 11% Asian; 3% other

Other study comments: 51% admitted; 7% transferred to another hospital; 40% discharged; 2% left against medical advice. Attending physicians trained in completion of data forms. Inter-rater reliability also checked in convenience sample (subgroup)

Diagnostic tests
Index test: San Francisco Syncope Rule, sl. modified: questionnaire on history of congestive heart failure; haemocrit < 30%; abnormal ECG result (any non-sinus rhythm not new changes (no old ECG); patient complaint of shortness of breath; triage systolic bp < 90 mm Hg; time: in ED (n=477)

Reference standard: Follow up: phone interview by research nurse; then 2 independent emergency physicians reviewed ED documentation, inpatient records and telephone forms; records for all with potentially serious outcome reviewed by a panel of 3 ED physicians; time 7 days (n=463)

Comparator test: Treating physician’s decision to hospitalise the patient; time: in ED (n=477).

for Target Condition/Outcome: death, MI, arrhythmia, PE, stroke, TIA, SAH/nontrauma hemorrhage, aortic dissection, new SHD, sig hemorrh/anemia needing transfusion; procedure to treat syncope cause; readmission for related event

1.7 Decision rules for recurrence of TLoC review

Diagnostic tests
Index test: OESIL score determined from data collection by study team: based on age >65 y, clin history of cardiovascular disease, syncope without prodromal symptoms, abnormal ECG; time: initially (n=100)

Reference standard: review of discharge medical records to determine the diagnosis; patients contacted by phone to determine recurrence of syncope and GP confirmation where necessary; time 3-6 months (n=100)

 Comparator test: Serum troponin T measured at least 4 hours after syncope; time: initially (n=100).

for Target Condition/Outcome: Recurrence of syncope
1.8 12-lead ECG review

Diagnostic Test: 12 lead ECG

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birnbaum 2008 prospective cohort study; study held in USA.</td>
<td>TLoC population: unselected patients. Prior tests: Unclear or Not stated. ED patients with acute syncope or near syncope as reason for presentation; surveillance of ED tracking system to identify all possible patients; seizures and drug related TLoC excluded Definition of TLoC: transient loss of consciousness (acute syncope) or sensation of impending but not actual loss of consciousness (near syncope). Did not specifically require return to nonfocal neurologic function.</td>
<td>Index test: abnormal ECG (any non-sinus rhythm or any new changes); time: in ED (n=730) Reference standard: Follow up determined by research associates by phone using structured data collection instrument; outcomes reviewed by study investigators and disagreements resolved through discussion; time 7 days (n=713) Comparator test: Decision to admit patient by ED physician independently of the decision rule; time: ED (n=738). Other comparator tests: 3. Individual patient history characteristics. for Target Condition/Outcome: Short term serious o/c: death, MI, arrhythmia, PE, stroke, SAH, sig hemorrhage needing transfusion; procedural intervention to treat syncope cause; any condn likely to/ causing return to ED; hospitalisation for related event</td>
</tr>
</tbody>
</table>

| Colivicchi 2003 prospective cohort study; study held in Italy. | TLoC population: unselected patients. Prior tests: Unclear or Not stated. Consecutive patients older than 12 years presenting with TLoC to ED; no more details on enrolment Definition of TLoC: Syncope: a sudden and transient loss of consciousness and of postural tone with spontaneous recovery; presyncope excluded. | Index test: 12-lead ECG abnormal findings; time: initially (n=270) Reference standard: contact with family physicians or through telephone follow up and outpatient visitation; not stated who did this; time 12 months (n=270) for Target Condition/Outcome: all-cause DEATH ONLY within 12 months of initial evaluation |

| Setting: Emergency Department. EDs of 6 general community hospitals in 1 region [Nov 1997-Jan 1998]. | Patient characteristics: age: mean 59.5 years (SD 24.3; range 14-88 years); i.e some children; sex: 46.3% male; some patients with existing heart disease (29% had a history of CV disease); history of TLoC: 32% had previous syncopal spells Comorbidities: 34% hypertension; 29% CV disease; 12% diabetes mellitus. Other details: 15% had syncope-related traumatic injuries; 35% syncope without prodromes; 30% abnormal ECG | |

| Funding: None that would create a conflict of interest | Other study comments: Diagnostic accuracy results only possible for derivation cohort (numbers with different risk scores given) so likely bias introduced. 31/239 deaths | |
Study

Grossman 2007
prospective cohort study; study held in USA.

Setting: Emergency Department. large urban teaching hospital ED; consecutive patients with syncope.

Funding: none reported

Participants

TLoC population: unselected patients. Prior tests: No patients had a prior test. consecutive patients presenting 24h /7days for 8 months; only syncope; seizures excluded

Definition of TLoC: sudden and transient (< 5 min) loss of consciousness, producing a brief period of unresponsiveness and loss of postural tone, ultimately resulting in spontaneous recovery requiring no resuscitation.

Inclusion criteria: 18 years or older who met definition of syncope; at least 1 episode of syncope.

Exclusion criteria: near syncope; persistent altered mental status; alcohol or illicit drug related LoC; seizure; coma; hypoglycaemia; TLoC caused by head injury.

Patient characteristics: age: mean 57.8 years (SD 24.2); sex: 42% male; some patients with existing heart disease (35% had history of heart disease); history of TLoC all had at least 1 episode of syncope; 20% had recurrent syncope

Comorbidities: Other details: 2% family history of sudden death

Other study comments: Rule is combination of ACEP, San Francisco SR and expert opinion. If a patient had a risk factor then admitted to hospital otherwise sent home; overall 69% admitted. 94% included in study. Validation study. Univariate analysis also.

Quinn 2004
prospective cohort study; study held in USA.


Funding: 1st author received an NIH grant. Same authors developed SFSR - some potential for conflict of interest.

Participants

TLoC population: unselected patients. Prior tests: Unclear or Not stated. ED patients with acute syncope or near syncope; 73% as primary complaint; prospective screening and review of patient logs to identify all possible patients; seizures and drug related TLoC excluded

Definition of TLoC: syncope is a transient loss of consciousness with return to pre-existing neurologic function; near syncope not defined.

Inclusion criteria: acute syncope or near syncope as a reason for their presentation in ED.

Exclusion criteria: patients with head trauma-caused or alcohol or illicit drug-related LoC; patients with a definite seizure; patients with LoC associated with an altered mental status.

Patient characteristics: age: mean 62.1 years (range 10 to 102 years); sex: 41% male; some patients with existing heart disease (4.9% had MI; 4.4% had arrhythmia; 0.7% structural HD; 0.7% PE); history of TLoC: not stated although some had more than 1 episode

Comorbidities: not stated. Other details: race not stated

Other study comments: Derivation study; 55% admitted; all had some form of follow up (96% directly and the rest through checks with death register and local hospitals). Univariate analysis.

Diagnostic tests

Index test: 12 lead ECG; time: in ED (n=362)

Reference standard: Follow up with structured form, by phone and using medical record; time 30 days and subsequent med records (n=293)

for Target Condition/Outcome: patients with (1) an adverse outcome (incl. death, PE, stroke; ventricular or atrial dysrhythmia; intracranial bleed; MI) or (2) critical intervention (incl. pacemaker, percutaneous coronary intervention, surgery) within 30 d of initial visit
### Study

**Reed 2007 (ROSE pilot) prospective cohort study; study held in UK.**

**Setting:** Emergency Department. ED of large urban hospital (85,000 adult attendances per annum) [Nov 2005-Feb 2006].

**Funding:** unrestricted educational grant from Medtronic Europe and Netherlands Heart Foundation

**Participants**

TLoC population: unselected patients. Prior tests: No patients had a prior test.

Consecutive adult patients presenting with TLoC to ED; identified by ED staff, then checked patient records; previously recruited patients excluded. Only 38% eligible patients enrolled.

**Diagnosis of TLoC:** Syncope: a transient loss of consciousness with an inability to maintain postural tone followed by spontaneous recovery.

Inclusion criteria: Patients presenting with syncope aged 16 years and older.

Exclusion criteria: patients younger than 16 years; those previously recruited; those with a history of seizure with prolonged post-ictal phase; patients unable to give either written or verbal informed consent.

Patient characteristics: age: median 71 years (IQR 47-81); missed group median 62.5 years (IQR 29-78); p=0.047; sex: 48% male; some patients with existing heart disease (no details); history of TLoC: not stated

Comorbidities: not stated. Other details: Distribution of risk groups skewed towards more serious end -> possible exclusion of younger patients with vasovagal syncope.

Other study comments: Pilot for ROSE study; recruitment doctors trained for 15 min to identify syncope: 62% patients missed (younger); study gp skewed towards more serious risk. Admission >=12 h in ED. Scores for SFSR & OESIL determined by study team from data forms.

**Diagnostic tests**

Index test: 12 lead ECG as part of standardised assessment; time: initially (n=99)

Reference standard: review of local hospital records re inpatients and outpatients; death register and primary care records; not stated who did this; time 3 months (n=99)

Comparator test: San Francisco Syncope Rule; time: initially (n=99).

Other comparator tests: 3/initial assessment based on ESC, AAP & ACP g2s; standardised assessment with 75 variables (11 clinical features, 9 med history, 11 current meds; 28 exam; 26 ECG) (n=99).

**Sun 2008 prospective cohort study; study held in USA.**

**Setting:** Emergency Department. urban, academic ED with emergency medicine residency (40,000 visits per annum) [April 2005 to April 2006].

**Funding:** unrestricted educational grant from American Geriatrics Society award (1st author)

**Participants**

TLoC population: unselected patients. Prior tests: Unclear or Not stated.

Adult ED patients with syncope or near syncope admitted 8am-10pm 7/7 days; review of ED intake log showed 76% eligible patients identified and screened; no differences between included and missed.

**Definition of TLoC:** Sudden transient loss of consciousness (=syncope); sensation of imminent loss of consciousness without actual syncope (=near syncope).

Inclusion criteria: adult patients with complaint of acute syncope or near syncope.

Exclusion criteria: head trauma-associated LoC; intoxication; patients with a witnessed seizure; ongoing confusion (incl. baseline cognitive impairment /dementia); age < 18 y; inability to speak English or Spanish; do-not-resus/DN intubate status; no follow-up contact info..

Patient characteristics: age: 29% <40y, 23% 40-59y, 25% 60-79y, 24% >80y; sex: 44% male; some patients with existing heart disease (30% had a cardiac history); history of TLoC: not stated

Comorbidities: Following outcomes: arrhythmia 33/461; myocardial ischaemia 2; aortic flow obstruction 5; cardiomyopathy 2; heart transplant complication 2.

Other details: 9% Hispanic; 78% white; 9% black, 11% Asian, 3% other; 65% had syncope as chief complaint

Other study comments: SAME pts as SUN 2007; diagnostic ECG = ECG abnormality related to cardiac event. Inter-rater reliability also checked in convenience sample (subgroup)

**Diagnostic tests**

Index test: 12-lead ECG and history of cardiac comorbidities structured form (abnormal changes incl non-sinus rhythm, left/right bundle branch block, etc); carried out by emergency med residents with 2-4 y experience; time: in ED (n=446; 31 did not receive ECG)

Reference standard: Follow up: phone interview by research assst; then 2 independent emergency physicians reviewed ED docs (incl ECGs), inpatient records & telephone forms; records for all with cardiac event reviewed by a panel of 3 ED physicians; also diagnostic ECGs noted; time 14 days (n=461)

for Target Condition/Outcome: sudden death, MI, arrhythmia (VT-3, sick sinus disease, etc) structural heart disease (aortic outflow obstruction, CM, heart transplant complications); acute cardiac intervention (e.g. pacemaker)
1.9 12-lead ECG automatic versus clinician read

**Study**

Charbit 2006
- Study held in: France
- Setting: recovery room after anaesthesia
- Funding: solely from institution/department
- Inclusion criteria: patients admitted to recovery room after anaesthesia
- Exclusion criteria: cardiac arrhythmias or bundle branch block.
- Patient characteristics: age: 45 (16) years; sex: 57% female
- Comorbidities: not stated.
- Other study comments: Bazett formula: QTcb = QT/(square root of RR); Fridericia formula: QTcf = QT/(cube root of RR)

Christov 2001
- Study held in: Bulgaria and Italy
- Setting: Cardiology
- Funding: NATO Individual Fellowship
- Inclusion criteria: patients from an annotated atrial flutter-fibrillation database: ECGs collected routinely in cardiology dept; >80% abnormal
- Exclusion criteria: Intensive noise in V1 signals preventing accurate detection of P-wave onset and T-wave end.
- Patient characteristics: age: not stated; sex: not stated
- Comorbidities: not stated. Other details: patients from an annotated atrial flutter-fibrillation database: ECGs collected routinely in cardiology dept; >80% abnormal

Denny 2007
- Study held in USA
- Setting: Hospital several departments (departments of biomedical informatics and medicine)
- Funding: National Library of Medicine grants
- Inclusion criteria: all inpatients admitted for 2-30 days from 1999-2003.
- Exclusion criteria: not stated
- Patient characteristics: age: not stated; sex: not stated
- Comorbidities: not stated.
- Other study comments: database of 44808 ECGs with cardiologist-generated free text impression and machine calculated QT intervals and heart rate

**Participant**

Population: postoperative patients. Prior tests: Unclear or Not stated.

**Diagnostic tests**

Index test: standard 12 lead ECG using Pagewriter M1770 (Hewlett Packard); corrected QTc calculated using Bazett or Fridericia formula; time: not stated (n=108)

Reference standard: analysed by one investigator; RR and QT intervals measured in chest lead with maximal T wave amplitude using digitising pad (SummaSketch III Professional); QTc (Bazett or Fridericia) averaged over 3-7 consecutive beats; time not stated (n=108)

for Target Condition/Outcome: prolonged QT interval (over 450ms for women and 440ms for men)
**Study**  
**Fatemi 2008**  
Study held in Iran  
Setting: Hospital several departments (Medical Science Research Institute and University hospital; ECGs from cardiac care unit and cardiac emergency ward)  
Funding: grants from Mashhad University

**Participant**  
Population: database of ECGs from patients in cardiac care unit and cardiac emergency ward. Prior tests: Unclear or Not stated.  
Inclusion criteria: patients admitted to CCU and Cardiac Emergency Ward.  
Exclusion criteria: not stated.

**Kaneko 2005**  
Study held in Japan  
Setting: Hospital several departments (several hospitals in Japan)  
Funding: not stated

**Participant**  
Population: general population plus specific patient group.  
patients with Brugada syndrome; other ECGs  
Definition of TLoC: not TLOC.  
Inclusion criteria: patients with Brugada syndrome; other ECGs.  
Exclusion criteria: not stated.  
Patient characteristics: age: not stated; sex: not stated; Unclear/not stated with existing heart disease (diagnoses not given for all patients); patients admitted to CCU and Cardiac Emergency Ward  
Comorbidities: not stated.

**Taha 2000**  
Study held in USA  
Setting: unclear  
Funding: lead author employed by GE Marquette Medical Systems

**Participant**  
Population: database of cardiologist-read ECGs; population unclear.  
Inclusion criteria: database of 4172 ECGs. Exclusion criteria: not stated.  
Patient characteristics: age: not stated; sex: not stated.  
Comorbidities: not stated

**Diagnostic tests**

**Fatemi 2008**  
Index test: 3-channel digital ECG device (GE industry of Germany); time: not stated (n=200)  
Reference standard: 4 cardiologists; time not stated (n=200)

**Kaneko 2005**  
Index test: ST segment abnormalities defined as characteristic of Brugada syndrome (several sets of rules) (n=21621)  
Reference standard: "classified by cardiologists"; time not stated (n=21621)

**Taha 2000**  
Index test: time-based criteria for detecting atrial flutter or fibrillation (12SL MAC-Rhythm, GE Marquette Medical Systems, Milwaukee, WI); time: not stated (n=4172)  
Reference standard: expert cardiologist; time not stated (n=4172)

**Other study comments**: 97 ECGs from 27 patients with Brugada syndrome plus 21,524 other ECGs (10,564 from population health checkups; 9740 from university hospital; 1220 CSE database)

**Other study comments**: database of 4172 ECGs; frequency domain measures of QRST- subtracted signals to differentiate between atrial flutter and fibrillation versus neither of these

**Other study comments**: database of 4172 ECGs; frequency domain measures of QRST- subtracted signals to differentiate between atrial flutter and fibrillation versus neither of these
2 Initial assessment – more details on index tests

The index tests in chapter 3 are described in more detail below: it should be noted that each test includes a description of signs and symptoms or test results under the headings of cardiac cause, vascular cause and other cause. When considering the test, all three sections should be referred to.

2.1 Cardiac cause

<table>
<thead>
<tr>
<th>Study</th>
<th>cardiopulmonary cause</th>
<th>structural heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Syncope Criteria (Grossman 2007)</td>
<td>Signs and symptoms of acute coronary syndrome:</td>
<td>Signs and symptoms of acute coronary syndrome:</td>
</tr>
<tr>
<td></td>
<td>● ECG changes VT, VF, SVT, rapid AF or new STT wave change</td>
<td>● chest pain of possible cardiac origin</td>
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<tr>
<td></td>
<td>Worrying cardiac history:</td>
<td>● ischaemic ECG changes (ST elevation or deep (&gt;0.1mV) ST depression)</td>
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<tr>
<td></td>
<td>● history of VT, VF</td>
<td>● complaint of shortness of breath</td>
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<tr>
<td></td>
<td>● history of pacemaker</td>
<td>Worrying cardiac history:</td>
</tr>
<tr>
<td></td>
<td>● history of ICD</td>
<td>● history of CAD, incl deep q waves, hypertrophic/ dilated cardiomyopathy</td>
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<tr>
<td></td>
<td>● prehospital use of antidysrhythmic medication excluding beta blockers or calcium channel blockers</td>
<td>● history of congestive heart failure or LV dysfunction</td>
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<td></td>
<td>Family history:</td>
<td>Family history:</td>
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<tr>
<td></td>
<td>● 1st degree relative with Brugada's or long QT syndromes</td>
<td>● 1st degree relative with sudden death, HOCM</td>
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<td></td>
<td>Signs of conduction disease:</td>
<td>Valvular heart disease:</td>
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<tr>
<td></td>
<td>● multiple syncopal episodes within the last 6 months</td>
<td>● heart murmur noted in history or on ED examination</td>
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<td>● rapid heart beat by patient history</td>
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<tr>
<td></td>
<td>● syncope during exercise</td>
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<td></td>
<td>● QT interval &gt; 500 ms</td>
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<td></td>
<td>● 2nd or 3rd degree heart block or intraventricular block</td>
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<td></td>
<td>Persistent (&gt; 15 min) abnormal vital signs in ED:</td>
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<td></td>
<td>● sinus rate &lt; 50 beats/min or &gt; 100 beats/min</td>
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<tr>
<td>San Francisco Syncope Rule (Quinn 2005)</td>
<td>● abnormal ECG result (any non-sinus rhythm or any new changes)</td>
<td>● history of congestive heart failure</td>
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<tr>
<td></td>
<td></td>
<td>● complaint of shortness of breath</td>
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<tr>
<td>Study</td>
<td>Cardiopulmonary Cause</td>
<td>Diagnoses</td>
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<td>----------------------------------------------------------------------</td>
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<tr>
<td><strong>Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL) score</strong> (Covicchi 2004; Reed 2007)</td>
<td>Arrhythmia</td>
<td>Structural heart disease</td>
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<tr>
<td>History findings:</td>
<td></td>
<td></td>
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<tr>
<td>● age &gt; 65 years</td>
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<tr>
<td>● no prodromal symptoms</td>
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<tr>
<td>ECG findings</td>
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<tr>
<td>● Atrial fibrillation or flutter</td>
<td></td>
<td></td>
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<tr>
<td>● Supraventricular tachycardia</td>
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<tr>
<td>● Multifocal atrial tachycardia</td>
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<tr>
<td>● Frequent or repetitive premature supraventricular or ventricular complexes</td>
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<td>● Sustained or non-sustained ventricular tachycardia</td>
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<td>● Paced rhythms</td>
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<tr>
<td>● Complete atrioventricular block</td>
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<tr>
<td>● Mobitz I or II atrioventricular block</td>
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<tr>
<td>● Bundle branch block</td>
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<tr>
<td>● Intraventricular conduction delay</td>
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<tr>
<td>History findings:</td>
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<td></td>
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<tr>
<td>● Age &gt; 65 years</td>
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<td></td>
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<tr>
<td>● No prodromal symptoms</td>
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<tr>
<td>Initial evaluation (but unclear which was index test) (Alboni 2001)</td>
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<td></td>
</tr>
<tr>
<td>● Sinus bradycardia &lt; 40 beats per minute</td>
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<tr>
<td>● Repetitive sinoatrial blocks</td>
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<td></td>
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<tr>
<td>● Sinus pauses &gt; 3sec</td>
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<tr>
<td>● Mobitz II or advanced 2nd or 3rd degree atrioventricular block</td>
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<td>● Atrial fibrillation with a slow ventricular response</td>
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<td>(mean heart rate &lt; 50 beats/min)</td>
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<tr>
<td>● Sustained supraventricular tachycardia or ventricular tachycardia</td>
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<tr>
<td>Initial evaluation (ESC guidelines) certain diagnosis (van Dijk 2008)</td>
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<tr>
<td>● Sinus bradycardia &lt; 40 beats per minute</td>
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<tr>
<td>● Repetitive sinoatrial blocks</td>
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<tr>
<td>● Sinus pauses &gt; 3sec in absence of negatively chronotropic medications</td>
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<tr>
<td>● Mobitz II 2nd or 3rd degree atrioventricular block</td>
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<td>● Alternating left and right bundle branch block</td>
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<tr>
<td>● Rapid paroxysmal supraventricular tachycardia or ventricular tachycardia</td>
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<tr>
<td>● Pacemaker malfunction with cardiac pauses</td>
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<tr>
<td>Initial evaluation (ESC guidelines) highly likely diagnosis (van Dijk 2008)</td>
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<tr>
<td>● Symptoms present with ECG evidence of acute ischaemia with or without myocardial ischaemia</td>
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<tr>
<td>Study</td>
<td>Cardiopulmonary Cause</td>
<td>Diagnoses</td>
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**Transient loss of consciousness: full guideline DRAFT (January 2010)**
<table>
<thead>
<tr>
<th>Initial evaluation symptoms only (Sheldon 2003)</th>
<th>• any presyncope</th>
<th>• any presyncope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial evaluation symptoms + history (Sheldon 2003)</td>
<td>• any presyncope</td>
<td>• any presyncope</td>
</tr>
<tr>
<td>12-lead ECG (Sun 2008)</td>
<td><strong>History findings:</strong>&lt;br&gt;• history of ventricular arrhythmia, supraventricular rhythms incl AF or flutter, bradycardia, sick sinus syndrome, implanted pacemaker or defibrillator&lt;br&gt;<strong>ECG findings:</strong>&lt;br&gt;• any non-sinus rhythm&lt;br&gt;• left or right bundle branch block&lt;br&gt;• sinus bradycardia &lt; 50 beats per minute&lt;br&gt;• abnormal conduction interval excluding 1st degree block</td>
<td><strong>History findings:</strong>&lt;br&gt;• coronary artery disease&lt;br&gt;• congestive heart failure&lt;br&gt;• aortic stenosis&lt;br&gt;• pulmonary heart disease&lt;br&gt;<strong>ECG findings:</strong>&lt;br&gt;• Q/ST/T changes consistent with acute or chronic ischaemia&lt;br&gt;• left axis deviation&lt;br&gt;• left or right ventricular hypertrophy</td>
</tr>
<tr>
<td>ACP guidelines for admission; high risk (Crane 2002)</td>
<td><strong>History findings:</strong>&lt;br&gt;• history of VT&lt;br&gt;<strong>ECG findings:</strong>&lt;br&gt;• serious bradycardia&lt;br&gt;• serious tachycardia&lt;br&gt;• long QT interval&lt;br&gt;• Bundle branch block</td>
<td><strong>History findings:</strong>&lt;br&gt;• history of coronary artery disease&lt;br&gt;• history of congestive cardiac failure&lt;br&gt;• symptoms of chest pain&lt;br&gt;• physical signs of CCF&lt;br&gt;• physical signs of significant valve disease&lt;br&gt;<strong>ECG findings:</strong>&lt;br&gt;• ischaemia</td>
</tr>
<tr>
<td>ACP guidelines for admission; moderate risk (Crane 2002)</td>
<td>• suspicion of arrhythmia&lt;br&gt;• age over 70 years</td>
<td>• suspicion of coronary heart disease&lt;br&gt;• syncope during exertion or with injury&lt;br&gt;• TLoC with rapid heart action</td>
</tr>
<tr>
<td>Study</td>
<td>cardiopulmonary cause</td>
<td>structural heart disease</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------------------</td>
<td>-------------------------------------------------</td>
</tr>
</tbody>
</table>
| ACEP guidelines for cardiac syncope (admission); level B (Elesber 2005) | **History findings:** ● history of ventricular arrhythmias; premature ventricular contractions that were frequent (>10 per hour), repetitive (≥2 consecutive) or multifocal | **History findings:** ● history of congestive cardiac failure ● associated chest pain or other symptoms of acute coronary syndrome ● physical signs of significant CCF ● physical signs of significant valve disease  
**ECG findings:** ● ischaemia |
| ACEP guidelines for cardiac syncope (admission); level C (Elesber 2005) | ● age over 60 years | ● history of coronary artery disease or congenital heart disease ● syncope during exertion in younger patients without an obvious, benign cause for the syncope ● Family history of unexpected sudden death  
**ECG findings:** ● 3rd degree atrioventricular block |
| Sarasin risk score - strongly suspected cause of syncope (Sarasin 2003) | **ECG findings:** ● 3rd degree atrioventricular block |  
**History findings:** ● age > 65 years  
**ECG findings:** ● Atrial fibrillation ● sinus pause ≥2 & <3s ● sinus bradycardia >35bpm & ≤45 ● conduction disorders (bundle branch block, 2nd degree Mobitz I AV block, bifascicular block) ● signs of old myocardial infarction or ventricular hypertrophy ● multiple premature ventricular beats |
| Sarasin risk score - suspected arrhythmia cause (Sarasin 2003) |  
**History findings:** ● age > 65 years  
**ECG findings:** ● P wave duration longer (≥120 ms or non-sinus rhythm) | **History findings:** ● history of congestive heart failure |
| Graf risk score for rhythmic syncope (Graf 2008) | ● age increasing (in categories ≤45; 45-65 y; > 65y) ● number of prodromes (decreasing; bigger effect for prodromes <1) |  
**History findings:** ● P wave duration longer (≥120 ms or non-sinus rhythm) |
2.2 **Vascular cause**

<table>
<thead>
<tr>
<th>Study</th>
<th>Neurally Mediated</th>
<th>Vasovagal</th>
<th>Situational</th>
<th>Orthostatic Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boston Syncope Criteria</strong> (Grossman 2007)</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>San Francisco Syncope Rule</strong> (Quinn 2005)</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Haematocrit &lt; 30, Triage systolic bp &lt; 90 mm Hg</td>
</tr>
<tr>
<td><strong>Osservatorio Epidemiologico sulla Sincope nel Lazio</strong> (OESIL) score (Covicchi 2004; Reed 2007)</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Initial evaluation (but unclear which was index test)</strong> (Alboni 2001)</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Decrease in systolic bp of at least 20 mm Hg during 5 min after the patient assumed the upright position</td>
</tr>
</tbody>
</table>

- **Volume depletion:**
  - GI bleeding by haemoccult or history
  - Haematocrit < 30
  - Dehydration not corrected in the ED per treating physician discretion
  - Persistent (> 15 min) abnormal vital signs in the ED without need of concurrent interventions:
    - Respiratory rate > 24 breaths / min
    - Oxygen saturation < 90%
    - Systolic bp < 90 mm Hg

- **Precipitating events:**
  - Such as fear, severe pain, strong emotional, instrumentation identified in the absence of another competing diagnosis
  - Syncope during or immediately after urination, defecation, cough or swallowing

- **Decrease in systolic bp of at least 20 mm Hg during 5 min after the patient assumed the upright position**
<table>
<thead>
<tr>
<th>Study</th>
<th>Neurally mediated</th>
<th>Vasovagal</th>
<th>Situational</th>
<th>Orthostatic Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED guidelines: high risk (admit) (Reed 2007)</td>
<td></td>
<td></td>
<td></td>
<td>Clinical examination:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>● systolic bp &lt; 90 mm Hg</td>
</tr>
<tr>
<td>ED guidelines: medium risk (consider discharge with early outpatient</td>
<td></td>
<td></td>
<td></td>
<td>● decrease in bp of</td>
</tr>
<tr>
<td>review) (Reed 2007)</td>
<td></td>
<td></td>
<td></td>
<td>20 mm Hg on standing</td>
</tr>
<tr>
<td>Initial evaluation (ESC guidelines) certain diagnosis (van Dijk 2008)</td>
<td></td>
<td>● precipitating events (such as fear, severe pain, emotional distress, instrumentation, or prolonged standing) which are associated with typical prodromal symptoms</td>
<td>● syncope during or immediately after urination, defecation, cough or swallowing</td>
<td>● documentation of orthostatic hypotension associated with syncope or presyncope ● decrease in systolic bp of 20 mm Hg or a decrease of systolic bp to &lt;90 mm Hg is defined as orthostatic hypotension regardless of whether or not symptoms occur</td>
</tr>
<tr>
<td>Initial evaluation (ESC guidelines) highly likely diagnosis (van</td>
<td>● absence of cardiac disease ● long history of syncope ● preceded by unpleasant sight, sound, smell or pain ● prolonged standing or crowded hot places ● nausea/vomiting associated with syncope ● during/in the absorptive state after meal ● with head rotation, pressure on carotid sinus ● after exertion</td>
<td></td>
<td></td>
<td>● after standing up ● temporal relationship with start of medication leading to hypotension or changes of dose ● prolonged standing especially in crowded hot places ● presence of autonomic neuropathy or Parkinsonism ● after exertion</td>
</tr>
<tr>
<td>Dijk 2008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>study</td>
<td>neurally mediated</td>
<td>vasovagal</td>
<td>situational</td>
<td>orthostatic hypotension</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Initial evaluation symptoms only (Sheldon 2003)                       | ● any presyncope  
 ● diaphoresis before TLoC                                       | ● any presyncope  
 ● prolonged standing or sitting  
 ● diaphoresis before TLoC | ● any presyncope                                                                 | ● any presyncope  
 ● prolonged standing or sitting  
 ● diaphoresis before TLoC                                                                 |
| Initial evaluation symptoms + history (Sheldon 2003)                  | ● any presyncope  
 ● diaphoresis before TLoC                                       | ● any presyncope  
 ● prolonged standing or sitting  
 ● diaphoresis before TLoC | ● any presyncope                                                                 | ● any presyncope  
 ● prolonged standing or sitting  
 ● diaphoresis before TLoC                                                                 |
2.3 Other causes of TLoC

<table>
<thead>
<tr>
<th>study</th>
<th>hypovolaemia</th>
<th>neurological</th>
<th>cerebrovascular event (i.e. subarachnoid haemorrhage; stroke)</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Syncope Criteria (Grossman 2007)</td>
<td>none</td>
<td>none</td>
<td>Primary CNS event (i.e. subarachnoid haemorrhage; stroke)</td>
<td>none</td>
</tr>
<tr>
<td>San Francisco Syncope Rule (Quinn 2005)</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL) score (Covicchi 2004; Reed 2007)</td>
<td>none</td>
<td>none</td>
<td>History findings: clinical history of stroke or transient ischaemic attack</td>
<td>none</td>
</tr>
<tr>
<td>initial evaluation (but unclear which was index test) (Alboni 2001)</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
</tbody>
</table>

ED guidelines: medium risk (consider discharge with early outpatient review) (Reed 2007)

Clinical examination:
- TLoC preceded by tremors, confusion, hunger and a hyperadrenergic state, and glycaemia was < 40 mg/dl
- drug-induced: clear temporal relationship between drug assumption and syncope could be proven

Clinical examination:
- suspicion of cerebrovascular accident or subarachnoid haemorrhage
- syncope associated with headache

Clinical examination:
- trauma associated with collapse
<table>
<thead>
<tr>
<th>study</th>
<th>hypovolaemia</th>
<th>neurological</th>
<th>cerebrovascular</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial evaluation (ESC guidelines) certain diagnosis (van Dijk 2008)</td>
<td>none</td>
<td>(Not necessarily ‘certain diagnosis’) • Confusion after attack for more than 5 min • Tonic-clonic movements, automatism, tonguebiting, blue face, epileptic aura none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Initial evaluation (ESC guidelines) highly likely diagnosis (van Dijk 2008)</td>
<td>none</td>
<td>• with arm exercise • differences in blood pressure or pulse in the 2 arms none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Initial evaluation symptoms only (Sheldon 2003)</td>
<td>• any presyncope</td>
<td>• waking with cut tongue • abnormal behaviour (as witnessed), witnessed unresponsiveness, unusual posturing or limb jerking • LoC with emotional stress • head turning to one side during LoC</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Initial evaluation symptoms + history (Sheldon 2003)</td>
<td>• any presyncope</td>
<td>• LoC with emotional stress • head turning to one side during LoC • Unresponsiveness during LoC History findings: • number of spells &gt;30 none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>ACP guidelines for admission; high risk (Crane 2002)</td>
<td>none</td>
<td>History findings: • physical signs of stroke or focal neurology none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>ACP guidelines for admission; moderate risk (Crane 2002)</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>study</td>
<td>hypovolaemia</td>
<td>neurological</td>
<td>cerebrovascular</td>
<td>other</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
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<td>--------------</td>
<td>-----------------</td>
<td>-------</td>
</tr>
<tr>
<td>ACEP guidelines for cardiac syncope (admission); level B (Elesber 2005)</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>ACEP guidelines for cardiac syncope (admission); level C (Elesber 2005)</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Sarasin risk score - strongly suspected cause of syncope (Sarasin 2003)</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Sarasin risk score - suspected arrhythmia cause (Sarasin 2003)</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Graf risk score for rhythmic syncope (Graf 2008)</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Graf risk score for vasovagal and psychogenic pseudosyncope (Graf 2008)</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
</tbody>
</table>
3 Second stage tests – included studies tables

3.1 Ambulatory ECG - suspect arrhythmia review

3.1.1 Diagnostic Test: Holter monitoring 24-hour

<table>
<thead>
<tr>
<th>Study</th>
<th>Participant</th>
<th>Diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boudoulas 1979 non-randomised comparative study; study held in USA. Setting: Cardiology. Funding: National Institutes of Health and Central Ohio Heart Chapter of the American Heart Association</td>
<td>TLoC population: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test. syncope or presyncope (dizziness or lightheadedness) Inclusion criteria: patients with syncope or presyncope (dizziness or lightheadedness). TLoC history: not stated Comorbidities: not stated. Other details: patients with syncope or presyncope (dizziness or lightheadedness) Other study comments: 2 tests within 1 week</td>
<td>Index test: 24 hour ambulatory heart rate recording (Avionics Electrocardiocorder Model 400); automatic recording of all ECG; diary for symptoms; time: 24 hours (n=119) Comparator test: maximum multistage treadmill exercise test Bruce protocol; time: 1 day (n=119); for Target Condition/Outcome: sinus brady below 40 bpm awake; paroxysmal VT (170 bpm); high grade AV block; frequent ventricular premature contractions, effective rate less than 40 bpm; repetitive pairs PVCs; VT</td>
</tr>
<tr>
<td>Boudoulas 1983 case series; study held in USA. Setting: Cardiology. Funding: not stated</td>
<td>TLoC population: unclear/not stated. Prior tests: All patients had at least 1 prior test. syncope or presyncope; had had EEG (some also had CT or cerebral angiography) Inclusion criteria: syncope or presyncope. Exclusion criteria: obvious cause of syncope or significant arrhythmia on resting ECG. Patient characteristics: age: not stated; sex: not stated; some patients with a history of heart disease; TLoC history: not stated Comorbidities: not stated. Other details: see below Other study comments: case series; 24 hour monitoring and electrophysiological study within 1 week</td>
<td>Index test: 24 hour ambulatory ECG (Avionics model 660-A); whole rhythm analysed; symptom diary; time: 24 hours (n=65) Comparator test: referenced but not described in this paper; time: 1 day (n=65); for Target Condition/Outcome: sinus brady less than 40 bpm awake; sinoatrial exit block; paroxysmal VT (rate over 170 bpm); repetitive pairs premature ventricular beats; VT</td>
</tr>
<tr>
<td>Brembilla-Perrot 2001 case series; study held in France. Setting: Cardiology. Funding: not stated</td>
<td>TLoC population: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test. referred with syncope or presyncope and myocardial infarction Definition of TLoC: not stated. Exclusion criteria: patients with syncope, MI and complete bundle branch block. Inclusion criteria: patients with MI. Exclusion criteria: uncertain diagnosis of MI, incomplete or uncertain conduction disturbance, technical or practical problems with recordings, amiodarone in last 6 mo, another prior MI, bypass surgery, or associated cardiac or non-cardiac condition that could affect SAECG. Patient characteristics: age: median age 65 years (range 26 to 82 years); sex: 90% male; All patients with existing heart disease (MI and BBB); TLoC history: not stated Comorbidities: not stated. Other details: see below Other study comments: case series</td>
<td>Index test: Holter monitor analysed with ELATEC system; time: 24 hours (n=130) Comparator test: &quot;performed according to the literature&quot;; post-absorptive, non-sedated state; time: 1 day (n=130); for Target Condition/Outcome: non-sustained ventricular tachycardia (3 consecutive beats or tachycardia less than 10 seconds)</td>
</tr>
</tbody>
</table>
### Study

<table>
<thead>
<tr>
<th>Brembilla-Perrot 2004</th>
<th>TLoC population: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test.</th>
<th>Index test: Holter monitoring (Elatec); time: 24 hours (n=119) for Target Condition/Outcome: ventricular arrhythmias (couplets or nonsustained VT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brembilla-Perrot 2004 case series; study held in France.</td>
<td>Definition of TLoC: a short loss of consciousness. Inclusion criteria: Coronary disease with history of MI and/or multiple coronary stenoses on angiography and LVEF below 40%. Exclusion criteria: unstable angina, MI in last mo, coronary angioplasty/bypass last 6 wk, paroxysmal 2nd/3rd degree AV block, sustained SVT or VT, clinical HF not controlled by furosemide, uncontrolled electrolyte abn, significant non-cardiac dis, long term amiodarone. Patient characteristics: age: mean 65 (11.5) years, range 25 to 80 years; sex: 85% male; All patients with existing heart disease (coronary disease with history of MI and/or multiple coronary stenoses on angiography and LVEF below 40%); TLoC history: unexplained syncope or dizziness and at least 1 episode of syncope Comorbidities: not stated. Other details: see below Other study comments: Group 1 of study</td>
<td>Index test: Holter monitoring (Elatec); time: 24 hours (n=61) for Target Condition/Outcome: ventricular arrhythmias (couplets or nonsustained VT)</td>
</tr>
<tr>
<td>Sarasin 2005 case series; study held in Switzerland.</td>
<td>TLoC population: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test. Exclusion criteria: unstable angina, MI in last mo, coronary angioplasty/bypass last 6 wk, paroxysmal 2nd/3rd degree AV block, sustained SVT or VT, clinical HF not controlled by furosemide, uncontrolled electrolyte abn, significant non-cardiac dis, long term amiodarone. Patient characteristics: age: mean 62 (10) years, range 27 to 78 years; sex: 85% male; All patients with existing heart disease (idiopathic dilated cardiomyopathy, normal coronary angiogram, LVEF below 40%); TLoC: TLoC history: unexplained syncope or dizziness and at least 1 episode of syncope Comorbidities: not stated. Other details: see below Other study comments: Group 2 of study</td>
<td>Index test: Holter monitoring (Elatec); time: 24 hours (n=140) for Target Condition/Outcome: prespecified: sinus pause 3s or more; sinus brady 35bpm or less; AF + slow ventricular response (RR 3s or more); SVT 30s or more at 180bpm or more with hypotension; Mobitz 2 2nd degree/complete AV block; VT 30s or more</td>
</tr>
</tbody>
</table>

### Participant

- **TLoC population**: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test.
- **Inclusion criteria**: Coronary disease with history of MI and/or multiple coronary stenoses on angiography and LVEF below 40%.
- **Exclusion criteria**: unstable angina, MI in last mo, coronary angioplasty/bypass last 6 wk, paroxysmal 2nd/3rd degree AV block, sustained SVT or VT, clinical HF not controlled by furosemide, uncontrolled electrolyte abn, significant non-cardiac dis, long term amiodarone.
- **Patient characteristics**: age: mean 65 (11.5) years, range 25 to 80 years; sex: 85% male; All patients with existing heart disease (coronary disease with history of MI and/or multiple coronary stenoses on angiography and LVEF below 40%); TLoC history: unexplained syncope or dizziness and at least 1 episode of syncope.
- **Comorbidities**: not stated. Other details: see below
- **Other study comments**: Group 1 of study.

### Funding

- **Primary Hospital**: Hospital University Medical School; major primary and tertiary hospital for the area.
- **Secondary Hospitals**: several departments, main teaching hospital of Geneva.
- **Funding**: not stated.
3.1.2 Diagnostic Test: Holter monitoring 48-hour

**Study**
Arya 2005
Case series; study held in Iran.
Setting: Cardiology. arrhythmia clinic.
Funding: none stated

**Participant**
TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.

syncope or presyncope; had had clinical assessment including BP, ECG and echo

Inclusion criteria: recurrent unexplained syncope and single episode associated with injury, or presyncope.

Exclusion criteria: none stated.

Patient characteristics: age: mean 53 years (16.9 years); sex: 57% male; some patients with existing heart disease (71% had heart disease); recurrent unexplained syncope or single episode associated with injury, or presyncope.

Comorbidities: Other details: referred to arrhythmia clinic

**Diagnostic tests**
Index test: 2 x 24-hour Holter recordings (VISTA); all 48 hours of recording analysed; time: 48 hours (n=49)

Other comparator tests: case series: no comparator.

for Target Condition/Outcome: main ECG finding (non-sustained VT 3 beats or more; sinus pause 3s or more; symptomatic bradycardia below 30 beats/min; paroxysmal atrial fibrillation; sustained SVT above 150 beats/min; VT above 100 beats/min; Mobitz type II 2nd or 3rd degree AV block)

Ringqvist 1989
Case series; study held in Sweden.
Setting: Hospital several departments.
Departments of Clinical Physiology and Internal Medicine.
Funding: not stated

**Participant**
TLoC population: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test.

patients referred for investigation of syncope from Department of Internal Medicine or GP

Definition of TLoC: not stated.

Inclusion criteria: patients referred for investigation of syncope; clinical examination had ruled out other causes of symptoms than arrhythmia.

Exclusion criteria: none.

Patient characteristics: age: mean age 70 (13) years; sex: not stated; some patients with existing heart disease (46% had cardiac diagnosis (MI 18 pts, angina 22 pts, valve disease 1 pt, cardiomyopathy 2 pts); 24% hypertension; TLoC history: 22 patients had single episodes; 18 had 2-3 episodes; 23 had multiple episodes

Comorbidities: Hypertension 15 pts. Other details: Clinical examination had ruled out other causes of symptoms than arrhythmia

Other study comments: case series

3.1.3 Diagnostic Test: external event recorder

**Study**
Rothman 2007
RCT; study held in USA.
Setting: Cardiology. Multicentre.
Funding: Cardionet Inc

**Participant**
TLoC population: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test.

high clinical suspicion of malignant arrhythmia; syncope or presyncope; non-diagnostic 24 hour Holter or telemetry in last 45 days

Definition of TLoC: syncope or presyncope (transient dizziness, lightheadedness, unsteadiness or weak spells without LOC).

Inclusion criteria: high clinical suspicion of malignant arrhythmia; syncope or presyncope; non-diagnostic 24 hour Holter or telemetry in last 45 days.

Exclusion criteria: NYHA Class IV heart failure, MI in last 3 months, unstable angina, candidate for or recent valve surgery, sustained VT or VF, complex ectopy, below 18 years, other condition prohibiting completion of or compliance with protocol.

Patient characteristics: age: mean age 56 years; sex: around 30% male; some patients with existing heart disease (around 49% hypertension; 20% coronary artery disease; 5% MI; 5% congestive heart failure).

TLoC history: not stated

Comorbidities: not stated. Other details: non-diagnostic 24 hour Holter or telemetry in last 45 days. Other study comments: RCT

**Diagnostic tests**
Index test: portable 1 or 2 channel FM cassette recorders (SRA-Helige); patient activated; symptom diary; time: 48 hours (n=63)
for Target Condition/Outcome: prespecified: sinus brady below 40bpm 1 min; sinus arrest 3s or more; SVT heart rate 180 or more over 10s; VT 3 or more beats; AV block Mobitz II/3rd degree; paroxysmal AF 180 bpm or more for 4 beats; AF or flutter rate below 40 at least 1min/RR 4s/more

Index test: external loop event monitoring; patient or automatically activated; time: up to 30 days (minimum 25 days) (n=52)
Comparator test: mobile cardiac outpatient telemetry (MCOT; CardioNet): continual recording; time: up to 30 days (n=62).

for Target Condition/Outcome: prespecified: pauses; complete AV block; Mobitz type 2 2nd deg block; AF/flutter; rate over 120bpm + symptoms; over 150 - symptoms; brady below 40bpm + symptoms; sustained (over 10s)/symptomatic SVT over 120bpm; VT over 100bpm over 3 beats
### 3.1.4 Diagnostic Test: implantable event recorder - patient activated

#### Study
- **Brignole 2001**: case series; study held in Multinational. Setting: Hospital several departments. Funding: not stated
- **Garcia-Civera 2005**: case series; study held in Spain. Setting: Cardiology. Funding: not stated
- **Krahn 1999**: time: case series; study held in multinational. Setting: Hospital several departments. Funding: supported in part by the Heart and Stroke Foundation of Ontario

#### Participant
- **TLoC population**: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test. Bundle branch block and negative EPS, carotid sinus massage, echo, 24-hour ECG. Definition of TLoC: syncope of uncertain aetiology. Inclusion criteria: patients with any type of bundle branch block and negative EPS.

**Patient characteristics**: age: mean 71 (8) years; sex: 83% male; some patients with existing heart disease (54% had structural heart disease); TLoC history: mean 4.6 (6.1) episodes

**Comorbidities**: not stated. Other details: see below

**Other study comments**: case series

- **TLoC population**: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test. suspected arrhythmic syncope and negative EPS, ECG, carotid sinus massage, BP, 24 hour ambulatory ECG (other tests if clinically indicated)

**Inclusion criteria**: suspected arrhythmic syncope (because of structural heart disease, abnormal ECG, significant asymptomatic arrhythmia on Holter, paroxysmal palpitations before syncope, family history of sudden death) and negative EPS; at least 1 syncope in last year

**Exclusion criteria**: not stated.

**Patient characteristics**: age: mean 63.5 (15) years; sex: 72% male; some patients with existing heart disease (63% had structural heart disease); TLoC history: at least 1 syncope in last year

**Comorbidities**: not stated. Other details: see below

**Other study comments**: case series

- **TLoC population**: patients with a suspected arrhythmia but 12-lead ECG normal.

**Prior tests**: All patients had at least 1 prior test. undiagnosed after history, examination, ECG and at least 24 hours ambulatory monitoring

**Definition of TLoC**: transient loss of consciousness with spontaneous recovery. Inclusion criteria: 2 syncopal episodes in previous 12 months or 1 syncope plus presyncope.

**Exclusion criteria**: unlikely to survive 1 year; unable to consent; previously implanted programmable device; pregnant or of childbearing age and not on reliable contraception.

**Patient characteristics**: age: mean 59 (18) years; sex: 52% male; some patients with existing heart disease (62% had heart disease); TLoC history: mean 5.1 episodes in previous 12 months

**Comorbidities**: not stated. Other details: see below

**Other study comments**: case series no comparator; extra info added in from Krahn 2001 (832) - same patients

#### Diagnostic tests
- **Test**
  - **Index test**: Reveal; patient activated; time: median 48 days (IQR 16 to 100); seen every 3 months, until an event or until battery ran down (n=52)

  **Target Condition/Outcome**: symptom/rhythm correlation; events recorded were prolonged asystolic pause (AV block or sinus arrest); AF; unclear which other arrhythmias would have been included

- **Test**
  - **Index test**: Reveal ILR implanted; patient activated; time: mean 9.2 (5.9) months; seen every 3 months; followed yup until diagnosis reached, battery expired or patient died (n=81)

  **Target Condition/Outcome**: symptom/rhythm correlation; prespecified arrhythmic syncope if high degree AV block or VT; neurally mediated if sinus bradycardia up to 40 bpm or sinus pause 3 seconds or more; indeterminate if sinus rhythm

- **Test**
  - **Index test**: Reveal; patient activated; time: mean 10.5 (4) months; follow up after each event; device in until syncope/presyncope; 18 months follow up; end of battery life; or patient or investigator chose to remove it sooner (n=85)

  **Target Condition/Outcome**: arrhythmia or exclusion of arrhythmic cause: found: bradycardia below 50bpm; tachycardia (sustained SVT; atrial flutter with rapid ventricular response) not prespecified


### Study

**Menozzi 2002**
- Case series; study held in multinational.
- Setting: Hospital cardiologists
- Funding: not stated

### Participant

TLoC population: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test.
- Suspected tachycardia cause; carotid sinus massage, echo, 24-hour ambulatory ECG not diagnostic
- Definition of TLoC: syncope of uncertain origin
- Inclusion criteria: patients with overt heart disease and negative electrophysiologic study; at risk of ventricular arrhythmia due to previous MI, cardiomyopathy, reduced LVEF or non-sustained VT
- Exclusion criteria: bundle branch block.
- Patient characteristics: age: mean age 66 (13) years; sex: 89% male; All patients with existing heart disease (at risk of ventricular arrhythmia due to previous MI, cardiomyopathy, reduced LVEF or non-sustained VT);
- TLoC history: median 2 (IQR 1-4) episodes in last 2 years
- Comorbidities: not stated. Other details: see below
- Other study comments: case series no comparator

### Diagnostic tests

Index test: Reveal; patient activated; time: mean 16 (11) months; seen every 3 months until diagnosis, end of battery life or patient died (n=35)
- For Target Condition/Outcome: ECG during syncope: arrhythmias found (not prespecified) were: AV block plus asystole; sinus tachy plus sinus brady plus sinus arrest; sinus tachy 120bpm; AF (+ or - asystole)

### 3.2 Ambulatory ECG - suspect NM syncope review

#### 3.2.1 Diagnostic Test: Holter monitoring 48-hour

### Study

**Fitchet 2003**
- Case series; study held in UK.
- Setting: Cardiology, cardiologist-run syncope clinic or tertiary referral centres.
- Funding: not stated

### Participant

TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: Unclear or Not stated.
- Blackouts suggestive of vasovagal syncope
- Definition of TLoC: blackouts suggestive of vasovagal syncope.
- Inclusion criteria: blackouts suggestive of vasovagal syncope.
- Exclusion criteria: contraindications to HUT test.
- Patient characteristics: age: mean 50 (20) years, range 16-88 years; sex: 58% female; some patients with existing heart disease (7% had IHD and 1% impaired left ventricular function); TLoC history: previous syncope burden 22 (20) range 1-50 episodes over 8.8 (10.9) years (range 0.02 to 60.0).
- Comorbidities: not stated. Other details: see below
- Other study comments: case series

### Diagnostic tests

Index test: Holter monitor (no further details); time: 48 hours (n=118)
- Comparator test: fasting 2 to 4 hours; supine 20 minutes; tilt to 60 degrees for 45 minutes; if negative at 30 minutes, GTN 400 microg sublingually or isoprenaline IV 1 microg/min, increasing according to heart rate response to a maximum of 5microg/min for 15 minutes; time: Maximum duration 65 minutes (n=118).

- For Target Condition/Outcome: events recorded during TLOC were sinus tachy, sinus rhythm, AF; major arrhy not during TLOC were nonsustained VT or SVT; AF; sinus brady; minor ones were isolated vent ectopics/bigeminy/trigeminy/couplets; 1st degree heart block (not prespecified)
3.2.2 Diagnostic Test: implantable event recorder - patient activated

**Study**
- Moya 2001
  - case series; study
- Multinational
  - Setting: Hospital
  - several departments.
  - Funding: not stated

**Participant**
- TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. normal ECG, tilt test positive
- Definition of TLoC: syncope of uncertain origin.
- Inclusion criteria: no significant structural heart disease; 3 or more episodes in last 2 years; interval of 6 months or more between 1st & last episode; history, examination, ECG, carotid sinus massage, echo, 24-hour ECG not diagnostic; tilt test positive.
- Exclusion criteria: none.
- Patient characteristics: age: mean 64 (15) years; sex: 38% male; some patients with existing heart disease (31% had heart disease);
- TLoC history: 3 or more episodes in last 2 years
- Comorbidities: not stated. Other details: see below
- Other study comments: case series no comparator; tilt positive patients i.e. suspected NMS

**Diagnostic tests**
- Index test: Reveal; patient activated; time: mean 10 (5) months; seen every 3 months until diagnosis, battery ran down or end of study (maximum 36 months) (n=29) for Target Condition/Outcome: ECG/syncope: findings (not prespecified): asystole

3.2.3 Diagnostic Test: implantable event recorder - patient and automatically activated

**Study**
- Brignole 2006
  - case series; study
  - held in
  - multinational.
  - Setting: Hospital
  - several departments.
  - Multicentre.
  - Funding: supported by grant from
  - Medtronic Europe

**Participant**
- TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. patients with suspected neurally mediated syncope
- Definition of TLoC: neurally mediated syncope defined by exclusion of cardiac, orthostatic, carotid sinus, subclavian steal and non-syncopal TLOC.
- Inclusion criteria: at least 30 years; 3 or more clinically severe syncopal episodes in last 2 years (high number of episodes affecting quality of life or high risk of physical injury due to unpredictability).
- Exclusion criteria: significant ECG or cardiac abnormalities; orthostatic hypotension or carotid sinus syncope; subclavian steal; non-syncopal TLOC.
- Patient characteristics: age: mean age 66 years (14 years); sex: 45% male; some patients with existing heart disease (cardiac disease 14%); history of TLoC: 3 or more clinically severe syncopal episodes in last 2 years; median 6 (IQR 4-10) episodes.
- Comorbidities: not stated. Other details: see below
- Other study comments: case series no comparator. Of 103 pts with ILR ECG documented syncope, 53 had specific treatment & 50 did not; these groups compared in Phase II (result

**Diagnostic tests**
- Index test: Reveal Plus; automated or patient activated; time: up to 24 months; median 9 months; follow up every 3 months or to event or to max 24 months (n=392) for Target Condition/Outcome: ECG documented syncope: asystolic pause over 3 seconds (AV block or sinus arrest); bradycardia; tachyarrhythmia (paroxysmal AF; paroxysmal SVT; VT)

**Other**
- Deharo 2006
  - case series; study
  - held in France.
  - Setting: Cardiology.
  - University cardiology department.
  - Funding: not stated

**Participant**
- TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. vasovagal syncope; positive HUT
- Definition of TLoC: recurrent vasovagal syncope (diagnosed by history, examination, carotid sinus massage, ECG, positive HUT).
- Inclusion criteria: frequent syncope severely impairing quality of life (i.e. more than 5 episodes in previous 2 years; interval of >6 months between 1st and last episode); absence of heart disease and cardiovascular treatment.
- Exclusion criteria: none.
- Patient characteristics: age: mean age 60.2 (17.1) years; sex: 56% female; no patients with existing heart disease (heart disease excluded);
- TLoC history: mean 6.9 episodes per year
- Comorbidities: not stated. Other details: see below
- Other study comments: case series no comparator

**Diagnostic test**
- Index test: Reveal or Reveal Plus; patient or automatically activated; time: planned duration 18 months; device interrogated after 1 month then every 3 months and after event; all followed to 18 months except 2 explanted (infection/neoplasia) (n=25) for Target Condition/Outcome: severe bradycardia during syncope (less than 40 bpm for at least 10 seconds); asystole (ventricular pause over 3 seconds); tachycardia over 165 bpm
### 3.3 Ambulatory ECG - unexplained recurrent TLoC review

#### 3.3.1 Diagnostic Test: Holter monitoring 24-hour

<table>
<thead>
<tr>
<th>Study</th>
<th>Participant</th>
<th>Diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aronow 1993</td>
<td>TLoC population: unclear/not stated. Prior tests: All patients had at least 1 prior test.</td>
<td>Index test: 24 hour ambulatory ECG (Avionics model 445); time: 24 hours (n=148) for Target Condition/Outcome: symptom/rhythm correlation: pauses &gt;3s; sustained VT; AF with ventricular rate &gt;190 beats per minute; nonsustained VT; other complex ventricular arrhythmias</td>
</tr>
<tr>
<td></td>
<td>elderly patients with unexplained syncope; vasodepressor, drug-induced, carotid sinus, neurological syncope, orthostatic hypotension, valvular heart disease, HCM, acute MI, PE, hypoglycaemia excluded</td>
<td>All patients had at least 1 prior test. time: 24 hours (n=100) for Target Condition/Outcome: abnormalities of rhythm whether associated with TLoC or not: major abnormalities defined as VT; pauses over 2 seconds; bradycardia below 30 bpm; high grade AV block; minor: ventricular ectopy; supraventricular ectopy; paroxysmal SVT; paroxysmal AF</td>
</tr>
<tr>
<td></td>
<td>Definition of TLoC: sudden transient loss of consciousness with inability to maintain postural tone; not seizure, vertigo, dizziness, coma, shock or other altered consciousness.</td>
<td>TLoC history: not stated. Other details: elderly patients. Comorbidities: not stated. Other study comments: case series no comparator; additional data added in from Aronow 1992 (same patients) number 823.</td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria: elderly patients with unexplained syncope. Exclusion criteria: vasodepressor, drug-induced, carotid sinus, neurological syncope, orthostatic hypotension, valvular heart disease, hypertrophic cardiomyopathy, acute MI, pacemaker malfunction, pulmonary embolus, hypoglycaemia.</td>
<td>Other study comments: case series no comparator; test appeared to be used as triage to inform whether patients should be admitted or not. Test carried out “in case syncope might be linked to abnormalities of rhythm or cardiac conduction”</td>
</tr>
<tr>
<td></td>
<td>Patient characteristics: age: mean age 82 (range 62 to 97) years; sex: 68% female; some patients with existing heart disease (48% had coronary artery disease); TLoC history: not stated. Other details: elderly patients.</td>
<td>TLoC history: not stated. Other details: little info. Comorbidities: not stated. Other study comments: case series no comparator; test appeared to be used as triage to inform whether patients should be admitted or not. Test carried out “in case syncope might be linked to abnormalities of rhythm or cardiac conduction”</td>
</tr>
<tr>
<td>Comolli 1993</td>
<td>TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. negative clinical examination, routine haematological tests, chest x-ray, ECG</td>
<td>Index test: Holter monitor (Kontron tape); time: 24 hours (n=287) for Target Condition/Outcome: abnormalities of rhythm whether associated with TLoC or not: major abnormalities defined as VT; pauses over 2 seconds; bradycardia below 30 bpm; high grade AV block; minor: ventricular ectopy; supraventricular ectopy; paroxysmal SVT; paroxysmal AF</td>
</tr>
<tr>
<td></td>
<td>Definition of TLoC: syncopal episodes. Inclusion criteria: negative clinical examination, routine haematological tests, chest x-ray, ECG. Exclusion criteria: none stated. Patient characteristics: age: mean 67 years (range 19 to 86) years; sex: 54% female; Unlclear/not stated with existing heart disease (not stated); TLoC history: not stated. Comorbidities: not stated. Other details: little info.</td>
<td>Other study comments: case series no comparator; test appeared to be used as triage to inform whether patients should be admitted or not. Test carried out “in case syncope might be linked to abnormalities of rhythm or cardiac conduction”</td>
</tr>
<tr>
<td>Lacroix 1981</td>
<td>TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. syncope of unknown aetiology (some patients had had exercise tests &amp; echo). Definition of TLoC: not defined. Inclusion criteria: syncope of unknown aetiology. Exclusion criteria: documented arrhythmia at presentation; Wolff-Parkinson-White syndrome. Patient characteristics: age: mean age 61 (14) years; sex: 58% male; some patients with existing heart disease (46% had coronary heart disease and 19% had other heart disease); TLoC history: mean 4 episodes per patient; 1st episode mean of 16 months before referral. Comorbidities: not stated. Other study comments: case series</td>
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<td></td>
<td>Index test: Holter two-lead monitor in 94 patients and bedside 24-hour monitoring in 6 patients; time: 24 hours (n=100) for Target Condition/Outcome: symptom/rhythm correlation: not prespecified; rhythms found were VTAF; wide complex tachy; SVT; atrial flutter; ventricular pause over 3sAV block (Mobitz type I or II)</td>
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<td></td>
<td>Other study comments: case series</td>
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Transient loss of consciousness: full guideline DRAFT (January 2010)
3.3.2 Diagnostic Test: Holter monitoring 48-hour

Study
Rockx 2005
RCT; study held in Canada.
Setting: Cardiology, patients referred from community or ED.
Funding: Physician Services Inc, Toronto

Participant
TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test, referred for ambulatory monitoring; 41 had had prior Holter; 31 echo; 13 tilt test
Definition of TLoC: patients had diagnosis of syncope, presyncope or both.
Inclusion criteria: patients had diagnosis of syncope, presyncope or both, referred for ambulatory monitoring.
Exclusion criteria: none.
Patient characteristics: age: mean age 56 (20) years; sex: 44% male; some patients with existing heart disease (33% had heart disease);
TLoC history: median 1 prior episode (mean 50+/−12); symptoms for a median of 6.5 months (mean 41 +/-94 months)
Comorbidities: not stated. Other details: see below
Other study comments: same study as Sivakumaran 2003 (number 821) - additional data added in here from that paper

Diagnostic tests
Index test: Holter monitoring 48 hours; time: 48 hours (n=51)
for Target Condition/Outcome: prespecified: sinus pause over 3s; complete heart block; Mobitz type 2 2nd degree block; AF with slow ventricular response (RR over 3s); symptomatic sinus brady below 40bpmSVT over 10s or symptomatic; VT

3.3.3 Diagnostic Test: Holter monitoring 72-hour

Study
Kapoor 1991
case series; study held in USA.
Setting: Hospital several departments. General internal medicine and cardiology.
Funding: not stated

Participant
TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test, unexplained syncope but normal clinical examination findings for 3 x 24-hour periods and normal 12-lead ECG
Definition of TLoC: sudden transient loss of consciousness with inability to maintain postural tone.
Inclusion criteria: unexplained syncope but normal clinical examination findings for 3 x 24-hour periods and normal 12-lead ECG.
Exclusion criteria: cardiac arrest or no LOC.
Patient characteristics: age: mean age 61 years; sex: 59% female; Unclear/not stated with existing heart disease (not stated);
TLoC history: 55/95 patients had had multiple episodes
Comorbidities: not stated. Other details: see below
Other study comments: case series no comparator

Diagnostic tests
Index test: Holter 3 x 24 hours (more than 80% of patients on consecutive days); time: 72 hours (n=95)
for Target Condition/Outcome: major rhythm abnormalities (+/- symptoms) found (not prespecified): VT 3 or more beats; pauses over 2s; brady below 30bpm; complete heart block; other: ventricular ectopy; Mobitz type 1 heart block; brady 30-39bpm; SVT 10 or more beats over 150bpm; AF
### 3.3.4 Diagnostic Test: external event recorder

<table>
<thead>
<tr>
<th>Study</th>
<th>Participant</th>
<th>Diagnostic tests</th>
</tr>
</thead>
</table>
| Fogel 1997     | TLoC population: unclear/not stated. Prior tests: All patients had at least 1 prior test.  
patients presenting for evaluation of syncope or presyncope; had had examination, 12 lead ECG, noninvasive investigation of cardiac function; those with heart disease had EP | Index test: continuous loop event recorder (King of Hearts, Instromedics) or handheld or wrist recorder (Cardiodiary and Cardiomemo-Instromedics, or WristRecorder-Ralin); patient activated; time: usually 4 weeks; less if an event; extended if no event (n=62) for Target Condition/Outcome: symptom/rhythm correlation: detected arrhythmias were SVT; paroxysmal AF; prolonged pause following AF (not prespecified) |
| Setting: Cardiology. |                                                                                         |                                                                                  |
| Funding: not stated |                                                                                         |                                                                                  |
| Linzer 1990    | TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. 
unexplained syncope; referred from all sources including tertiary inpatient and outpatient hospital, ER, Veterans Affairs medical centre, private physicians, syncope clinic; Holter indeterminate at 24 hours | Index test: external event recorder; patients activated (Instromedix instant replay or King of Hearts); time: up to 1 month; recording stopped if diagnostic event (n=57) for Target Condition/Outcome: symptom/rhythm correlation: prespecified: sinus pause over 3s; SVT over 190bpm; complete AV block; Mobitz II 2nd degree block; VT over 10s; AF with slow ventricular response (RR interval over 3s); alternating bundle branch block; VT over 30s |
| Setting: Hospital several departments. |                                                                                         |                                                                                  |
| General Internal Medicine, Cardiology. |                                                                                         |                                                                                  |
| Funding: Charles A Dana Foundation, Duke Women’s Auxiliary, National Institutes of Health |                                                                                         |                                                                                  |
| Rockx 2005     | TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. 
referred for ambulatory monitoring; 41 had prior Holter; 31 echo; 13 tilt test | Index test: external event recorder; time: worn until 2 clinical episodes occurred or 1 month elapsed (n=49)  
Comparator test: Holter monitoring 48 hours; time: 48 hours (n=51). for Target Condition/Outcome: prespecified: sinus pause over 3s; complete heart block; Mobitz type 2 2nd degree block; AF with slow ventricular response (RR over 3s); symptomatic sinus brady below 40bpmSVT over 10s or symptomatic; VT |
| Setting: Cardiology. |                                                                                         |                                                                                  |
| patients referred from community or ED. |                                                                                         |                                                                                  |
| Funding: Physician Services Inc, Toronto |                                                                                         |                                                                                  |
Transient loss of consciousness: full guideline DRAFT (January 2010)  Page 45 of 100

3.3.5 Diagnostic Test: implantable event recorder - patient activated

Index test: Reveal; patient activated; time: mean 18 (9) months; 1st syncopal event analysed; follow up every 3 months to maximum of 36 months (n=56)
Other comparator tests: "control group" of 15 patients tilt and ATP test negative (exclude as too few patients).
for Target Condition/Outcome: events recorded were AV block; sinus arrest; sinus bradycardia (less than 40 bpm); sinus rhythm; sinus tachycardia; AF; ectopic atrial tachycardia; bradycardia; long ventricular pause; but not prespecified which were counted as arrhythmia.

Donato 2003 case series; study held in Italy.
Setting: Hospital several departments. multicentre in Italy.
Funding: not stated

TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.
history, examination, ECG, carotid sinus massage, echo and 24-hour ambulatory ECG not diagnostic; some pts also had EPS; ATP test and tilt test positive
Definition of TLoC: "adenosine sensitive syncope".
Inclusion criteria: over 40 years old; 3 or more previous syncopes; at least 6 months between 1st and last episode; clinically severe (high frequency or high risk).
Exclusion criteria: see above.
Patient characteristics: age: mean 69 years (10 years); sex: 61% female; some patients with existing heart disease (28% had structural heart disease);
TLoC history: median 6 syncopal episodes (range 4-10)
Comorbidities: not stated. Other details: unexplained syncope
Other study comments: significance of positive ATP test unclear. 7 of 15 "control" patients had arrhythmia during TLOC and 2 had no rhythm variations

Index test: continuous loop event recorder (R Test Evolution, Novacor SA, France) no further details; time: mean 6.7 (1.7) days (n=113) for Target Condition/Outcome: prespecified: sinus pause 3s/more/symptom+ pause 2s/more; sinus brady 35bpm or less/symptomatic brady 40bpm/less; AF+slow ventricular response (RR 3s/more); 30s/more SVT 180bpm/more or + systolic BP 90mmHg/less; 2nd deg (Mob 2) /complete AV block; VT

Index test: CardioCall model VS 20; patient activated; time: mean 7 (3) weeks; range 1-10 weeks (n=24)
for Target Condition/Outcome: symptom/rhythm correlation; recorded (not prespecified): sinus tachycardia (rate not specified); atrial flutter

Index test: CardioCall model VS 20; patient activated; time: mean 7 (3) weeks; range 1-10 weeks (n=24)
for Target Condition/Outcome: symptom/rhythm correlation; recorded (not prespecified): sinus tachycardia (rate not specified); atrial flutter

Schuchert 2003 case series; study held in Germany. "Medical Clinic III".
Setting: unclear.
Funding: not stated

TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.
tilt test, ECG and echo negative, no suggestion of vasovagal trigger mechanism
Definition of TLoC: recurrent syncope of unknown origin.
Inclusion criteria: more than 2 episodes syncope in last 6 months, negative tilt test, no overt structural heart disease.
Exclusion criteria: none.
Patient characteristics: age: mean 51 (14) years; sex: 63% female; no patients with existing heart disease (no overt structural heart disease);
TLoC history: mean 3 (4) syncopes in last 6 months (range 0-20)
Comorbidities: not stated. Other details: recurrent syncope and negative tilt test. Other study comments: case series no comparator

Donato 2003 case series; study held in Italy.
Setting: Hospital several departments. multicentre in Italy.
Funding: not stated

TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.
history, examination, ECG, carotid sinus massage, echo and 24-hour ambulatory ECG not diagnostic; some pts also had EPS; ATP test and tilt test positive
Definition of TLoC: "adenosine sensitive syncope".
Inclusion criteria: over 40 years old; 3 or more previous syncopes; at least 6 months between 1st and last episode; clinically severe (high frequency or high risk).
Exclusion criteria: see above.
Patient characteristics: age: mean 69 years (10 years); sex: 61% female; some patients with existing heart disease (28% had structural heart disease);
TLoC history: median 6 syncopal episodes (range 4-10)
Comorbidities: not stated. Other details: unexplained syncope
Other study comments: significance of positive ATP test unclear. 7 of 15 "control" patients had arrhythmia during TLOC and 2 had no rhythm variations

Donato 2003 case series; study held in Italy.
Setting: Hospital several departments. multicentre in Italy.
Funding: not stated

TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.
history, examination, ECG, carotid sinus massage, echo and 24-hour ambulatory ECG not diagnostic; some pts also had EPS; ATP test and tilt test positive
Definition of TLoC: "adenosine sensitive syncope".
Inclusion criteria: over 40 years old; 3 or more previous syncopes; at least 6 months between 1st and last episode; clinically severe (high frequency or high risk).
Exclusion criteria: see above.
Patient characteristics: age: mean 69 years (10 years); sex: 61% female; some patients with existing heart disease (28% had structural heart disease);
TLoC history: median 6 syncopal episodes (range 4-10)
Comorbidities: not stated. Other details: unexplained syncope
Other study comments: significance of positive ATP test unclear. 7 of 15 "control" patients had arrhythmia during TLOC and 2 had no rhythm variations
Funding: multinational.
Setting: Multinational.

Krahn 1998
Study case series; study held in Canada.
Setting: Cardiology.

Definition of TLoC: syncope of unknown cause.
Inclusion criteria: syncope of unknown cause; ambulatory or in-hospital monitoring, tilt table and EPS negative.
Exclusion criteria: none.
Patient characteristics: age: mean 58.8 years (17.1); sex: 71% male; some patients with existing heart disease (46% had heart disease); TLoC history: mean 7.2 (5.4) previous episodes in 2 years
Comorbidities: not stated. Other details: see below
Other study comments: case series no comparator

Krahn 2002
Study case series; study held in Multinational.
Setting: Hospital several departments, multinational.

Definition of TLoC: recurrent syncope or syncope associated with injury.
Inclusion criteria: recurrent syncope or syncope associated with injury.
Exclusion criteria: none.
Patient characteristics: age: mean age 57 years (18); sex: 57% male; some patients with existing heart disease (33% had structural heart disease); TLoC history: median number of previous episodes 4
Comorbidities: not stated. Other details: see below
Other study comments: case series no comparator; some of these patients included in Krahn 1995 (n=24) or Krahn 1999 (n=81)

Moya 2001
Study case series; study held in Multinational.
Setting: Hospital several departments, multinational.

Definition of TLoC: syncope of uncertain origin.
Inclusion criteria: no significant structural heart disease; 3 or more episodes in last 2 years; interval of 6 months or more between 1st & last episode; history, examination, ECG, carotid sinus massage, echo, 24-hour ECG not diagnostic; tilt test negative.
Exclusion criteria: none.
Patient characteristics: age: mean 63 (17) years; sex: 55% male; some patients with existing heart disease (32% had heart disease); TLoC history: 3 or more episodes in last 2 years
Comorbidities: not stated. Other details: see below
Other study comments: case series no comparator; tilt test negative patients i.e. unexplained after secondary tests

Diagnosis TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. ambulatory or in-hospital monitoring, tilt table and EPS negative in all patients.

Index test: ILR (Medtronic); patient activated; time: up to 12 months; mean 4.6 (3.8) months; device explanted if diagnosis made or no event in 2 years (battery life) (n=24) for Target Condition/Outcome: symptom/rhythm correlation or exclusion of arrhythmia: found: bradycardia; bradytachy; AV block; sinus arrest; SVT; VT (not prespecified)

Index test: Reveal; patient activated; time: mean 93 (107) days; follow up every 1-2 months for at least 6 months or stop after event (n=206) for Target Condition/Outcome: symptom/rhythm correlation: prespecified: bradycardia below 50bpm; tachycardia above 150bpm
Comorbidities:

Funding:

Setting:

Study  
Nierop 2000  
Participant:
TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.

Definition of TLoC: syncope=temporary and reversible LoC.

Inclusion criteria: 2 or more witnessed episodes of syncope of unknown origin in previous 12 months or 1 episode with significant trauma; able to handle activator.

Exclusion criteria: prior MI, ejection fraction <0.40, dilated/hypertrophic cardiomyopathy, nonsustained VT (Holter), aortic valve disease, LVO obstruction, orthostatic hypotension, vasavagal syncope, hypersensitive carotid sinus; >80 yr using >3 cardioactive drugs; dementia.

Patient characteristics: age: mean age 65 (17) years (range 29 to 87 years); sex: 57% female; some patients with existing heart disease (9% had heart disease);

TLoC history: mean event rate in prior 12 months was 5.2 +/- 3.2 months (median 4 months, range 1-13 months)

Comorbidities: not stated. Other details: see below

Other study comments: case series no comparator

Diagnostic tests:
Index test: Reveal; patient activated; time: 11 (8) months; seen every 3 months (n=35) for Target Condition/Outcome: symptom-rhythm correlation: findings (not prespecified): bradycardia below 40bpm; asystole over 3s; tachycardia 180-220bpm

Seidl 2000  
Participant:
TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.

unexplained syncope and negative laboratory investigations (e.g. ECG, Holter, echo, tilt table, EPS, external loop recorder but not all patients had all of these)

Definition of TLoC: sudden transient loss of consciousness with spontaneous recovery without resuscitative measures.

Inclusion criteria: unexplained syncope (sudden TLOC with spontaneous recovery without resuscitative measures) and negative investigations.

Exclusion criteria: none.

Patient characteristics: age: mean age 56 years; sex: 50% male; some patients with existing heart disease (40% had heart disease);

TLoC history: mean 6.3 episodes in previous 12 months; mean duration 5.7 (8.9) years.

Comorbidities: not stated.

Other study comments: case series no comparator
### 3.3.6 Diagnostic Test: implantable event recorder - patient and automatically activated

<table>
<thead>
<tr>
<th>Study</th>
<th>Participant</th>
<th>Diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boersma 2004 case series; study held in multinational. Setting: Cardiology. Funding: European Society of Cardiology</td>
<td>TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. Recurrent unexplained syncope despite CSM, echo, exercise test, 24 hour Holter, tilt test and EPS. Definition of TLoC: not defined. Inclusion criteria: at least 3 episodes of syncope in last 6 months with negative screening; device could be activated by patient; follow up likely to be completed; implantation technically feasible. Exclusion criteria: none. Patient characteristics: age: mean age 57 years (17 to 79 years); sex: 51% female; some patients with existing heart disease (17 had echo abnormalities; 7 valve disease; 2 MI; 2 dilated cardiomyopathy; 8 left ventricular hypertrophy); TLoC history: duration median 18 months (3 to 120 months); at least 3 episodes of syncope in last 6 months (median 4) Comorbidities: not stated. Other details: see below Other study comments: case series no comparator</td>
<td>Index test: Reveal in 17 patients or Reveal Plus in 26 patients; patient or automatic activation; time: median 18 months (range 1-18 months); device interrogated every 3 months &amp; after an event (n=43) for Target Condition/Outcome: symptom/rhythm correlation: lower &amp; upper detection thresholds set at 40 and 180 beats per minutes respectively; events were AV block; AF plus brady-tachycardia syndrome; AF; extreme bradycardia to asystole; VT; sinus arrest</td>
</tr>
<tr>
<td>Brignole 2005 case series; study held in Italy. Setting: Cardiology. 2 hospitals receiving referrals (in or outpatients) for assessment of syncope. Funding: none stated</td>
<td>TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had 1 prior test. Unexplained syncope; all had &quot;negative workup&quot; Definition of TLoC: not defined; Syncope excluded. Inclusion criteria: severe (high risk or high frequency) syncope and negative workup. i.e. very frequent with reduced quality of life; or recurrent and unpredictable (no prodrome) so high risk of trauma; or occurred during high risk activity (e.g. driving). Exclusion criteria: presyncope. Patient characteristics: age: mean 69 years (11 years); sex: 55% male; some patients with existing heart disease (38% structural heart disease); TLoC history: mean number of previous syncopes=11 (SD 5) Comorbidities: Other details: see below Other study comments: case series no comparator. Of the patients aged 65 or over, 44/78 had ECG recorded during syncope and 42 of these had arrhythmia. Of those under 65 years, 8/25 had ECG of which 5 were arrhythmia.</td>
<td>Index test: Reveal or Reveal Plus; automatic or patient activated; time: mean follow up 14 months (10 months); device interrogated every 3 months or after event; if battery ran down, pt could have 2nd ILR (n=103) for Target Condition/Outcome: ECG diagnosis during 1st recorded syncope (syncope considered due to cardiac cause if sudden onset AV block, bradycardia, atrial or ventricular tachyarrhythmia during syncope)</td>
</tr>
<tr>
<td>Ermis 2003 case series; study held in USA. Setting: Hospital several departments. Cardiac arrhythmia centre, veterans administration medical centre, county medical centre, heart centre. Funding: Minnesota Medical Foundation</td>
<td>TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: Unclear or Not stated. Patients with syncope who received an ILR; prior tests not stated Definition of TLoC: not defined. Inclusion criteria: more than 2 syncopal episodes in previous year or significant injury with a syncope event. Exclusion criteria: not stated. Patient characteristics: age: mean age 64 (22) years; sex: 54% male; some patients with existing heart disease (9/50 had structural heart disease); TLoC history: not stated Other details: more than 2 syncopal episodes in previous year or significant injury with a syncope event</td>
<td>Index test: Reveal Plus (Medtronic); patient or automatic activation; time: mean 14.3 (7.9) months; to extraction of ILR or maximum 31 months to end of study (n=50) for Target Condition/Outcome: ILR set to detect heart rates of more than 165 bpm or less than 40 bpm or asystole more than 3 seconds; SVT; VT; asystole; complete AV block; Torsades de Pointes; sinus brady less than 60bpm; sinus tachy; premature ventricular extrasystoles predefined</td>
</tr>
</tbody>
</table>
**Study**

Farwell 2006

RCT; study held in UK.

Setting: unclear.

general hospital

including (but may not be only) A&E.

Funding: partly supported by grants from Medtronic UK

---

**Participant**

TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. basic workup plus Holter/tilt test as indicated

Definition of TLoC: not defined apart from “syncope”.

Inclusion criteria: 16 yr or over; acute syncope; 2 or more unexplained TLoCs in last 12 months; no pacing indication after basic clinical workup (tilt test & Holter if clinically indicated).

Exclusion criteria: see above.

Patient characteristics: age: median 74 yr (IQR 61 to 81 yr); sex: 54% female; some patients with existing heart disease (around 50% had prior IHD);

TLoC history: mean 1.3 TLoC per year

Comorbidities: not stated. Other details: adults presenting with syncope

Other study comments: Eastbourne Syncope Assessment Study (EaSyAS)

---

**Diagnostic tests**

Index test: Reveal Plus set to record 3 patient activations + 5 automatic activations; time: median 17 months (IQR 9-23 months); maximum 34 months (n=103)

Comparator test: conventional investigation and management; time: median 17 months (n=98).

for Target Condition/Outcome: set to record ventricular pasuuses more than 3 seconds; ventricular rate less than 40 bpm or more than 165 bpm; events recorded were bradycardia, SVT or VT (no further details and not prespecified)

---

**Study**

Krahn 2001

RCT; study held in Canada.

Setting: Cardiology.

Arhythmia service.

Funding: Heart and Stroke Foundation of Ontario

---

**Participant**

TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.

Had had clinical assessment, postural BP, 24 hour ambulatory monitoring or telemetry, echocardiogram; could have had other neurological or cardiovascular testing, tilt test or loop recorder.

Definition of TLoC: unexplained syncope not further defined.

Inclusion criteria: referred to arrhythmia clinic; those with typical history for neurally mediated syncope excluded.

Exclusion criteria: Left ventricular ejection fraction below 35%; unlikely to survive 1 year; unable to provide follow up or consent; typical presentation of neurally mediated syncope excluded.

Patient characteristics: age: mean 66 yr (14 yr); sex: 55% male; some patients with existing heart disease (38% had heart disease);

TLoC history: recurrent in 53 patients; 7 had single episode judged to warrant cardiovascular testing

Comorbidities: not stated. Other details: referred to arrhythmia clinic; those with typical history for neurally mediated syncope excluded.

Other study comments: If undiagnosed after 1st strategy, pts offered crossover to other strategy: diagnosis in 1/6 (17%) conventional and 8/13 (62%) ILR (p=0.069). Conventional gp only had 2-4 weeks ELR & if tilt & EP negative, immediately offered ILR (diff follow up times)

---

**Study**

Krahn 2004

case series; study held in Canada.

Setting: Cardiology.

Funding: Heart and Stroke Foundation of Ontario

---

**Participant**

TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.

patients referred to arrhythmia service for investigation of syncope; 24 hour Holter negative

Definition of TLoC: not defined.

Inclusion criteria: aged 30 years or more; left ventricular ejection fraction 35% or more and negative conventional monitoring.

Exclusion criteria: LVEF below 35%; unlikely to survive 1 year; unable to give consent or follow up; typical presentation of neurally mediated syncope.

Patient characteristics: age: mean age 67 (16) years; sex: 55% female; some patients with existing heart disease (42% structural heart disease);

TLoC history: median 4 episodes; median duration 0.9 years

Other details: recurrent unexplained syncope or single episode associated with physical injury that warranted cardiovascular investigation

Other study comments: case series

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**Index tests**

Index test: Reveal ILR; patient activated; time: follow up at 1 week, 1, 2, 3, 6, 9 and 12 months and after event (aimed for full 1 year monitoring) (n=30)

Comparator test: conventional plus external recorder plus tilt and electrophysiological testing; time: ELR 2-4 weeks; pts offered ILR immediately if tilt & EP negative (n=30).

for Target Condition/Outcome: symptom/rhythm correlation (not prespecified): found bradycardia; tachycardia
**Study**

Lombardi 2005 case series; study held in Italy. Setting: Hospital several departments, cardiology or neurology. Funding: not stated

**Participant**

TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.

unexplained syncope: cardiac diagnosis excluded (from history, examination, echo, Holter, telemetry, positive tilt test) and neurological diagnosis excluded (CT/MRI/EEG)

Definition of TLoC: unexplained syncope.

Inclusion criteria: at least 2 unexplained syncopal episodes and negative neurological and cardiovascular workup.

Exclusion criteria: cardiac diagnosis (from history, examination, echo, Holter, telemetry, positive tilt test) or neurological diagnosis (CT/MRI/EEG).

Patient characteristics: age: mean 60 (15) years (range 28-84 years); sex: 62% male; some patients with existing heart disease (atherosclerosis 12%, dilated cardiomyopathy 6%, hypertension 3%, aortic stenosis 3%); TLoC history: 2 syncopal episodes within 1 year

Comorbidities: diabetes 9%, atherosclerosis 12%, dilated cardiomyopathy 6%, thyroid disease 6%, hypertension 3%, aortic stenosis 3%, epilepsy 3%. Other details: see below

Other study comments: case series no comparator

**Diagnostic tests**

Index test: Reveal Plus; patient activated or automatic; time: mean 7 (4) months, range 1-14 months; device explanted after diagnosis made or if no syncope after 14 months (n=34) for Target Condition/Outcome: symptom/rhythm correlation; device set to record heart rate below 40bpm or over 160bpm or asystole over 3s. Rhythms found were bradycardia/asystole or AF.

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**Study**

Pezawas 2007 case series; study held in Austria. Setting: Cardiology. Hospital cardiology centre. Funding: not stated

**Participant**

TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.

unexplained syncope after neurological investigation, ECG, carotid sinus massage, BP, echo, 24 hour ECG

Definition of TLoC: unexplained syncope.

Inclusion criteria: at least 2 syncopal episodes before ILR implantation.

Exclusion criteria: EPS suspicious of conduction problem or non-sustained VT.

Patient characteristics: age: mean age 55 (17) years(range 25-79 years); sex: 51% female; some patients with existing heart disease (47% had heart disease); TLoC history: mean number of episodes before ILR 2.4 (1.1) in patients with structural heart disease vs. 5.2 (2.6) in those without

Comorbidities: 63% hypertension, 13% diabetes, 30% depression, 7% stroke, 1% epilepsy. Other details: see below

Other study comments: case series no comparator

**Diagnostic tests**

Index test: Reveal Plus; patient or automatically activated; time: mean 16 (8) months; seen every 3 months to diagnosis or end of ILR life (n=70) for Target Condition/Outcome: set to record pauses 3s or more; heart rate 40 or below or 160 or above; prespecified arrhythmias: asystole (sinus arrest, sinus brady + AV block or AV block); brady (decrease of rate by over 30% or rate below 40 for 10s); tachy (AF; SVT; VT)

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**Study**

Pierre 2008 case series; study held in France. Setting: Cardiology.

Funding: funding for open access publication provided by Medtronic

**Participant**

TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.

cardiac investigations including EPS

Definition of TLoC: recurrent syncope.

Inclusion criteria: at least 3 episodes syncope.

Exclusion criteria: orthostatic hypotension, abnormal 24 hour ECG, positive tilt test, neurological abnormality, abnormal EPS or carotid sinus massage, inducible VT or SVT, LVEF<30-35%, candidates for prophylactic ICD.

Patient characteristics: age: mean 64.3 (17.30 years; sex: 60% male; some patients with existing heart disease (22% had heart disease);

TLoC history: mean 4.9 (3.8)

Comorbidities: not stated. Other details: syncope of unknown aetiology

Other study comments: case series no comparator

**Diagnostic tests**

Index test: Reveal Plus; patient activated or automatic; time: mean 10.2 (5.2) months; seen every 3 months until diagnosis or end of battery life (14 months) (n=95) for Target Condition/Outcome: set to record brady below 30bpm; ventricular arrest over 3s; tachy above 180bpm during 32 beats; rhythms found (not prespecified): complete AV block; VF; sustained/ nonsustained VT; AF with fast ventricular response; SVT; sinus arrest
3.4 Further details about ambulatory ECG studies

3.4.1 Population categories

For the category, “unexplained syncope after secondary tests”, we have defined two subcategories:

(i) indicates that those with positive tests were excluded from the study and
(ii) indicates that tests were carried out but patients were not excluded on the basis of a positive test.

<table>
<thead>
<tr>
<th>Study name</th>
<th>category of patients</th>
<th>population details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aronow 1993</td>
<td>unexplained syncope</td>
<td>elderly patients with unexplained syncope; vasodepressor, drug-induced, carotid</td>
</tr>
<tr>
<td></td>
<td>after secondary tests</td>
<td>sinus, neurological syncope, orthostatic hypotension, valvular heart disease, HCM,</td>
</tr>
<tr>
<td></td>
<td>(i)</td>
<td>acute MI, PE, hypoglycaemia excluded</td>
</tr>
<tr>
<td>Arya 2005</td>
<td>suspected arrhythmia</td>
<td>syncope or presyncope; had had clinical assessment including BP, ECG and echo</td>
</tr>
<tr>
<td>Ashby 2002</td>
<td>unexplained syncope</td>
<td>unexplained syncope (n=41) or presyncope (n=7); tests included echo, EER, EPS,</td>
</tr>
<tr>
<td></td>
<td>after secondary tests</td>
<td>tilt table, EEG</td>
</tr>
<tr>
<td>Boersma 2004</td>
<td>unexplained syncope</td>
<td>recurrent unexplained syncope despite CSM, echo, exercise test, 24 hour Holter,</td>
</tr>
<tr>
<td></td>
<td>after secondary tests</td>
<td>tilt test and EPS. A positive tilt test or abnormal Holter was not a reason for</td>
</tr>
<tr>
<td></td>
<td>(ii)</td>
<td>exclusion</td>
</tr>
<tr>
<td>Boudoulas 1979</td>
<td>suspected arrhythmia</td>
<td>syncope or presyncope (dizziness or lightheadedness); prior ECG (Holter not</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mentioned</td>
</tr>
<tr>
<td>Boudoulas 1983</td>
<td>suspected arrhythmia</td>
<td>syncope or presyncope; had had EEG (some also had CT or cerebral angiography);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>prior ECG (Holter not mentioned)</td>
</tr>
<tr>
<td>Brembilla-Perrot 2001</td>
<td>suspected arrhythmia</td>
<td>referred with syncope or presyncope and myocardial infarction. Prior ECG (Holter not mentioned)</td>
</tr>
<tr>
<td>Brembilla-Perrot 2004</td>
<td>suspected arrhythmia</td>
<td>coronary disease with history of MI and/or multiple coronary stenoses on angiography and LVEF below 40%. Prior ECG (Holter not mentioned)</td>
</tr>
<tr>
<td>Brembilla-Perrot 2004</td>
<td>suspected arrhythmia</td>
<td>idiopathic dilated cardiomyopathy, normal coronary angiogram, LVEF below 40%</td>
</tr>
<tr>
<td>Brignole 2001</td>
<td>suspected arrhythmia</td>
<td>Bundle branch block and negative EPS, carotid sinus massage, echo, 24-hour ECG;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tilt test (but not excluded because of this)</td>
</tr>
<tr>
<td>Brignole 2005</td>
<td>unexplained syncope</td>
<td>unexplained syncope; all had “negative workup” (likely to include Holter)</td>
</tr>
<tr>
<td></td>
<td>after secondary tests</td>
<td></td>
</tr>
<tr>
<td>Brignole 2006</td>
<td>Ambulatory ECG -</td>
<td>patients with suspected neurally mediated syncope. Holter not mentioned; Most</td>
</tr>
<tr>
<td></td>
<td>suspect NM syncope</td>
<td>patients had a tilt test before IER, but all included</td>
</tr>
<tr>
<td>Study name</td>
<td>category of patients</td>
<td>population details</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Brignole</td>
<td>Ambulatory ECG - suspect NM syncope</td>
<td>causes other than neurally mediated excluded (e.g. by carotid sinus massage, ECG) Holter not mentioned; Most patients had a tilt test before IER, but all included</td>
</tr>
<tr>
<td>Comolli 1993</td>
<td>unexplained syncope after initial tests</td>
<td>negative clinical examination, routine haematological tests, chest x-ray, ECG (negative ECG = inclusion criterion). Not Holter</td>
</tr>
<tr>
<td>Cumbee 1990</td>
<td>unexplained syncope after secondary tests (i)</td>
<td>92% previous Holter; 46% previous EPS; patients excluded if cause of syncope already known</td>
</tr>
<tr>
<td>Deharo 2006</td>
<td>Ambulatory ECG - suspect NM syncope</td>
<td>vasovagal syncope, because of history, physical exam, CSM, positive HUT included Prior ECG (Holter not mentioned)</td>
</tr>
<tr>
<td>Donateo 2003</td>
<td>unexplained syncope after secondary tests (ii)</td>
<td>history, examination, ECG, carotid sinus massage, echo and 24-hour ambulatory ECG all not diagnostic; some pts also had EPS; ATP test and tilt test positive (inclusion criteria)</td>
</tr>
<tr>
<td>Ermis 2003</td>
<td>unexplained syncope after initial tests</td>
<td>patients with syncope who received an IER; prior tests not stated (refers to ESC guidelines 2001)</td>
</tr>
<tr>
<td>Farwell 2006</td>
<td>unexplained syncope after secondary tests (i)</td>
<td>history + physical exam, ECG plus Holter in patients with suspected cardiac syncope (Holter positive patients were excluded as were those diagnosed on basis of initial assessment); tilt test &amp; CSM in all patients (patients with asystolic tilt/CSM results were excluded)</td>
</tr>
<tr>
<td>Fitchet 2003</td>
<td>Ambulatory ECG - suspect NM syncope</td>
<td>blackouts suggestive of vasovagal syncope. Holter vs Tilt test. Not done previously</td>
</tr>
<tr>
<td>Fogel 1997</td>
<td>unexplained syncope after secondary tests (i)</td>
<td>patients presenting for evaluation of syncope or presyncope; had had examination, 12 lead ECG, noninvasive investigation of cardiac function; those with heart disease had EPS. 10/62 had previous negative tilt. Holter not mentioned</td>
</tr>
<tr>
<td>Garcia-Civera 2005</td>
<td>suspected arrhythmia</td>
<td>suspected arrhythmic syncope and negative EPS, ECG, carotid sinus massage, BP, 24 hour ambulatory ECG (other tests if clinically indicated) – not excluded on this basis. Tilt test carried out and all included.</td>
</tr>
<tr>
<td>Gibson 1984</td>
<td>unexplained syncope after initial tests</td>
<td>referred for syncope of unknown cause; no evidence of prior tests</td>
</tr>
<tr>
<td>Kabra 2009</td>
<td>unexplained syncope after secondary tests (i)</td>
<td>unexplained syncope/palpitations/ presyncope/ dizziness; 35% had had CT head; 27% EEG; 55% Holter or event monitoring; 54% tilt table; 42% EPS;</td>
</tr>
<tr>
<td>Kapoor 1991</td>
<td>unexplained syncope after initial tests</td>
<td>unexplained syncope but normal clinical examination findings, history and normal 12-lead ECG</td>
</tr>
<tr>
<td>Study name</td>
<td>category of patients</td>
<td>population details</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Krahn 1998</td>
<td>unexplained syncope after secondary tests (i)</td>
<td>ambulatory or in-hospital monitoring, tilt table and EPS negative in all patients</td>
</tr>
<tr>
<td>Krahn 1999</td>
<td>suspected arrhythmia</td>
<td>undiagnosed after history, examination, ECG and at least 24 hours ambulatory monitoring</td>
</tr>
<tr>
<td>Krahn 2000</td>
<td>unexplained syncope after initial tests</td>
<td>not stated: retrospective study; no evidence of prior tests</td>
</tr>
<tr>
<td>Krahn 2001</td>
<td>unexplained syncope after secondary tests (i)</td>
<td>Had had clinical assessment, postural BP, 24 hour ambulatory monitoring or telemetry, echocardiogram; could have had other neurological or cardiovascular testing. Patients could have had a tilt test or loop recorder recording if symptoms suggested repeat testing was needed. Patients were excluded if they had a clear diagnosis of neurally mediated syncope on initial assessment.</td>
</tr>
<tr>
<td>Krahn 2002</td>
<td>unexplained syncope after secondary tests (i)</td>
<td>syncope of unknown origin; pts had had ECG, Holter or telemetry; some had tilt testing and/or EPS</td>
</tr>
<tr>
<td>Krahn 2004</td>
<td>unexplained syncope after secondary tests (i)</td>
<td>patients referred to arrhythmia service for investigation of syncope; 24 hour Holter negative</td>
</tr>
<tr>
<td>Kuhne 2007</td>
<td>unexplained syncope after secondary tests (i)</td>
<td>patients referred with syncope; some patients had had echo; 24 hour Holter negative; other prior tests unclear</td>
</tr>
<tr>
<td>Lacroix 1981</td>
<td>unexplained syncope after secondary tests (i)</td>
<td>syncope of unknown aetiology (some patients had had exercise tests &amp; echo); positive test for arrhythmia excluded</td>
</tr>
<tr>
<td>Linzer 1990</td>
<td>unexplained syncope after secondary tests (i)</td>
<td>unexplained syncope; referred from all sources including tertiary inpatient and outpatient hospital, ER, Veterans Affairs medical centre, private physicians, syncope clinic; Holter indeterminate at 24 hours</td>
</tr>
<tr>
<td>Lombardi 2005</td>
<td>unexplained syncope after secondary tests (i)</td>
<td>unexplained syncope: cardiac diagnosis excluded (from history, examination, echo, Holter, telemetry, positive tilt test) and neurological diagnosis excluded (CT/MRI/EEG)</td>
</tr>
<tr>
<td>Mason 2003</td>
<td>suspected arrhythmia</td>
<td>recurrent unexplained syncope; patients had had ECG (20), event recorders (16) EPS (17) stress test (19) tilt test (32), cardiac catheterisation (12)</td>
</tr>
<tr>
<td>Menozzi 2002</td>
<td>suspected arrhythmia</td>
<td>suspected tachycardia cause; carotid sinus massage, echo, 24-hour ambulatory ECG not diagnostic</td>
</tr>
<tr>
<td>Morrison 1997</td>
<td>unexplained syncope after secondary tests (ii)</td>
<td>trauma patients admitted to level I trauma centre with syncope or possible syncope; patients had routine laboratory tests; 83% had echo; 72% carotid duplex examination; 64% CT head; 20% EEG; positive tests did not exclude from having Holter</td>
</tr>
<tr>
<td>Moya 2001</td>
<td>Ambulatory ECG - suspect NM syncope</td>
<td>normal ECG, tilt test positive</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Unexplained Syncope Event and Tests Reported</td>
</tr>
<tr>
<td>----------</td>
<td>-------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Moya</td>
<td>2001</td>
<td>Unexplained syncope after secondary tests</td>
</tr>
<tr>
<td>Nierop</td>
<td>2000</td>
<td>Unexplained syncope after secondary tests</td>
</tr>
<tr>
<td>Pezawas</td>
<td>2007</td>
<td>Unexplained syncope after secondary tests</td>
</tr>
<tr>
<td>Pierre</td>
<td>2008</td>
<td>Unexplained syncope after secondary tests</td>
</tr>
<tr>
<td>Porterfield</td>
<td>1999</td>
<td>Unexplained syncope after initial tests</td>
</tr>
<tr>
<td>Ringqvist</td>
<td>1989</td>
<td>Suspected arrhythmia</td>
</tr>
<tr>
<td>Rockx</td>
<td>2005</td>
<td>Unexplained syncope after secondary tests</td>
</tr>
<tr>
<td>Rothman</td>
<td>2007</td>
<td>Suspected arrhythmia</td>
</tr>
<tr>
<td>Sarasin</td>
<td>2001</td>
<td>Unexplained syncope after secondary tests</td>
</tr>
<tr>
<td>Sarasin</td>
<td>2005</td>
<td>Suspected arrhythmia</td>
</tr>
<tr>
<td>Saxon</td>
<td>1990</td>
<td>Suspected arrhythmia</td>
</tr>
<tr>
<td>Schernthaner</td>
<td>2008</td>
<td>Unexplained syncope after secondary tests</td>
</tr>
<tr>
<td>Schuchert</td>
<td>2003</td>
<td>Unexplained syncope after secondary tests</td>
</tr>
<tr>
<td>Seidl</td>
<td>2000</td>
<td>Unexplained syncope after secondary tests</td>
</tr>
<tr>
<td>Zeldis</td>
<td>1980</td>
<td>Unexplained syncope after secondary tests</td>
</tr>
</tbody>
</table>
### 3.4.2 TLoC frequency (previous episodes), duration of monitoring and time to first syncope, frequency x duration, category for freq x duration

<table>
<thead>
<tr>
<th>Study name</th>
<th>Frequency of TLoC (number per year)</th>
<th>Duration of monitoring (days) [Time to first syncope]</th>
<th>Frequency x duration</th>
<th>Frequency x duration (a) &lt; 0.1; (b) 0.1 to 0.99; (c) 1 to 10; (d) &gt;10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aronow 1993</td>
<td>NS</td>
<td>1 [NA]</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Arya 2005</td>
<td>NS</td>
<td>1 1\textsuperscript{st} day + 1 2\textsuperscript{nd} day [NA]</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Ashby 2002</td>
<td>NS</td>
<td>168 [mean 2.8 (2.1) months = 84 days]</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Boersma 2004</td>
<td>6</td>
<td>540 [NA]</td>
<td>6/365 x 540 = 8.9</td>
<td>c</td>
</tr>
<tr>
<td>Boudoulas 1979</td>
<td>NS</td>
<td>1 [NA]</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Boudoulas 1983</td>
<td>NS</td>
<td>1 [NA]</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Brembilla-Perrot 2001</td>
<td>NS</td>
<td>1 [NA]</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Brembilla-Perrot 2004</td>
<td>NS</td>
<td>1 [NA]</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Brignole 2001</td>
<td>1.5</td>
<td>48 [37% had event after median 48 days (range 2–367 days)]</td>
<td>1.5/365 x 48 = 0.2</td>
<td>b</td>
</tr>
<tr>
<td>Brignole 2005</td>
<td>NS</td>
<td>420 [not stated]</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Brignole 2006</td>
<td>3</td>
<td>270 [36% patients had event after median 9 months (IQR 3–17)]</td>
<td>3/365 x 270 = 2.2</td>
<td>c</td>
</tr>
<tr>
<td>Brignole 2006b</td>
<td>2</td>
<td>365 [26% of patients had syncope documented after mean of 3 months (90 days)]</td>
<td>2/365 x 365 = 2</td>
<td>c</td>
</tr>
<tr>
<td>Comolli 1993</td>
<td>NS</td>
<td>1 [NA]</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Cumbee 1990</td>
<td>NS</td>
<td>mean 42d, median 28d, range 3–140 d</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Deharo 2006</td>
<td>6.9</td>
<td>510 [12/25 had events; time to 1\textsuperscript{st} event mean 4.8 months (SD 4.7)]</td>
<td>6.9/365 x 510 = 9.6</td>
<td>c</td>
</tr>
<tr>
<td>Donateo 2003</td>
<td>1.5</td>
<td>540 [16/36 activated device for syncope: median time 9 months (range 1–36)]</td>
<td>1.5/365 x 540 = 2.2</td>
<td>c</td>
</tr>
<tr>
<td>Study name</td>
<td>Frequency of TLoC (number per year)</td>
<td>Duration of monitoring (days)</td>
<td>Frequency x duration</td>
<td>Frequency x duration (a) &lt; 0.1; (b) 0.1 to 0.99; (c) 1 to 10; (d) &gt;10)</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------------------------------</td>
<td>-----------------------------</td>
<td>---------------------</td>
<td>-------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ernis 2003</td>
<td>NS</td>
<td>429</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Farwell 2006</td>
<td>1.5</td>
<td>510</td>
<td>1.5/365 x 510 = 2.1</td>
<td>c</td>
</tr>
<tr>
<td>Fitchet 2003</td>
<td>2.5</td>
<td>2 [NA]</td>
<td>2.5/365 x 2 = 0.01</td>
<td>a</td>
</tr>
<tr>
<td>Fogel 1997</td>
<td>NS</td>
<td>28 [NA]</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Garcia-Civera 2005</td>
<td>3.5</td>
<td>276</td>
<td>3.5/365 x 276 = 2.6</td>
<td>c</td>
</tr>
<tr>
<td>Gibson 1984</td>
<td>NS</td>
<td>1 [NA]</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kabra 2009</td>
<td>NS</td>
<td>10 months (300 days)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Kapoor 1991</td>
<td>NS</td>
<td>3 [NA]</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Krahn 1998</td>
<td>3.6</td>
<td>138</td>
<td>3.6/365 x 138 = 1.4</td>
<td>c</td>
</tr>
<tr>
<td>Krahn 1999</td>
<td>5.1</td>
<td>315</td>
<td>5.1/365 x 315 = 4.4</td>
<td>c</td>
</tr>
<tr>
<td>Krahn 2000</td>
<td>NS</td>
<td>2 Holter; 30 IER [NA]</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Krahn 2001</td>
<td>2.6</td>
<td>365</td>
<td>2.6/365 x 365 = 2.6</td>
<td>c</td>
</tr>
<tr>
<td>Krahn 2002</td>
<td>NS</td>
<td>6 months (180 days)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Krahn 2004</td>
<td>4.4</td>
<td>365</td>
<td>4.4/365 x 365 = 4.4</td>
<td>c</td>
</tr>
<tr>
<td>Kuhn 2007</td>
<td>NS</td>
<td>1 [NA]</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Lacroix 1981</td>
<td>3</td>
<td>1 [NA]</td>
<td>3/365 x 1 = 0.08</td>
<td>a</td>
</tr>
<tr>
<td>Linzer 1990</td>
<td>10</td>
<td>30</td>
<td>10/365 x 30 = 0.8</td>
<td>b</td>
</tr>
<tr>
<td>Lombardi 2005</td>
<td>2</td>
<td>210</td>
<td>2/365 x 210 = 1.2</td>
<td>c</td>
</tr>
<tr>
<td>Mason 2003</td>
<td>NS</td>
<td>333</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Syncope occurred in 1/365 x c

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<table>
<thead>
<tr>
<th>Study name</th>
<th>Frequency of TLoC (number per year)</th>
<th>Duration of monitoring (days)</th>
<th>Frequency x duration</th>
<th>Frequency x duration (a)</th>
<th>Study name</th>
<th>Frequency of TLoC (number per year)</th>
<th>Duration of monitoring (days)</th>
<th>Frequency x duration</th>
<th>Frequency x duration (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morrison 1997</td>
<td>NS 1 [NA]</td>
<td></td>
<td>NS NS</td>
<td></td>
<td>Moya 2001 (tilt positive)</td>
<td>1.5 300 [8/29 (28%) of patients had recurrence at a median of 59 days (range 22–98)]</td>
<td>1.5/365 x 300 = 1.2 c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moya 2001 (tilt negative)</td>
<td>2 270 [24/82 (29%) of patients had recurrence at a median of 105 days (range 47–226)]</td>
<td>2/365 x 270 = 1.5 c</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nierop 2000</td>
<td>5.2 330 [44 events (syncope or presyncope) in mean of 11 months follow up; of these 37 in 1st 6 months and 7 in months 7–12, but cannot calculate mean time to recurrence per patient as patients could have more than 1 event]]</td>
<td>5.2/365 x 330 = 4.7 c</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pezawas 2007</td>
<td>NS 480 [recurrence in 60/70 patients with actuarial recurrence rate 30% at 3 months, 65% at 12 months and 91% at 24 months in those with structural heart disease and 35%, 68% and 87% without]</td>
<td>NS NS</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pierre 2008</td>
<td>NS 306 [43/95 (45.2%) of patients had recurrence at a mean time of 5.4 (4.6) months = 162 days]</td>
<td>NS NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rockx 2005</td>
<td>1.8 2 for 48 hour Holter; 30 for EER [median time to diagnosis 16 days (mean 17 (13) days for loop)]</td>
<td>Holter: 1.8/365 x 2 = 0.01; 1.8/365 x 30 = 0.15 Holter: a; EER: b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rothman 2007</td>
<td>NS NS [median time to diagnosis was 10 and 6 days for EER and telemetry respectively. Diagnosis corresponded to TLoC]</td>
<td>NS NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarasin 2001 Holter</td>
<td>NS 1 [NA]</td>
<td></td>
<td>NS NS</td>
<td></td>
<td>Sarasin 2001 EER</td>
<td>NS 7 [NA]</td>
<td></td>
<td>NS NS</td>
<td></td>
</tr>
</tbody>
</table>

Transient loss of consciousness: full guideline DRAFT (January 2010)
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<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>[NA]</th>
<th>Duration</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarasin 2005</td>
<td>NS</td>
<td>1</td>
<td>[NA]</td>
<td>NS</td>
<td>1/365 x 270 = 0.7 b</td>
</tr>
<tr>
<td>Saxon 1990</td>
<td>NS</td>
<td>1</td>
<td>[NA]</td>
<td>NS</td>
<td>1/365 x 50 = 0.8 b</td>
</tr>
<tr>
<td>Schernthaner 2008</td>
<td></td>
<td>270</td>
<td>[40/55 (73%) of patients had recurrence at a mean time of 7.6 (6.6) months = 228 days]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schuchert 2003</td>
<td>6</td>
<td>50</td>
<td>[median time to TLoC 103 days (range 1 to 704 days) after tilt test in 8/24 patients.]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seidl 2000</td>
<td>6.3</td>
<td>324</td>
<td>[NA]</td>
<td>6.3/365 x 324 = 5.6 c</td>
<td></td>
</tr>
<tr>
<td>Zeldis 1980</td>
<td>NS</td>
<td>1</td>
<td>[NA]</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
### 3.4.3 Arrhythmias detected in the studies

<table>
<thead>
<tr>
<th>Study name</th>
<th>Index test (group)</th>
<th>Index test time</th>
<th>Target condition</th>
<th>Arrhythmia detected (% refers to percentage of patients with brady or tachyarrhythmia out of total patients)</th>
<th>Bradyarrhythmias proportion of a) arrhythmias during TLoC; b) arrhythmias not during TLoC and c) all arrhythmias found</th>
</tr>
</thead>
</table>
| Aronow 1993 Holter 24h (4) | 24 hours | symptom/rhythm correlation: pauses >3s; sustained VT; AF with ventricular rate >190 beats per minute; nonsustained VT; other complex ventricular arrhythmias | pause >3s: 21; nonsustained VT: 25; sustained VT: 3; AF: 3; other complex ventricular arrhythmias: 48 out of 148 patients (i.e. brady 14%; tachy 22%; others unclear) | a) 21/100=21%  
b) 0  
c) 21/100=21% |
| Arya 2005 Holter 24h (1) | 48 hours | main ECG finding (nonsustained VT 3 beats or more; sinus pause 3s or more; symptomatic bradycardia below 30 beats/min; paroxysmal atrial fibrillation; sustained SVT above 150 beats/min; VT above 100 beats/min; Mobitz type II 2nd or 3rd degree AV block) | nonsustained VT: 5; sinus pause: 3; AV block: 2 out of 49 patients (i.e. tachy 10%, brady 8%) for day 1; day 2: nonsustained VT: 6; sinus pause >3s: 3; symptomatic sinus brady: 1; sustained SVT: 1 | Day 1:  
a) 5/10 = 50%  
b) 0  
c) 5/10=50%  
Day 2:  
a) 4/11= 36%  
b) 0  
c) 4/11= 36% |
| Boersma 2004(4) | median 18 months (range 1-18 months); device interrogated every 3 months & after an event | symptom/rhythm correlation: lower & upper detection thresholds set at 40 and 180 beats per minutes respectively; events were AV block; AF plus brady-tachycardia syndrome; AF; extreme bradycardia to asystole; VT; sinus arrest | during TLoC: brady/asystole: 7; AV block: 1; paroxysmal AF with brady-tachy syndrome: 1; AF: 1; VT: 1 (i.e. brady 9/43=21% and tachy 2/43=5%) not during TLoC: 1 sinus arrest | a) 9/11=82%  
b) 1/1=100%  
c) 10/12=83% |
| Boudoulas 1979 Holter 24h (1) | 24 hours | sinus brady below 40 bpm awake; paroxysmal SVT (170 bpm); high grade AV block; frequent ventricular premature contractions, effective rate less than 40 bpm; repetitive pairs PVCs; VT | sinus brady or SA exit block: 12; SVT: 16; high grade AV block: 2; malignant ventricular dysrhythmias: 31 (incl. VT 4 and PVCs 30); more than 1 cause: 12 out of 119 patients (i.e. brady 12%, tachy 40%, but those with more than 1 cause unknown) | a) not stated  
b) not stated  
c) 14/73=19% |

**Bradyarrhythmias**: proportion of a) arrhythmias during TLoC; b) arrhythmias not during TLoC and c) all arrhythmias found.
<table>
<thead>
<tr>
<th>Study name</th>
<th>Index test time</th>
<th>Target condition</th>
<th>Arrhythmia detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boudoulas 1983</td>
<td>24 hours</td>
<td>sinus brady less than 40 bpm awake; sinoatrial exit block; paroxysmal SVT (rate over 170 bpm); repetitive pairs premature ventricular beats; VT</td>
<td>SVT: 12; VT or premature ventricular beats or couplets: 8; profound bradycardia: 7; AV block: 4 out of 65 patients (i.e. tachy 31%; brady 17%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a) not stated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>b) not stated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>c) 11/31=35%</td>
</tr>
<tr>
<td>Brembilla-Perrot 2001</td>
<td>24 hours</td>
<td>non-sustained ventricular tachycardia (3 consecutive beats or tachycardia less than 10 seconds)</td>
<td>nonsustained VT: 42/130 patients (i.e. tachy 32%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a) not stated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>b) not stated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>c) 0%</td>
</tr>
<tr>
<td>Brignole 2006</td>
<td>up to 24 months; median 9 months; follow up every 3 months or to event or to max 24 months</td>
<td>ECG documented syncope: asystolic pause over 3 seconds (AV block or sinus arrest); bradycardia; tachyarrhythmia (paroxysmal AF; paroxysmal SVT; VT)</td>
<td>during TLoC: asystole: 57 (AV block 16 + 41 sinus arrest); bradycardia: 4; tachyarrhythmia: 9 (SVT 5 + AF 3 + VT 1); sinus tachy 7 out of 392 patients (i.e. brady 16%, tachy 4%); not during TLoC: 11 asystole/brady + 4 tachy (AV nodal re-entrant tachycardia: 1; non-sustained VT: 2; 1 patient had antiarrhythmic drugs but arrhythmia not specified (assume tachy)) (i.e. brady 3%, tachy 1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a) 61/77=79%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>b) 11/15=73%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>c) 72/92=78%</td>
</tr>
<tr>
<td>Comolli 1993</td>
<td>24 hours</td>
<td>abnormalities of rhythm whether associated with TLoC or not: major abnormalities defined as VT; pauses over 2 seconds; bradycardia below 30 bpm; high grade AV block</td>
<td>During TLoC: 2VT; 1 normal rhythm out of 3 patients with TLoC (i.e. tachy 1%); not during TLoC: VT 23; pause &gt; 2s: 11; bradycardia &lt;30bpm: 13; high-grade AV block: 8 out of 287 patients (i.e. brady 11%, tachy 8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a) 0/2=0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>b) 32/55=58%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>c) 32/57=56%</td>
</tr>
<tr>
<td>Deharo</td>
<td>planned duration 18 mo;</td>
<td>severe bradycardia during syncope (less than 40 bpm)</td>
<td>during TLoC: 4 sinus bradycardia + 1 sinus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a) 6/7=86%</td>
</tr>
<tr>
<td>Study name (group)</td>
<td>Index test time</td>
<td>Target condition</td>
<td>Arrhythmia detected</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------</td>
<td>------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>2006 IER pt &amp; auto activated (2)</td>
<td>device interrogated after 1 mo + every 3 mo and after event; all followed to 18 mo except 2 explanted (infection/neoplasia)</td>
<td>for at least 10 seconds; asystole (ventricular pause over 3 seconds); tachycardia over 165 bpm</td>
<td>arrest + 1 AV block = 6; sinus tachy: 1 out of 25 patients (i.e. brady 24%; tachy 4%)</td>
</tr>
<tr>
<td>Donateo 2003 IER pt activated (4)</td>
<td>mean 18 (9) months; 1st syncopal event analysed; follow up every 3 months to maximum of 36 months</td>
<td>events recorded were AV block; sinus arrest; sinus bradycardia (less than 40 bpm); sinus rhythm; sinus tachycardia; AF; ectopic atrial tachycardia; bradycardia; long ventricular pause; but not prespecified which were counted as arrhythmia</td>
<td>AV block 3; AV block + sinus arrest 1; sinus arrest 5; sinus brady 2 = bradycardia: 11; sinus tachycardia: 1; rapid AF: 1; ectopic atrial tachycardia: 1 out of 36 patients (i.e. brady 31%, tachy 8%)</td>
</tr>
<tr>
<td>Ermis 2003 IER pt &amp; auto activated (3)</td>
<td>mean 14.3 (7.9) months; to extraction of IER or maximum 31 months to end of study</td>
<td>IER set to detect heart rates of more than 165 bpm or less than 40 bpm or asystole more than 3 seconds; SVT; VT; asystole; complete AV block; Torsades de Pointes; sinus brady less than 60bpm; sinus tachy; premature ventricular extrasystoles predefined</td>
<td>During TLoC: SVT: 2; VT: 1; sinus brady: 1 out of 50 patients (i.e. brady 2%, tachy 6%); not during TLoC (grade I in paper i.e. arrhythmia definitely causing syncope but not occurring during TLoC): 13 patients but cannot break down by brady/tachy</td>
</tr>
<tr>
<td>Farwell 2006 IER pt &amp; auto activated (4)</td>
<td>median 17 months (IQR 9-23 months); maximum 34 months</td>
<td>set to record ventricular auses more than 3 seconds; ventricular rate less than 40 bpm or more than 165 bpm; events recorded were bradycardia, SVT or VT (no further details and not prespecified)</td>
<td>bradycardia: 15; tachycardia: 5 (2 VT + 3 SVT) out of 101 patients (i.e. brady 15%, tachy 5%)</td>
</tr>
<tr>
<td>Study name (group)</td>
<td>Index test time</td>
<td>Target condition</td>
<td>Arrhythmia detected</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------</td>
<td>------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Fitchet 2003</td>
<td>48 hours</td>
<td>events recorded during TLoC were sinus tachy, sinus rhythm, AF; major arrhy not during TLoC were</td>
<td>during TLoC: AF 2; sinus tachy 8 out of 118 patients (i.e. tachy 7%); not during</td>
</tr>
<tr>
<td>Study name (group)</td>
<td>Index test time</td>
<td>Target condition</td>
<td>Arrhythmia detected</td>
</tr>
<tr>
<td>-------------------</td>
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<td>---------------------</td>
</tr>
<tr>
<td>Holter 48h (2)</td>
<td></td>
<td>nonsustained VT or SVT; AF; sinus brady; minor ones were isolated vent ectopics/bigeminy/trigeminy/couples; 1st degree heart block (not prespecified)</td>
<td>TLoC: nonsustained VT 7; AF 13; nonsustained SVT 5; sinus brady 4 (i.e. tachy 21%; brady 3%)</td>
</tr>
<tr>
<td>Fogel 1997 EER (4)</td>
<td>usually 4 weeks; less if an event; extended if no event</td>
<td>symptom/rhythm correlation: detected arrhythmias were SVT; paroxysmal AF; prolonged pause following AF (not prespecified)</td>
<td>detected arrhythmias were SVT; paroxysmal AF; prolonged pause following AF (not prespecified)</td>
</tr>
<tr>
<td>Garcia-Civera 2005 IER pt activated (1)</td>
<td>mean 9.2 (5.9) months; seen every 3 months; followed up until diagnosis reached, battery expired or patient died</td>
<td>symptom/rhythm correlation: prespecified arrhythmic syncope if high degree AV block or VT; neurally mediated if sinus bradycardia up to 40 bpm or sinus pause 3 seconds or more; indeterminate if sinus rhythm</td>
<td>during TLoC: AV block: 12; sinus brady: 5; sinus pause: 4; VT: 6 out of 81 patients (i.e. brady = 26%; tachy = 7%)</td>
</tr>
<tr>
<td>Kapoor 1991 Holter 72h (4)</td>
<td>72 hours</td>
<td>major rhythm abnormalities (+/- symptoms) found (not prespecified): VT 3 or more beats; pauses over 2s; brady below 30bpm; complete heart block; other: ventricular ectopy; Mobitz type I heart block; brady 30-39bpm; SVT 10 or more beats over 150bpm; AF</td>
<td>VT: 19; pause &gt;2s: 8; bradycardia: 1; complete heart block: 1 out of 95 patients (i.e. brady 11%, tachy 20%)</td>
</tr>
<tr>
<td>Krahn 1998 IER pt activated (4)</td>
<td>up to 12 months; mean 4.6 (3.8) months; device explanted if diagnosis made or no event in 2 years (battery life)</td>
<td>symptom/rhythm correlation or exclusion of arrhythmia: found: bradycardia; bradycardia; AV block; sinus arrest; SVT; VT (not prespecified)</td>
<td>during TLoC: AV block: 3; brady tachy: 3; sinus arrest: 2; SVT: 1; VT: 1 out of 24 patients (i.e. brady: 8/24=33%; tachy 2/24=8%)</td>
</tr>
</tbody>
</table>

Transient loss of consciousness: full guideline DRAFT (January 2010)
cope; 18 months follow up; end of battery life; or patient or investigator chose to remove it sooner

<table>
<thead>
<tr>
<th>Study name (group)</th>
<th>Index test time</th>
<th>Target condition</th>
<th>Arrhythmia detected</th>
<th>Brady propn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krahn 2001 IER pt activated (4)</td>
<td>follow up at 1 week, 1, 2, 3, 6, 9 and 12 months and after event (aimed for full 1 year monitoring)</td>
<td>symptom/rhythm correlation (not prespecified): found bradycardia; tachycardia</td>
<td>during TLoC: bradycardia: 10; tachycardia: 1 out of 60 patients (i.e. brady 17%; tachy 1.7%)</td>
<td>a) 10/11 = 91% b) none c) 10/11 = 91%</td>
</tr>
<tr>
<td>Krahn 2002 IER pt activated (4)</td>
<td>mean 93 (107) days; follow up every 1-2 months for at least 6 months or stop after event</td>
<td>symptom/rhythm correlation: prespecified: bradycardia below 50bpm; tachycardia above 150bpm</td>
<td>bradycardia: 35 out of 206 patients (17%); tachycardia: 12 (6%)</td>
<td>a) 35/47 = 74% b) none c) 35/47 = 74%</td>
</tr>
<tr>
<td>Krahn 2004 IER pt &amp; auto activated (4)</td>
<td>follow up at 1, 2, 4, 8, 12 weeks and every 3 months thereafter to event or 1 year of end of battery life (14-20 months)</td>
<td>IER set to record pause over 3s or heart rate below 40 or above 160bpm; prespecified arrhythmias: pause over 5s; 3rd degree AV block over 10s, rate below 30bpm for over 10s; over 10 beats wide complex tachy (VT); 30 beats narrow complex tachy over 180bpm</td>
<td>during TLoC: brady 10; tachy: 4 out of 60 patients (i.e. brady 17%, tachy 7%); not during TLoC: brady 7 (12%); tachy 2 (3%)</td>
<td>a) 10/14 = 71% b) 7/9 = 78% c) 17/23 = 74%</td>
</tr>
</tbody>
</table>

Symptom/rhythm correlation: found bradycardia; tachycardia during TLoC: bradycardia: 10; tachycardia: 1 out of 60 patients (i.e. brady 17%; tachy 1.7%)

Bradycardia: 10/11 = 91%

Tachycardia: 1 out of 60 patients (i.e. brady 17%; tachy 1.7%)

Krahn 2001 IER pt activated (4)

Follow up at 1 week, 1, 2, 3, 6, 9 and 12 months and after event (aimed for full 1 year monitoring)

Symptom/rhythm correlation (not prespecified): found bradycardia; tachycardia during TLoC: bradycardia: 10; tachycardia: 1 out of 60 patients (i.e. brady 17%; tachy 1.7%)

Krahn 2002 IER pt activated (4)

Mean 93 (107) days; follow up every 1-2 months for at least 6 months or stop after event

Symptom/rhythm correlation: prespecified: bradycardia below 50bpm; tachycardia above 150bpm 

Bradycardia: 35 out of 206 patients (17%); tachycardia: 12 (6%)

Krahn 2004 IER pt & auto activated (4)

Follow up at 1, 2, 4, 8, 12 weeks and every 3 months thereafter to event or 1 year of end of battery life (14-20 months)

IER set to record pause over 3s or heart rate below 40 or above 160bpm; prespecified arrhythmias: pause over 5s; 3rd degree AV block over 10s, rate below 30bpm for over 10s; over 10 beats wide complex tachy (VT); 30 beats narrow complex tachy over 180bpm

During TLoC: brady 10; tachy: 4 out of 60 patients (i.e. brady 17%, tachy 7%); not during TLoC: brady 7 (12%); tachy 2 (3%)

Bradycardia: 10/14 = 71%

Tachycardia: 7/9 = 78%

Bradycardia: 17/23 = 74%

Krahn 2001
IER pt activated (4)

Follow up at 1 week, 1, 2, 3, 6, 9 and 12 months and after event (aimed for full 1 year monitoring)

Symptom/rhythm correlation (not prespecified): found bradycardia; tachycardia during TLoC: bradycardia: 10; tachycardia: 1 out of 60 patients (i.e. brady 17%; tachy 1.7%)

Bradycardia: 10/11 = 91%

Tachycardia: none

Bradycardia: 10/11 = 91%

Krahn 2002
IER pt activated (4)

Mean 93 (107) days; follow up every 1-2 months for at least 6 months or stop after event

Symptom/rhythm correlation: prespecified: bradycardia below 50bpm; tachycardia above 150bpm

Bradycardia: 35 out of 206 patients (17%); tachycardia: 12 (6%)

Bradycardia: 35/47 = 74%

Tachycardia: none

Bradycardia: 35/47 = 74%

Krahn 2004
IER pt & auto activated (4)

Follow up at 1, 2, 4, 8, 12 weeks and every 3 months thereafter to event or 1 year of end of battery life (14-20 months)

IER set to record pause over 3s or heart rate below 40 or above 160bpm; prespecified arrhythmias: pause over 5s; 3rd degree AV block over 10s, rate below 30bpm for over 10s; over 10 beats wide complex tachy (VT); 30 beats narrow complex tachy over 180bpm

During TLoC: brady 10; tachy: 4 out of 60 patients (i.e. brady 17%, tachy 7%); not during TLoC: brady 7 (12%); tachy 2 (3%)

Bradycardia: 10/14 = 71%

Tachycardia: 7/9 = 78%

Bradycardia: 17/23 = 74%
### Transient loss of consciousness: full guideline DRAFT (January 2010)

**Study name** (group) | **Index test time** | **Target condition** | **Arrhythmia detected** | **Brady propn**
--- | --- | --- | --- | ---
Linzer 1990 EER (4) | up to 1 month; recording stopped if diagnostic event | 3sAV lock (Mobitz type I or II) | wide QRS complex tachy 1 out of 100 patients (i.e. brady 4%, tachy 17%); unclear if during TLoC or not | a) 5/7 = 71%  
 b) none  
 c) 5/7 = 71%
Lombardi 2005 IER pt & auto activated (4) | mean 7 (4) months, range 1-14 months; device explanted after diagnosis made or if no syncope after 14 months | symptom/rhythm correlation: prespecified; sinus pause over 3s; SVT over 190bpm; complete AV block; Mobitz II 2nd degree block; VT over 10s; AF with slow ventricular response (RR interval over 3s); alternating bundle branch block; VT over 30s | during TLoC: VT: 1; SVT: 1; AV block: 2; 2 prolonged asystole; 1 non-asystolic bradycardia of 57 patients (i.e. 3.5% tachy; 9% brady) | a) 9/13 = 69%  
 b) none  
 c) 9/13 = 69%
Menozzi 2002 IER pt activated (1) | mean 16 (11) months; seen every 3 months until diagnosis, end of battery life or patient died | ECG during syncope: arrhythmias found (not prespecified) were: AV block plus asystole; sinus tachy plus sinus brady plus sinus arrest; sinus tachy 120bpm; AF (+ or – asystole) | during TLoC: marked bradycardia/ asystole 6; AF with wide QRS tachy 2; AV block 3; symptomatic sinus tachy 2 = 13 out of 34 patients (i.e. brady 26%, tachy 12%) | a) 4/10 = 40%  
 b) none  
 c) 4/10 = 40%
Moya 2001b IER pt activated (2) | mean 10 (5) months; seen every 3 months until diagnosis, battery ran down or end of study (maximum 36 ECG/syncope: findings (not prespecified): asystole | ECG/syncope: findings (not prespecified): asystole | during TLoC: sinus arrest 5; bradycardia 1 out of 29 patients (i.e. brady 21%; tachy 0%) | a) 6/6 = 100%  
 b) none  
 c) 6/6 = 100%
<table>
<thead>
<tr>
<th>Study name (group)</th>
<th>Index test time</th>
<th>Target condition</th>
<th>Arrhythmia detected</th>
<th>Brady propn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moya 2001a IER pt activated (4)</td>
<td>mean 9 (5) months; seen every 3 months until diagnosis, battery ran down or end of study (maximum 36 months)</td>
<td>ECG/syncope: findings (not prespecified): asystole; brady below 40bpm; AV block</td>
<td>during TLoC: sinus arrest 10; AV block 1; bradycardia 2; sinus tachy 1; atrial tachy 1 = 15 out of 82 patients (i.e. brady 16%; tachy 2%)</td>
<td>a) 13/15 = 87% b) none c) 13/15 = 87%</td>
</tr>
<tr>
<td>Nierop 2000 IER pt activated (4)</td>
<td>11 (8) months; seen every 3 months</td>
<td>symptom-rhythm correlation: findings (not prespecified): bradycardia below 40bpm; asystole over 3s; tachycardia 180-220bpm</td>
<td>during TLoC: extreme bradycardia or asystole &gt;5s: 4; tachycardia: 6 out of 35 patients (i.e. brady 11%, tachy 17%)</td>
<td>a) 4/10 = 40% b) none c) 4/10 = 40%</td>
</tr>
<tr>
<td>Pezawas 2007 IER pt &amp; auto activated (4)</td>
<td>mean 16 (8) months; seen every 3 months to diagnosis or end of IER life</td>
<td>set to record pauses 3s or more; heart rate 40 or below or 160 or above; prespecified arrhythmias: asystole (sinus arrest, sinus brady + AV block or AV block); brady (decrease of rate by over 30% or rate below 40 for 10s); tachy (AF; SVT; VT)</td>
<td>during TLoC: sinus arrest 8; sinus brady with AV block: 6; AV block 2; bradycardia 2; sinus tachy 10; AF 5 out of 70 patients (i.e. brady 26%, tachy 21%)</td>
<td>a) 18/33 = 54% b) none c) 18/33 = 54%</td>
</tr>
<tr>
<td>Pierre 2008 IER pt &amp; auto activated (4)</td>
<td>mean 10.2 (5.2) months; seen every 3 months until diagnosis or end of battery life (14 months)</td>
<td>set to record brady below 30bpm; ventricular arrest over 3s; tachy above 180bpm during 32 beats; rhythms found (not prespecified): complete AV block; VF; sustained/ nonsustained VT; AF with fast ventricular response; SVT; sinus arrest</td>
<td>during TLoC: sinus arrest: 16; AV block: 5; VF: 1; VT: 3; AF: 1; SVT: 1 out of 95 patients (i.e. brady 22%; tachy 6%)</td>
<td>a) 21/27 = 78% b) none c) 21/27 = 78%</td>
</tr>
<tr>
<td>Ringqvist 1989 Holter 48h (1)</td>
<td>48 hours</td>
<td>prespecified: sinus brady below 40bpm 1 min; sinus arrest 3s or more; SVT heart rate 180 or more over 10s; VT 3 or more beats; AV block Mobitz II/3rd degree; paroxysmal AF 180 bpm or more for 4 beats; AF or flutter rate below 40</td>
<td>during TLoC: sinus arrest: 1; AV block: 2; AF: 1 out of 63 patients (i.e. brady 5%, tachy 2%); not during TLoC: sinus arrest 3; AV block 1; SVT 1; VT 1; atrial flutter 1; AF 1 (brady</td>
<td>a) 3/4 = 75% b) 4/8 = 50% c) 7/12 = 58%</td>
</tr>
<tr>
<td>Study name (group)</td>
<td>Index test time</td>
<td>Target condition</td>
<td>Arrhythmia detected</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
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<td></td>
</tr>
<tr>
<td>Rockx 2005 EER (4)</td>
<td>worn until 2 clinical episodes occurred or 1 month elapsed</td>
<td>prespecified: sinus pause over 3s; complete heart block; Mobitz type 2 2nd degree block; AF with slow ventricular response (RR over 3s); symptomatic sinus brady below 40bpm; SVT over 10s or symptomatic; VT</td>
<td>During TLoC: Loop recorder: 1/49 patients had paroxysmal AF with sinus pauses up to 5.2s on conversion to sinus rhythm (i.e. brady 2%; tachy 0%); not during TLoC: none. Holter: no arrhythmias diagnosed during or not during TLoC</td>
<td></td>
</tr>
<tr>
<td>Rothman 2007 EER (1)</td>
<td>up to 30 days (minimum 25 days)</td>
<td>prespecified: pauses; complete AV block; Mobitz type 2 2nd deg block; AF/flutter; rate over 120bpm + symptoms; over 150 - symptoms; brady below 40bpm + symptoms; sustained (over 10s)/symptomatic SVT over 120bpm; VT over 100bpm over 3 beats</td>
<td>unclear – numbers don’t add up between text and table</td>
<td></td>
</tr>
<tr>
<td>Sarasin 2001 EER (4)</td>
<td>mean 6.7 (1.7) days</td>
<td>prespecified: sinus pause 3s/more/symptom+ pause 2s/more; sinus brady 35bpm or less/symptomatic brady 40bpm/less; AF+slow ventricular response (RR 3s/more); SVT 30s/more 180bpm/more or + systolic BP 90mmHg/less; 2nd deg (Mob 2)/complete AV block; VT</td>
<td>3/113 had arrhythmia (not stated which)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study name (group)</th>
<th>Index test time</th>
<th>Target condition</th>
<th>Arrhythmia detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarasin 2001 Holter 24h (4)</td>
<td>24 hours</td>
<td>prespecified: sinus pause 3s/more/symptom+ pause 2s/more; sinus brady 35bpm or less/symptomatic brady 40bpm/less; AF+slow ventricular response (RR 3s/more); SVT 30s/more 180bpm/more or + systolic BP 90mmHg/less; 2nd deg (Mob 2)/complete AV block; VT</td>
<td>9/122 had arrhythmia (not stated which)</td>
</tr>
</tbody>
</table>

Transient loss of consciousness: full guideline DRAFT (January 2010)
<table>
<thead>
<tr>
<th>Authors</th>
<th>Duration</th>
<th>Prescribed Criteria</th>
<th>During TLoC:</th>
<th>Results</th>
</tr>
</thead>
</table>
| Sarasin   | 24 hours          | sinus pause 3s or more; sinus brady 35bpm or less; AF + slow ventricular response (RR 3s or more); SVT 30s or more at 180bpm or more or with hypotension; Mobitz 2 2nd degree/complete AV block; VT 30s or more | sinus pause >3s: 3; bradycardia: 2; AV block: 2; VT: 2 out of 140 patients (i.e. brady 5%, tachy 1%); not during TLoC: none | a) 7/9 = 78%  
             |                   |                                                                                     |                                                                            | b) none  
             |                   |                                                                                     |                                                                            | c) 7/9 = 78% |
| Schuchert  | mean 7 (3) weeks; | symptom/rhythm correlation; recorded (not prespecified): sinus tachycardia (rate not specified); atrial flutter | sinus tachycardia: 1; (i.e. tachy 4%); not during TLoC: sinus tachycardia: 6; atrial flutter: 2; paced rhythm 2 out of 24 patients (i.e. tachy 42%; brady 0%) | a) 0/1 = 0%  
             | EER (4)           | range 1-10 weeks                                                                 |                                                                            | b) 0/10 = 0%  
             |                   |                                                                                     |                                                                            | c) 0/11 = 0% |
| Seidl     | mean 10.8 (4.3)   | recorded (not prespecified): brady below 50bpm; AV nodal re-entry tachycardia; SVT; torsades de pointes; frequent ventricular premature beats; mixed brady + ventricular premature beats + nonsustained VT | during TLoC: 21 brady (<50bpm); 5 SVT; 1 Torsades de Pointes; 1 pacemaker problem; 1 AV nodal re-entry tachy; 2 ventricular premature beats; 1 multiple rhythms (brady, ventricular premature beats and nonsustained VT) of 133 patients (i.e. brady 17%, tachy 8%) | a) 22/32 = 69%  
             | IER pt activated  | months; device implanted until syncope/presyncope or patient or investigator wanted to remove it |                                                                            | b) none  
             | (4)               |                                                                                     |                                                                            | c) 22/32 = 69% |
### 3.5 Exercise testing for arrhythmia review

#### 3.5.1 Diagnostic Test: exercise test

<table>
<thead>
<tr>
<th>Study</th>
<th>Participant</th>
<th>Diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boudoulas 1979</strong> non-randomised comparative study; study held in USA. Setting: Cardiology. Funding: National Institutes of Health and Central Ohio Heart Chapter of the American Heart Association</td>
<td>TLoC population: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test. syncope or presyncope (dizziness or lightheadedness) Definition of TLoC: syncope or presyncope (dizziness or lightheadedness). Inclusion criteria: patients with syncope or presyncope (dizziness or lightheadedness). Exclusion criteria: obvious cause of syncope on resting ECG. Patient characteristics: age: mean around 51 years; sex: 53% male; All patients with existing heart disease (all had cardiovascular disorders); TLoC history: not stated Comorbidities: not stated. Other details: patients with syncope or presyncope (dizziness or lightheadedness) Other study comments: 2 tests within 1 week; exercise test as index test versus ambulatory monitoring as reference standard</td>
<td>Index test: maximum multistage treadmill exercise test Bruce protocol; time: 24 hours (n=119) Reference standard: 24 hour ambulatory heart rate recording (Avionics Electrocardiocorder Model 400); automatic recording of all ECG; diary for symptoms; time 1 day (n=119) for Target Condition/Outcome: dysrhythmia</td>
</tr>
<tr>
<td><strong>Colivicchi 2002</strong> non-randomised comparative study; study held in Italy. Setting: Syncope unit. Cardiology/sports science. Funding: not stated</td>
<td>TLoC population: TLoC: exercise-related syncope: sudden transient loss of consciousness with inability to maintain postural tone and spontaneous recovery. Inclusion criteria: highly trained athletes with at least 2 witnessed episodes of syncope during or immediately after exercise in last 6 months. Exclusion criteria: none. Patient characteristics: age: mean age 21.4 (3.2) years; sex: 61% female; no patients with existing heart disease (no major cardiac abnormality on 12 lead ECG or echo); TLoC history: mean 4.66 spells before evaluation Comorbidities: none stated. Other details: athletes referred for recurrent unexplained episodes of exercise-related syncope Other study comments: case series</td>
<td>Index test: Exercise tolerance testing; Bruce protocol; time: 1 day (n=33) Comparator test: morning; fasting; 60 degrees for 30 minutes; if negative 1.25mg isosorbide dinitrate sublingually and tilt for 15 minutes; time: 1 day (n=33). for Target Condition/Outcome: diagnosis</td>
</tr>
<tr>
<td><strong>Doi 2002</strong> diagnostic test accuracy study; study held in Japan. Setting: Department of Internal Medicine. Funding: not stated</td>
<td>TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: ---. unexplained syncope; cardiovascular and cerebrovascular disease excluded by 12 lead ECG, echo, CT Inclusion criterion: Syncope during exercise (n=18) or exercise-unrelated syncope (n=26). Exclusion criteria: organic heart disease, thyroid dysfunction, paroxysmal atrial flutter-fibrillation. Patient characteristics: age: patients mean age 46 (19) years, range 13 to 79 years; controls: mean age 42 (18), 13 to 79 years; sex: patients: 59% male; controls 60% female; no patients with existing heart disease (no cardiovascular disease); TLoC history: syncope during exercise (n=18) or exercise-unrelated syncope (n=26); mean number of spells around 3 Comorbidities: 4 patients had impaired glucose tolerance test; 4 had untreated hypertension. Other details: see below Other study comments: case series; 44 patients and 20 control subjects</td>
<td>Index test: fasting; morning; modified rapid protocol: exercise of submaximal intensity for 3 minutes after each 1 minute step-up period; abrupt cessation without cool down; 10 minutes standing at end; time: 1 day (n=64) Reference standard: patients versus controls for Target Condition/Outcome: diagnosis</td>
</tr>
</tbody>
</table>
3.6 Tilt table for NMS review

3.6.1 Included studies table

<table>
<thead>
<tr>
<th>Study</th>
<th>Participant</th>
<th>Diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerts 1997</td>
<td>TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. History of typical vasovagal syncope; other causes excluded by ECG, BP, CSM, routine laboratory tests, CT, EEG, 24 hour Holter. Definition of TLoC: syncope preceded by provocative stimuli (stress, overloading, fatigue, illness, pain, blood) with prodrome (nausea, sweating, palpitations, pallor) with complete spontaneous recovery of consciousness and symptoms. Inclusion criteria: 32 patients with a history of typical vasovagal syncope + 20 healthy volunteers. Exclusion criteria: other causes of syncope (cardiac/neurological). Patient characteristics: age: mean age 43 (21) years, range 16 to 87 years; sex: 63% male; Unclear/not stated with existing heart disease (not stated); TLoC history: mean 3 episodes, range 1-20 episodes (not stated over what time period) Comorbidities: not stated. Other details: see below. Other study comments: 32 patients + 20 healthy volunteers (16 men + 4 women) who had never had syncope; mean age 27 (4) years; range 22 to 38 years.</td>
<td>Index test: supine 10 minutes; raised to 70 degrees for up to 45 minutes; if negative, isosorbide dinitrate 5mg sublingually; further 15 minutes tilt; time: maximum 70 minutes. Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope; comparison of classic HUT and HUT-ISO (but only done once)</td>
</tr>
<tr>
<td>Aerts 1999</td>
<td>TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. History of typical vasovagal syncope Definition of TLoC: TLOC with spontaneous recovery (awareness of imminent syncope or loss of postural control; syncope erect or sitting; pain, mental stress; lightheadedness; rapid recovery with recumbency). Inclusion criteria: 20 patients with a history of typical vasovagal syncope + 23 healthy volunteers (no syncope). Exclusion criteria: other causes of syncope (by neurological examination, CSM, BP, 12 lead ECG, routine laboratory tests, 24 hour Holter, echo, CT, EEG); cardiovascular or vasodilating drugs. Patient characteristics: age: patients mean age 41 (15) years; controls 25 (5) years (p=0.001); sex: patients: 50% male; controls 65% male (NS); Unclear/not stated with existing heart disease (not stated); TLoC history: mean 4 episodes, range 1 to 20 (not stated over what time period) Comorbidities: not stated. Other details: see below. Other study comments: 20 patients + 23 healthy controls.</td>
<td>Index test: between 9am and noon after overnight fast; 10 minutes supine; continuous IV infusion of isosorbide dinitrate 1microg/kg/min; dose increased by 1microg/kg/min every 5 minutes to maximum of 6microg/kg/min; tilt at 70 degrees for maximum of 30 minutes; time: maximum 40 minutes. Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope.</td>
</tr>
</tbody>
</table>
**Study**

Aerts 2005  
case control study;  
study held in  
Belgium, The  
Netherlands.  
Setting: Cardiology.  
Multinational.  
Funding: not stated

**Participant**

TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.  
12-lead ECG, routine laboratory tests, CT, Doppler flow of neck vessels, 24 hour Holter, echo ECG.  
Definition of TLoC: syncope provoked by emotional and orthostatic stress; situational (micturition, defecation, swallowing); prodrome (warmth, nausea, sweating, visual dimming, lightheadedness); symptom relief with recumbency.  
Inclusion criteria: physical and neurological examination normal.  
Exclusion criteria: carotid sinus hypersensitivity, orthostatic hypotension; cardiovascular or vasoactive drugs.  
Patient characteristics: age: mean age of patients 46 (19) years, range 16 to 78 years; controls 26 (6) years, range 20 to 40 year; sex: patients: 56% female; controls 83% male; no patients with existing heart disease (none); TLoC history: not stated  
Comorbidities: not stated. Other details: 43 patients with typical history of vasovagal syncope + 18 controls.  
Other study comments: 43 patients with typical history of vasovagal syncope+18 healthy controls; reproducibility of 2nd tilt 16 (12) days after 1st tilt: positive test (patients and controls) reproduced 100%; reproducibility of negative test 50% in patients and 93% in controls

Aerts 2005b  
case control study;  
study held in  
Belgium, The  
Netherlands.  
Setting: Cardiology.  
Multinational.  
Funding: not stated

TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.  
clinically suspected vasovagal syncope  
Definition of TLoC: At least 1 of: awareness of imminent syncope, loss of postural control; occurs in erect or sitting position; prodrome (warmth, nausea, sweating, visual dimming, precipitating anxiety of pain, mental stress, lightheadedness); rapid recovery with recumbency.  
Inclusion criteria: clinically suspected vasovagal syncope.  
Exclusion criteria: other causes of syncope (by neurological examination, CSM, BP, 12 lead ECG, routine laboratory tests, 24 hour Holter, echo, CT, EEG); cardiovascular or vasodilating drugs.  
Patient characteristics: age: patients: mean age 46 (16) years; control 40 (18) years; sex: patients: 53% male; control 52% male; no patients with existing heart disease (none); TLoC history: mean 3 spells (range 1-10; not stated over what time period)  
Comorbidities: not stated. Other details: see below  
Other study comments: 38 patients + 31 controls

Almqist 1989  
case control study;  
study held in USA.  
Setting: Department of Medicine.  
Funding: American Heart Association; Education ministry of China; Minnesota Medical Foundation

TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.  
12-lead ECG, ambulatory ECG, neurological evaluation (could include CT and/or EEG).  
Definition of TLoC: not defined.  
Inclusion criteria: at least 3 episodes of unexplained syncope or presyncope.  
Exclusion criteria: excessive obesity, haematologic or biochemical abnormality, drugs predisposing to orthostatic hypotension; left ventricular dysfunction (LVEF below 45%); contraindications to isoprotenerol.  
Patient characteristics: age: patients 14 to 80 years; controls 13 to 70 years; gender 54% male; controls 72% male; some patients with existing heart disease (21% had heart disease); TLoC history: at least 3 episodes of unexplained syncope or presyncope (no further details)  
Comorbidities: not stated.  
Other study comments: 24 patients with recurrent syncope and 18 controls without syncope referred for assessment of ventricular or supraventricular tachycardia

**Diagnostic tests**

Index test: between 9am and noon; fasting at least 4 hours; 10 minutes supine; tilt to 70 degrees for 30 minutes; if negative, 5mg isosorbide dinitrate for 15 minutes; time: maximum 55 minutes (n=61)  
Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope

Index test: HUT-GTN: between 9am and noon after overnight fast; no passive tilt phase; directly after attaining 70 degrees, 0.4mg nitroglycerin spray sublingually; maximum 30 minutes; time: maximum 30 minutes (n=69)  
Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope

Index test: 80 degrees for maximum of 10 minutes; if negative, supine with IV isoproterenol 1microg/min for 5 minutes; 80 degree tilt for maximum of 10 minutes; if negative, repeated with graded infusion rates up to 5microg/min; time: maximum not stated (n=42)  
Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope

**Index**

DRAFT FOR CONSULTATION
### Study

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<tr>
<td>Aslan 2002</td>
<td>TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. Unexplained syncope after CSM, BP, routine biochemical and haematological tests, 12 lead ECG, echo, neurological evaluation, exercise tests, 24 hour Holter, EPS, angiography.</td>
<td>Index test: supine rest 20-30 minutes; tilt to 80 degrees for 30 minutes; if negative, 2.5mg sublingual isosorbide dinitrate for additional 15 minutes; time: maximum 75 minutes (n=61) Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope</td>
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<td></td>
<td>Patient characteristics: age: mean age 45.4 (18) years; sex: 51% male; no patients with existing heart disease (none); TLoC history: median 3 episodes in last year (range 1 to 12 episodes).</td>
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<td>Comorbidities: not stated. Other details: see below. Other study comments: 18 controls mean age 45.8 (12) years, no TLoC/presyncope/ heart disease/disease known to cause autonomic dysfunction. 1st 25 patients tested again after 1-4 weeks; if passive -ve, isoproterenol 1 and 3 microg/min and 80 degree tilt for 10 minutes</td>
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<td>Athanasos 2003</td>
<td>TLoC population: unclear/not stated. Prior tests: Unclear or Not stated. Syncope of undetermined origin. Definition of TLoC: sudden, transient loss of consciousness due to decreased cerebral blood flow. Inclusion criteria: referred for HUT because of syncope of unknown origin. Exclusion criteria: not stated. Patient characteristics: age: patients mean age 39 (13) years; controls 32 (9); sex: patients: 54% female; controls: 54% male; Unclear/not stated with existing heart disease (not stated). TLoC history: not stated. Comorbidities: not stated. Other details: referred for HUT because of syncope of unknown origin Other study comments: 13 patients + 13 asymptomatic controls with no syncope history</td>
<td>Index test: HUT-GTN; Raviele protocol except glyceryl trinitrate for 15 not 25 minutes; time: total duration not stated (n=26) Reference standard: patients versus controls for Target Condition/Outcome: diagnosis; vasovagal syncope</td>
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<tr>
<td>Bartoletti 1999</td>
<td>TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. Unexplained syncope. Definition of TLoC: sudden transient loss of consciousness and loss of postural tone and spontaneous recovery. Inclusion criteria: patients with unexplained syncope. Exclusion criteria: not stated. Patient characteristics: age: mean age 55 (22) years; sex: 61% female; some patients with existing heart disease (coronary heart disease 6%); TLoC history: median number of episodes 3 (range 1-100); median duration 24 months (range 1-680) Comorbidities: 18% had arterial hypertension. Other details: see below Other study comments: all patients underwent both tests in randomised sequence with 24 to 72 hour interval</td>
<td>Index test: between 8.30 and 11.30 am; Raviele method: passive 60 degrees for 45 minutes; if negative, sublingual nitroglycerin spray 0.4mg and further 20 minutes; time: maximum duration 65 minutes (n=84) Comparator test: between 8.30 and 11.30 am; accelerated HUT-GTN method: passive 60 degrees for 5 minutes; if negative, sublingual nitroglycerin spray 0.4mg and further 20 minutes; time: maximum duration 25 minutes (n=84); for Target Condition/Outcome: vasovagal syncope</td>
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**Study**

Benchimol 2008

- Case control study;
- Study held in Brazil.

**Setting:** Unclear.
- University hospital, department not stated.
- Funding: None.

**Participant**

TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.
- ECG and echo normal or showed no association with symptoms
- Definition of TLoC: non-convulsive faints or unexplained falls (drop attacks).
- Inclusion criteria: patients referred for investigation of non-convulsive faints or unexplained falls of which 1st episode several months before.
- Exclusion criteria: carotid murmur, CVA or acute MI in previous 6 months or history of severe ventricular arrhythmia.
- Patient characteristics: age: mean 50 (24) years (range 10-96 years); sex: 66% female; Unclear/not stated with existing heart disease (not stated);
- TLoC history: 1st episode mean of 53 (100) months before
- Comorbidities: not stated. Other details: see below

Other study comments: 55 “controls” no history of seizures, faints or falls; mean age 57 (21) years, range 16-88 years. 3rd part: HUTT patients versus controls DTA; results not given for passive phase

**Diagnostic tests**

- Index test: 2-5pm after 12 hour fast; 1.25mg isosorbide dinitrate; time: passive 25 mins; sensitised 25 mins (n=259)
- Reference standard: patients versus controls
- Comparator test: 2-5pm after 12 hour fast; 1.25mg isosorbide dinitrate; time: passive 25 mins; sensitised 25 mins (n=55).

For Target Condition/Outcome: HUTT positive if symptoms occurred due to hypotension, bradycardia or both

**Brignole 1991**

- Case control study;
- Study held in Italy.
- Setting: Cardiology, referred from ED or inpatient service or ambulatory program.
- Funding: Not stated.

**Patient**

TLoC population: unclear/not stated. Prior tests: All patients had at least 1 prior test.
- Syncope of uncertain origin despite neurological examination, laboratory tests, 12 lead ECG, 24 hour monitoring, chest x-ray, echo (+ where indicated stress test, EEG, Doppler, CT, cardiac catheter, EPS, arteriography)
- Definition of TLoC: not defined.
- Exclusion criteria: postural hypotension, conversion reaction, seizure, TIA, subclavian steal, drug-induced syncope, aortic stenosis, pulmonary HT, hypertrophic cardiomyopathy, dysrythmia.
- Patient characteristics: age: patients: mean age 60 (18); controls 60 (17); sex: patients: 54% men; controls 57% male; some patients with existing heart disease (39% had structural heart disease); TLoC history: not stated
- Other study comments: 100 patients+ 25 healthy controls without syncope or presyncope matched on age and gender

**Diagnostic tests**

- Index test: 8 am to noon; non-fasting; 10 minutes supine; 60 degrees for 60 minutes; time: maximum 70 minutes (n=100)
- Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope

**Carlioz 1997**

- Non-randomised comparative study;
- Study held in France.

**Setting:** Cardiology.

**Funding:** Not stated.

**Patient**

TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.
- Blood test, carotid sinus massage, BP, 12 lead ECG, 24 hour ambulatory ECG, echo, exercise test, neurological examination
- Definition of TLoC: Syncope: transient loss of consciousness appearing suddenly or preceded by short prodromes (less than 10 seconds) with loss of postural tone and spontaneous recovery without therapeutic intervention.
- Inclusion criteria: young adults (under 30 years); at least 1 episode of syncope of unknown cause.
- Exclusion criteria: not stated.
- Patient characteristics: age: patients: mean age 20.9 (1.7) years; controls: 22.6 (2.7); sex: 98% male; Unclear/not stated with existing heart disease (not stated);
- TLoC history: mean 3.8 (1.6) unexplained losses of consciousness (not stated over what time period)
- Comorbidities: not stated. Other details: see below

Other study comments: 76 patients + 35 volunteers (no syncope, lipothympia, cardiopathy or other underlying disease); 1st batch of patients/controls had passive HUT; 2nd batch had HUT-ISO

**Diagnostic tests**

- Index test: patients not necessarily fasting; 10 minutes horizontal; passive tilt 60 degrees for 45 minutes; time: maximum 55 minutes (n=65)
- Reference standard: patients versus controls
- Comparator test: 10 minutes horizontal; 30 minutes passive tilt at 60 degrees; horizontal 5 minutes with 2microg/min isoproterenol; 60 degrees for 10 minutes; horizontal 5 minutes; then 5 microg/min isoproterenol; 60 degrees 10 minutes; time: maximum 70 minutes (n=46).

For Target Condition/Outcome: vasovagal syncope
**Study**

Del Rosso 1998 case control study; study held in Italy.
Setting: Cardiology.
Cardiology, internal medicine, Arrhythmology departments at hospitals.
Funding: not stated

**Participant**
TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.
unexplained syncope after ECG, carotid sinus massage (ambulatory 24 hour ECG, echo, EPS, EEG, CT as indicated)
Definition of TLoC: sudden transient loss of consciousness with inability to maintain postural tone and spontaneous recovery.
Inclusion criteria: unexplained syncope.
Exclusion criteria: structural heart disease, sick sinus syndrome, intraventricular conduction disturbance, orthostatic hypotension, chronic and paradoxical atrial fibrillation, permanent pacemaker
Participant characteristics: age: patients: mean age 49 (19) years, range 8 to 85 years; controls 45 (17) years, range 18 to 82 years; sex: 56% female; no patients with existing heart disease (excluded); TLoC history: mean 4 (5) episodes; mean duration of symptoms 62 (118) months
Comorbidities: 12% arterial hypertension. Other details: see below
Other study comments: case series: 202 patients with unexplained syncope + 34 controls (no history of syncope or presyncope or structural heart disease)

Del Rosso 2002 case control study; study held in Italy.
Setting: Syncope unit. Syncope units in secondary and tertiary hospitals.
Funding: not stated

**Participant**
TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.
unexplained syncope after BP, ECG, carotid sinus massage ambulatory 24 hour ECG, echo, EPS, EEG, CT where necessary)
Definition of TLoC: sudden transient loss of consciousness with inability to maintain postural tone and spontaneous recovery.
Inclusion criteria: referred from emergency room or from outpatients to syncope unit of the cardiology or geriatric medicine divisions at 3 hospitals.
Exclusion criteria: organic heart disease, sick sinus syndrome, orthostatic hypotension, carotid sinus syndrome, chronic and paroxysmal atrial fibrillation, permanent pacemakers, intraventricular conduction defects.
Patient characteristics: age: 100 aged 65 or more (mean 73 (6)); 224 under 65 yr (mean 41 (15) yr); sex: patients and controls 55% female; no patients with existing heart disease (excluded); TLoC history: mean 4 (5) episodes in each age band; mean duration 95 (195) months in older and 82 (136) months in younger group. Comorbidities: 11% arterial hypertension.
Other study comments: 324 patients + 64 controls (29 aged 65 years or more, mean 73 (6); 35 under 65 years (42 (13)); no history of syncope or presyncope

**Diagnostic tests**
Index test: HUT-GTN: after overnight fast, between 8.30 and 10.30 am; supine; 60 degrees for 20 minutes; if negative, sublingual nitroglycerin 400 microg and further 15 minutes; time: maximum 45 minutes (n=236)
Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope

**Study**

Doi 2002 diagnostic test accuracy study; study held in Japan.
Setting: Department of Internal Medicine.
Funding: not stated

**Participant**
TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal.
unexplained syncope; cardiovascular and cerebrovascular disease excluded by 12-lead ECG, echo, CT
Definition of TLoC: not defined.
Inclusion criteria: syncope during exercise (n=18) or exercise-unrelated syncope (n=26).
Exclusion criteria: organic heart disease, thyroid dysfunction, paroxysmal atrial flutter-fibrillation.
Patient characteristics: age: mean age 46 (19) years, range 13 to 79 years; sex: 59% male; no patients with existing heart disease (no cardiovascular disease); TLoC history: syncope during exercise (n=18; excluded) or exercise-unrelated syncope (n=26); mean number of spells 2.9 (1.8); range 1 to 8 over mean 6.4 years (mean age of onset 40.3 years; mean age at study start 46.7 years)
Comorbidities: 4 patients had impaired glucose tolerance test; 4 had untreated hypertension. Other details: see below
Other study comments: case series; 20 control subjects (60% female; mean age 42 (18) years, range 13 to 79 years)

**Diagnostic tests**
Index test: fasting; morning; 10 minutes rest; 80 degrees for 30 minutes; if negative 0.01-0.02microg/kg/min isoproterenol; increased 0.005micro every 5 minutes; total duration 45 minutes; time: maximum 45 minutes (n=44)
Reference standard: patients versus controls for Target Condition/Outcome: diagnosis

**Study**

Englund 1997 case control study;

**Participant**
TLoC population: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test.

**Diagnostic tests**
Index test: after 4 hours fasting; 10 minutes supine; 60 degrees for 45 minutes
Funding: Swedish Heart and Lung Foundation; Karolinska Institute

Setting: Hospital several departments, cardiology, medicine.

Inclusion criteria: patients with bifascicular block (left bundle branch block or right bundle branch block with left anterior or posterior fascicular block) and unexplained syncope.

Exclusion criteria: normal 24 hour Holter; or normal EPS; or 12 lead ECG normal; or TLoC history: stated.

Other study comments: 71 patients + 27 symptom-free controls (no history of syncope)

Fitzpatrick 1991

Case control study; study held in UK.

Setting: Cardiology.

Funding: not stated

TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. Recurrent unexplained syncope after surface ECG; 24 hour Holter, limited EPS.

Definition of TLoC: not defined.

Inclusion criteria: 2 or more episodes of syncope; normal cardiovascular and neurological assessment; non-invasive investigations (surface ECG, 24 hour Holter) did not suggest diagnosis; normal limited EPS.

Exclusion criteria: not stated.

Patient characteristics: age: Patients: mean age 69 (10) years; controls: 64 (12); sex: 58% male; controls 56% male; some patients with existing heart disease (3 had mild hypertension; 2 had mild stable angina); TLoC history: not stated

Comorbidities: not stated. Other details: see below.

Other study comments: 25 patients with bifascicular block and unexplained syncope + 25 controls with bifascicular block without syncope or dizzy spells

Index test: between 9am and noon after overnight fast; 60 degrees for 60 minutes; time: maximum 60 minutes (n=98)

Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope

Gielerak 2002

Case control study; study held in Poland.

Setting: Hospital several departments, internal medicine and cardiology.

Funding: not stated

TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. Syncope of unknown origin after echo, 12 lead ECG, 24 hour Holter and signal-averaged ECG, neurological examination (and in patients over 45 years Doppler ultrasound of carotid arteries), carotid sinus massage, laboratory tests.

Definition of TLoC: not defined.

Inclusion criteria: at least 2 syncopal episodes in last 6 months.

Exclusion criteria: organic heart disease; abnormalities on echo, 12 lead ECG, 24 hour Holter and signal-averaged ECG, neurological examination (and in patients over 45 years Doppler ultrasound of carotid arteries), carotid sinus massage, laboratory tests.

Patient characteristics: age: patients: mean age 34.8 (15.8) years, range 18 to 72 years; controls 33.7 (15.3), 18 to 69 years; sex: patients: 55% female; controls 58% male; no patients with existing heart disease (excluded); TLoC history: at least 2 syncopal episodes in last 6 months, mean 4.7 (3.5), range 2 to 14 in last 6 months

Comorbidities: not stated. Other details: see below.

Other study comments: case series: 40 patients + 24 healthy age-sex matched controls

Index test: Westminster protocol: overnight fast; between 9 and 11 am; supine 15 minutes: 60 degrees for 45 minutes; time: maximum 60 minutes (n=64)

Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope


**Study**

Gilligan 1992  
case control study;  
study held in UK.  
Setting: Cardiology.  
department of  
medicine (clinical  
cardiology).  
Funding: not stated  


**Participant**

TLoC population: unclear/not stated.  
Prior tests: All patients had at least 1  
prior test.  
patients with hypertrophic cardiomyopathy who had had echo, 48 hour Holter  
Definition of TLoC: sudden episode of loss of consciousness with spontaneous  
recovery.  
Inclusion criteria: hypertrophic cardiomyopathy and syncope.  
Exclusion criteria: age below 18 or over 70 years; overt heart failure;  
uncontrolled cardiac arrhythmia; severe mitral regurgitation; difficult echo;  
withdrawal of medication unacceptable; coronary artery disease; MI; other  
major systemic disease.  
Patient characteristics: age: mean age 48 (14) years, range 18 to 70 years; sex:  
56% female; All patients with existing heart disease (hypertrophic  
cardiomyopathy); TLoC history: syncope in last 5 years  
Comorbidities: not stated. Other details: see below  
Other study comments: case series: 17 patients with hypertrophic  
cardiomyopathy and syncope + 19 controls (HCM but not syncope)


**Diagnostic tests**

Index test: 30 mins supine; 30 degrees for 2  
mins; 60 degrees for 45 mins; if negative,  
supine 15 mins; isoprenaline 1microg/min for  
5 mins; 30 degrees for 30s and 60 degrees for  
10 mins; 5 mins supine; 2microg/min tilt 10  
min; 5 mins supine; 4microg/min tilt 10 min;  
time: maximum duration 135 minutes (n=36)  
Reference standard: patients versus controls  
for Target Condition/Outcome: vasovagal  
syncope


Graham 2001  
RCT; study held in  
UK.  
Setting: Cardiology.  
cardiovascular  
Investigation unit.  
Funding: Northern  
and Yorkshire  
Research and  
Development Health  
Services Research  
Committee  


**Participant**

TLoC population: patients with a history of recurrent syncope but 12-lead ECG  
normal.  
unexplained syncope after 12 lead ECG, supine and upright carotid sinus  
massage, 24 hour Holter, 24 hour ambulatory BP (EEG, echo, CT brain an  
dexercice test if indicated)  
Definition of TLoC: not defined.  
Inclusion criteria: patients with unexplained syncope referred to regional  
syncope facility; more than 2 episodes in previous year.  
Exclusion criteria: uncontrolled hypertension (190/100), tachyarrhythmia,  
recent MI, angina requiring more than occasional use of nitrate,  
cerebrovascular events.  
Patient characteristics: age: mean age 50 years (range 16 to 87 years); sex: 66%  
female; Unclear/not stated with existing heart disease (not stated);  
TLoC history: more than 2 episodes in previous year  
Comorbidities: not stated.  
Other study comments: case series of 48 patients + 14 healthy controls (no  
syncope or presyncope in past 5 years, no medication, normal ECG)  
who had glyceryl trinitrate tilt and isoprenaline tilt 1 week apart in  
random order if passive HUT negative


**Diagnostic tests**

Index test: HUT-GTN: supine 10 minutes;  
glyceryl trinitrate 800microg sublingually; 70  
degrees 25 minutes; time: maximum duration 35  
minutes (n=62)  
Reference standard: patients versus controls  
Comparator test: HUT-IS0: supine 5 mins; 70  
degrees 5 mins; isoprenaline 1microg/min for  
5 mins supine and 5 mins at 70 degrees; 2 min  
supine; 3microg/min for 5 mins supine and 5  
mins at 70 degrees; 2 mins supine;  
5microg/min for 5 mins supine and 5 mins at  
70 degrees; time: maximum duration 44  
minutes (n=62).  
for Target Condition/Outcome: vasovagal  
syncope


Graham 2001  
case control study;  
study held in UK.  
Setting: Cardiology.  
cardiovascular  
Investigation unit.  
Funding: Northern  
and Yorkshire  
Research and  
Development Health  
Services Research  
Committee  


**Participant**

TLoC population: patients with a history of recurrent syncope but 12-lead ECG  
normal.  
unexplained syncope after 12 lead ECG, supine and upright carotid sinus  
massage, 24 hour Holter, 24 hour ambulatory BP (EEG, echo, CT brain an  
dexercice test if indicated)  
Definition of TLoC: not defined.  
Inclusion criteria: patients with unexplained syncope referred to regional  
syncope facility; more than 2 episodes in previous year.  
Exclusion criteria: uncontrolled hypertension (190/100), tachyarrhythmia,  
recent MI, angina requiring more than occasional use of nitrate, cerebrovascular  
events.  
Patient characteristics: age: patients: mean age 50 years (range 16 to 87 years);  
controls: mean 44 (20) years; sex: patients: 66% female; controls: 54% female;  
Unclear/not stated with existing heart disease (not stated);  
TLoC history: median syncope frequency 1 per week (not stated how long for)  
Comorbidities: not stated. Other details: see below  
Other study comments: 88 patients + 26 controls


**Diagnostic tests**

Index test: between 2 and 4pm; fasting; supine  
10 minutes; 70 degrees 40 minutes; time:  
(n=114)  
Reference standard: patients versus controls  
for Target Condition/Outcome: vasovagal  
syncope
### Study
Grubb 1991b  
Case control study; study held in USA.  
Setting: Cardiology.  
Funding: not stated

### Participant
TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal.  
Prior tests: All patients had at least 1 prior test.  
Recurrent unexplained syncope despite 12 lead ECG, ambulatory ECG, exercise test, echo, neurological examination including EEG and CT (some also had EPS)  
Definition of TLoC: not defined.  
Inclusion criteria: at least 2 episodes in preceding 6 months.  
Exclusion criteria: not stated.  
Patient characteristics: age: patients: mean age 50 (16) years, range 13 to 80 years; controls: mean 37 years; sex: 56% male; controls: 67% male; some patients with existing heart disease (5 had organic heart disease); TLoC: history; total number of episodes ranged from 2 to 9; at least 2 episodes in preceding 6 months.  
Comorbidities: not stated.  
Other study comments: 25 patients + 6 controls (no history of syncope)

### Diagnostic tests
Index test: fasting; 80 degrees for 30 minutes; if negative, supine 5 minutes, IV isoproterenol 1μg/min 5 minutes; 80 degrees for 30 minutes; repeated with 2μg/min and 3μg/min; time: maximum duration 150 minutes (n=31)  
Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope

### Study
Grubb 1992b  
Case control study; study held in USA.  
Setting: Cardiology.  
electrophysiology laboratory of university hospital.  
Funding: not stated

### Participant
TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal.  
Prior tests: All patients had at least 1 prior test.  
elderly patients with recurrent idiopathic syncope; prior tests, BP, 12 lead ECG, exercise test, echo, ambulatory ECG, neurological exam including EEG and CT or MRI brain; CSM; some also had angiography, EPS  
Definition of TLoC: transient loss of consciousness and postural tone.  
Inclusion criteria: At least 2 syncopal episodes in previous 6 months; cause unknown despite tests.  
Exclusion criteria: not stated.  
Patient characteristics: age: patients unexplained: mean 73 (6) yr (range 65 to 89 yr); controls other syncope: mean 70 (4) years; sex: patients: 56% female; controls: 57% male; some patients with existing heart disease (5 had IHD; 2 had mitral valve prolapse (of 25)); history of TLoC: at least 2 syncopal episodes in previous 6 months; mean of 3.4 (1.5) episodes in all (not stated over what time period)  
Comorbidities: not stated.  
Other details: At least 2 syncopal episodes in previous 6 months; cause unknown despite tests.  
Other study comments: 25 patients with recurrent unexplained syncope + 7 controls with other causes of syncope

### Diagnostic tests
Index test: fasting; HUT 30 minutes at 80 degrees, if negative, 5 minutes supine, isoproterenol 1μg/min and tilt for 30 minutes, repeated at 2μg/min and 3μg/min; time: maximum 135 minutes (n=32)  
for Target Condition/Outcome: vasovagal syncope: bradycardia and/or hypotension on tilt test associated with LOC

### Study
Herrmosillo 2000  
Case control study; study held in Mexico.  
Setting: department of electrophysiology and division of clinical research.  
Funding: not stated

### Participant
TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal.  
Prior tests: All patients had at least 1 prior test.  
history of neurocardiogenic syncope  
Definition of TLoC: neurocardiogenic syncope: loss of consciousness occurring while standing; related to unpleasant, frightening or painful events; with weakness, sweating, pallor, palpitations, warmth, nausea, abnormal vision; recovery within seconds of supine rest.  
Inclusion criteria: typical history of neurocardiogenic syncope with recent episodes (at least 2 episodes in last 6 months).  
Exclusion criteria: structural heart disease, sick sinus syndrome, intraventricular conduction disturbance, orthostatic hypotension, chronic and paroxysmal atrial fibrillation, pacemaker.  
Patient characteristics: age: patients: mean 32.7 (14.8), range 15 to 77 years; controls: mean 32 (2), 25 to 70 years; sex: 74% female, 64% female; no patients with existing heart disease (excluded); TLoC: history; median 5 episodes, range 2 to 25 in the last 6 months.  
Comorbidities: not stated.  
Other details: other causes of syncope excluded by carotid sinus massage, BP, 12 lead ECG, ambulatory monitoring (EEG and CT brain when neurological disease suspected).  
Other study comments: 120 patients and 50 controls (healthy volunteers)

### Diagnostic tests
Index test: overnight fast; between 9 and 11am; 10 minutes supine; 70 degrees for 30 minutes; if negative, 30 minutes supine; isoproterenol 4μg/min for 10 minutes; 30 minutes supine; isosorbide dinitrate 5mg sublingual and tilt for 12 minutes; time: maximum duration 122 minutes (n=170)  
Reference standard: patients versus controls for Target Condition/Outcome: neurocardiogenic syncope
**Study**  
Lagi 1992  
*case control study; study held in Italy.*  
Setting: Hospital several departments, internal medicine and neurology.  
Funding: not stated

**Participant**  
TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.  
Previous discharge diagnosis of recurrent vasodepressor syncope  
Definition of TLoC: diagnosis based on prodrome, short duration of LOC, recovery on lying in less than 5 minutes without neurological sequelae, triggers (e.g. pain), normal 24 hour ECG and carotid sinus massage, no orthostatic hypotension.  
Inclusion criteria: at least 3 episodes of vasodepressor syncope (by above definition); at least 2 episodes of loss of consciousness after standing still for at least 10 minutes.  
Exclusion criteria: neurological, cardiovascular, metabolic or endocrine disorder, alcohol abuse, smoking, physical/neurological abnormality on examination.  
Patient characteristics: age: patients; mean age 47 years, range 22 to 70 years; controls; mean 42 years, range 18 to 67 years; sex: patients 56% female; controls 58% male; no patients with existing heart disease (excluded); TLoC history: at least 3 episodes of vasodepressor syncope in last 4 years  
Comorbidities: not stated. Other details: see below  
Other study comments: case series: 72 patients + 71 healthy volunteers

**Diagnostic tests**  
Index test: overnight fast; late morning after at least 2 hours rest; 60 degrees; duration not stated; time: duration not stated (n=143)  
Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope

**Study**  
Lazzeri 2000  
*case control study; study held in Italy.*  
Setting: Hospital several departments, internal medicine  
Funding: not stated

**Participant**  
TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.  
Explaned syncope referred for HUT  
Definition of TLoC: loss of consciousness not explained by history, examination, carotid sinus massage, BP, chest x-ray, exercise test, neurological examination and echo cardiography.  
Inclusion criteria: at least 1 episode of unexplained syncope in last 6 months.  
Exclusion criteria: heart failure, diabetes, neuropathy, coronary heart disease, arterial hypertension, other disease that could account for syncope, abnormal uranalysis or blood tests or ECG or echo.  
Patient characteristics: age: patients; mean age 35 (3) years, range 15 to 60 years; controls 36 (4), 15 to 60 years; sex: patients: 50% male; controls 55% male; no patients with existing heart disease (excluded); TLoC history: at least 1 episode of unexplained syncope in last 6 months  
Comorbidities: not stated. Other details: see below  
Other study comments: 44 patients with syncope + 20 healthy age and gender-matched controls (no syncope, presyncope or history of hypertension, cardiovascular, renal, respiratory, hepatic or metabolic disease

**Diagnostic tests**  
Index test: overnight fast; between 8 and 11am; supine 30 minutes; 60 degrees for 45 minutes; time: maximum duration 75 minutes (n=64)  
Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope

**Study**  
Micieli 1999  
*case control study; study held in Italy.*  
Setting: Department of neurology.  
Funding: not stated

**Participant**  
TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.  
Syncope of unknown aetiology after neurological and cardiological evaluation, blood tests, 12 lead ECG, Holter, psychological evaluation  
Definition of TLoC: transient loss of consciousness due to inadequate cerebral blood flow, with inability to maintain postural tone and spontaneous recovery; not seizure, vertigo, dizziness, shock, coma or other altered consciousness.  
Inclusion criteria: recent syncope: 1 or more episodes in last 3 months; in age range 18 to 60 years.  
Exclusion criteria: medical/neurological disease liable to alter BP control, cardiac disease, hypertension, migraine, intolerance to bromocriptine, inability or refusal to consent.  
Patient characteristics: age: mean age 33 years; range 18 to 59 years for patients and 20 to 55 years for controls; sex: 56% female; no patients with existing heart disease (excluded); TLoC history: mean of 3 episodes in last 6 months  
Comorbidities: not stated. Other study comments: 23 patients and 23 controls (no syncope or presyncope) matched by age (+/- 5 years) and gender

**Diagnostic tests**  
Index test: fasting; 9am; 10 minutes supine; 10 minutes 60 degrees; 10 minutes supine; performed in abeline condition and 60, 120, 180 and 240 minutes after bromocriptine 2.5mg orally; time: maximum duration 270 minutes (n=46)  
Reference standard: patients versus controls for Target Condition/Outcome: vasodepression by dopamine in neurally mediated syncope

**Study**  
Mittal 2004  
*case control study; study held in Italy.*  
Setting: Department of neurology.  
Funding: not stated

**Participant**  
TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.  
Definition of TLoC: transient loss of consciousness due to inadequate cerebral blood flow, with inability to maintain postural tone and spontaneous recovery; not seizure, vertigo, dizziness, shock, coma or other altered consciousness.  
Inclusion criteria: recent syncope: 1 or more episodes in last 3 months; in age range 18 to 60 years.  
Exclusion criteria: medical/neurological disease liable to alter BP control, cardiac disease, hypertension, migraine, intolerance to bromocriptine, inability or refusal to consent.  
Patient characteristics: age: mean age 33 years; range 18 to 59 years for patients and 20 to 55 years for controls; sex: 56% female; no patients with existing heart disease (excluded); TLoC history: mean of 3 episodes in last 6 months  
Comorbidities: not stated. Other study comments: 23 patients and 23 controls (no syncope or presyncope) matched by age (+/- 5 years) and gender

**Diagnostic tests**  
Index test: fasting; between 8 and 10am;
case control study;
study held in USA.
Setting: Cardiology.
Funding: National Institutes of Health, Rosenfeld Foundation, Michael Wolk Foundation, American Heart Association, Maurice and Corinne Greenberg Arrhythmia Research Grant, Raymond and Beverly Sackler Foundation, New York Cardiology Associates

lead ECG normal. Prior tests: All patients had at least 1 prior test. unexplained syncope after appropriate medical/neurological evaluation Definition of TLoC: syncope: transient loss of consciousness.
Inclusion criteria: unexplained syncope.
Exclusion criteria: presyncope only; on beta-blockers or SSRIs, pacemaker, implantable defibrillator, asthma, orthostatic intolerance or hypotension.
Patient characteristics: age: patients: mean age 54 (19) years; controls: 30 (10) years; sex: patients: 60% female; controls: 70% male; some patients with existing heart disease (14% had ECG abnormalities); TLoC history: 71% of patients had 3 or more episodes; 14% 2 and 15% 1 episode (not stated over what time period)
Comorbidities: not stated. Other details: ECG abnormalities: 6% sinus bradycardia; 1st degree AV delay 2%; left ventricular hypertrophy 4%
Other study comments: 129 patients + 30 controls (no syncope, structural heart disease, asthma, medication)

Morillo 1995
case control study;
study held in Canada.
Setting: department of medicine.
Funding: Heart and Stroke Foundation of Ontario, Heart and Stroke Foundation of Canada

TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. recurrent unexplained syncope after 12 lead ECG, 24 hour monitoring, echo (some patients had EPS)
Definition of TLoC: not defined.
Inclusion criteria: 2 or more undiagnosed syncopal episodes.
Exclusion criteria: not stated.
Patient characteristics: age: patients: mean age 40 (18) years; controls: 39 (16) years; sex: patients: 53% female; controls: 53% female; some patients with existing heart disease (8% structural heart disease); TLoC history: mean 12 (8) syncopal episodes (not stated over what time period)
Comorbidities: not stated.
Other study comments: 120 patients + 30 healthy controls (no syncope or presyncope)

Mussi 2001
case control study;
study held in Italy.
Setting: geriatrics and gerontology.
Funding: MURST grants

TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. unexplained syncope after neurological examination, routine laboratory tests, 12 lead ECG, 24 hour ECG and BP monitoring, carotid sinus massage (and echo, exercise test, coronary angiography, CT CNS, EEG, Doppler, EPS when necessary)
Definition of TLoC: transient and sudden loss of consciousness with an inability to maintain postural tone with spontaneous recovery; presyncope: symptoms of imminent syncope and difficulty maintaining postural tone. Inclusion criteria: elderly patients with at least 1 episode of syncope of unknown origin.
Exclusion criteria: not stated.
Patient characteristics: age: patients: mean age 71.6 (5.1) years, range 57 to 89 years; controls: 71.2 (5.5), range55 to 88 years; sex: 50% male; some patients with existing heart disease (5% had ischaemic heart disease); TLoC history: median 1 episode; range 1 to 12 episodes (not stated over what time period)
Comorbidities: 32% had hypertension; 12% diabetes. Other details: see below
Other study comments: 128 patients + 101 controls matched for age and gender (no cardiovascular drugs)

Study
Oraii 1999
RCT; study held in Iran.
Setting: Cardiology.

Participant

TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. unexplained syncope after BP, carotid sinus massage, routine laboratory tests, 12lead ECG, echo, 24 hour Holter (and exercise test, EPS, angiography or CT if supine 3 minutes; 60 degrees and immediately IV adenosine 150microg/kg for 3 minutes, if negative, supine 5 minutes; retitled with adenosine incremented by 75microg/kg; process repeated until adenosine effect observed; time: maximum duration not stated (n=159)
Reference standard: patients versus controls for Target Condition/Outcome: neurally mediated syncope

Diagnostic tests
Index test: HUT-GTN: overnight fast; between 8 and 10am; supine 10 minutes; Westminster protocol: 60 degrees for 45 minutes; if negative, sublingual nitroglycerin 0.4mg and further 20 minutes; time: maximum duration 75 minutes (n=229)
Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope

Oribe 1997
case control study;
study held in USA.
Setting: Cardiology.
Funding: not stated

TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. syncope of unknown cause despite 12 lead ECG; many patients also had 24 hour Holter and EEG; 38 had EPS
Definition of TLoC: syncope: transient alteration of consciousness followed by complete recovery without neurological deficits.
Inclusion criteria: referred for unexplained syncope; at least 1 episode in last 3 months.
Exclusion criteria: beta blockers, anticholinergics, fludrocortisone.
Patient characteristics: age: patients: mean age 51 years (95% CI 48 to 55); controls: 54 (48 to 55); sex: patients: 57% female; controls 55% female;
Unclear/not stated with existing heart disease (not stated);
TLoC history: mean 3.6 episodes, range 1 to 30 in all (not stated over what time period); at least 1 episode in 3 months prior to study
Comorbidities: not stated. Other details: see below
Other study comments: 201 patients + 102 age and gender matched controls (no syncope or synopal symptoms)

Oribe 1997
case control study;
study held in USA.
Setting: Cardiology.
Funding: not stated

TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. syncope of unknown cause despite 12 lead ECG; many patients also had 24 hour Holter and EEG; 38 had EPS
Definition of TLoC: syncope: transient alteration of consciousness followed by complete recovery without neurological deficits.
Inclusion criteria: referred for unexplained syncope; at least 1 episode in last 3 months.
Exclusion criteria: beta blockers, anticholinergics, fludrocortisone.
Patient characteristics: age: patients: mean age 51 years (95% CI 48 to 55); controls: 54 (48 to 55); sex: patients: 57% female; controls 55% female;
Unclear/not stated with existing heart disease (not stated);
TLoC history: mean 3.6 episodes, range 1 to 30 in all (not stated over what time period); at least 1 episode in 3 months prior to study
Comorbidities: not stated. Other details: see below
Other study comments: 201 patients + 102 age and gender matched controls (no syncope or synopal symptoms)

Increased by 1 microg/min at 10 minute intervals to max 4 microg/min or heart rate >150 bpm; time: maximum duration 100 minutes (n=85)
Reference standard: patients versus controls Comparator test: HUT-GTN: overnight fast; morning; supine 15 minutes; 70 degrees for 45 minutes; if negative, 400 microg sublingual GTN and 70 degrees for 20 minutes; time: maximum duration 80 minutes (n=85).
for Target Condition/Outcome: vasovagal syncope

Transient loss of consciousness: full guideline DRAFT (January 2010)
Study  
Parry 2008  
RCT; study held in UK.  
Setting: Hospital several departments. falls and syncope service, institute for ageing and health, department of geriatric medicine.  
Funding: British Heart Foundation  

Participant  
TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. unexplained syncope after 12 lead ECG, active stand to exclude orthostatic hypotension, 24 hour ECG, carotid sinus massage (in patients over 40 years), EPS, EEG, echo, 24 hour ambulatory ECG; referred to tertiary falls and syncope facility. Definition of TLoC: not defined.  
Inclusion criteria: patients with 2 or more episodes of unexplained syncope, or one episode where driving or occupation required definitive diagnosis, or disabling presyncope (5 or more episodes); aged 18 to 90 years.  
Exclusion criteria: clinically severe left ventricular outflow obstruction, critical mitral stenosis, proximal coronary artery stenoses, known severe cerebrovascular stenosis, previous adverse reaction to nitrates, inability to attend 2nd test.  
Patient characteristics: age: patients: mean age 58.0 (19.3) years; range 18 to 89 years; controls: 54.5 (19.4), 18 to 90 years; sex: patients: 60% female; controls: 54% female; some patients with existing heart disease (23% angina; 11% MI; 20% hypertension); TLoC history: 2 or more episodes of unexplained syncope, or one episode where driving or occupation required definitive diagnosis, or disabling presyncope (5 or more episodes); not stated over what time period  
Comorbidities: 2% diabetes. Other details: see below  
Other study comments: 149 patients + 83 asymptomatic controls (no history of syncope, presyncope or dizziness; similar age and gender distribution; no cardiovascular abnormalities on examination and 12 lead ECG); all had both tests 1 week apart in random order  

Diagnostic tests  
Index test: supine 10 minutes; 70 degrees for 40 minutes; time: maximum duration 50 minutes (n=232)  
Reference standard: patients versus controls Comparator test: HUT-GTN: supine 10 minutes; glyceryl trinitrate 800microg sublingually; 70 degrees for 20 minutes; time: maximum duration 30 minutes (n=232). for Target Condition/Outcome: vasovagal syncope
<table>
<thead>
<tr>
<th>Study</th>
<th>Participant</th>
<th>Diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Podoleanu 2004</td>
<td>TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. Syncope or presyncope; cause uncertain despite comprehensive medical and neurological investigation. Definition of TLoC: not defined. Inclusion criteria: at least 1 episode of syncope (98) or presyncope (13). Exclusion criteria: orthostatic hypotension, significant anaemia, endocrine abnormalities, abnormal EPS findings. Patient characteristics: age: mean age 55 (20) years, range 17 to 85 years; sex: 50% male; no patients with existing heart disease (excluded); TLoC history: mean 3 (5) episodes, range 1 to 28 episodes in 1 year. Comorbidities: not stated. Other details: see below. Other study comments: 111 patients + 23 normal controls (no history of syncope or presyncope) had test passive 1st then isoproterenol or the other order (randomised sequence).</td>
<td>Index test: HUT-GTN: overnight fast; morningsupine 15 minutes; 70 degrees for 30 min; if negative, 400μg nitroglycerin sublingually and tilt for 20 minutes; time: maximum duration 65 minutes (n=88). Reference standard: patients versus controls for Target Condition/Outcome: vaso-vagal syncope.</td>
</tr>
<tr>
<td>Prakash 2004</td>
<td>TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. Unexplained syncope (43, of which 28 recurrent) or presyncope (43) after 12-lead ECG. Definition of TLoC: sudden and transient loss of consciousness due to an acute reduction in cerebral blood flow. Inclusion criteria: unexplained syncope or presyncope. Exclusion criteria: diabetes, hypoglycaemia, orthostatic intolerance or hypotension, cardiac disease. Patient characteristics: age: patients mean 29.5 years, range 6 to 79 years; controls 30, range 8 to 55 years; sex: 52% female; no patients with existing heart disease (excluded); TLoC history: not stated. Comorbidities: not stated. Other details: see below. Other study comments: case series: 86 patients + 14 asymptomatic healthy controls.</td>
<td>Index test: 1-3 hours after light meal; between 9am and noon; supine 10 minutes; 70 degrees for 45 minutes; time: maximum duration 55 minutes (n=100). Reference standard: patients versus controls for Target Condition/Outcome: vaso-vagal syncope.</td>
</tr>
<tr>
<td>Shen 1999</td>
<td>TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. Syncope or presyncope; cause uncertain despite comprehensive medical and neurological investigation. Definition of TLoC: not defined. Inclusion criteria: at least 1 episode of syncope (98) or presyncope (13). Exclusion criteria: orthostatic hypotension, significant anaemia, endocrine abnormalities, abnormal EPS findings. Patient characteristics: age: mean age 55 (20) years, range 17 to 85 years; sex: 50% male; no patients with existing heart disease (excluded); TLoC history: mean 3 (5) episodes, range 1 to 28 episodes in 1 year. Comorbidities: not stated. Other details: see above. Other study comments: 111 patients + 23 normal controls (no history of syncope or presyncope) had test passive 1st then isoproterenol or the other order (randomised sequence).</td>
<td>Index test: fasting 6-10 hours; supine 10 minutes; 70 degrees for 45 minutes; 10-20 minutes supine; isoproterenol 0.05μg/kg/min for 5 minutes supine and 10 minutes at 70 degrees; time: maximum duration 90 minutes (n=111). Reference standard: patients versus controls for Target Condition/Outcome: vaso-vagal syncope.</td>
</tr>
</tbody>
</table>
**Study**

**Theodorakis 2000**

- **non-randomised**
- **comparative study**;
- **study held in Greece.**

**Setting:** Cardiology.

**Funding:** not stated

**Participant**

TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. Neurocardiogenic syncope; 12 lead ECG, echo (EPS, EEG, CT when needed)

**Definition:** TLoC: neurocardiogenic syncope: syncopal spells with symptoms of autonomic dysfunction (pallor, nausea, sweating).

**Inclusion criteria:** 2 or more syncopal spells with symptoms of autonomic dysfunction (pallor, nausea, sweating).

**Exclusion criteria:** structural heart disease, neurological disease.

**Patient characteristics:** age: patients: mean age 40 (17); controls: mean age 46 (15) years; sex: patients: 58% female; controls: 55% male; no patients with existing heart disease (excluded); TLoC history: mean 3.7 (2) episodes in last 6 months. Comorbidities: not stated.

**Other study comments:** 55 patients with positive history of neurocardiogenic syncope + 22 controls (nonspecific symptoms, no history of syncope or structural heart disease). All had 2 tests, 24 hours apart

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**Theodorakis 2003**

- **RCT; study held in Greece.**

**Setting:** Cardiology.

**Funding:** not stated

**Participant**

TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. Neurocardiogenic syncope; 12 lead ECG, echo (EPS, EEG, CT when needed)

**Definition:** TLoC: neurocardiogenic syncope: syncopal spells with symptoms of autonomic dysfunction (pallor, nausea, sweating).

**Inclusion criteria:** 2 or more syncopal spells with symptoms of autonomic dysfunction (pallor, nausea, sweating).

**Exclusion criteria:** structural heart disease, neurological disease.

**Patient characteristics:** age: patients: mean age 41 (16) years; controls: 46 (15); sex: patients: 52% female; controls: 56% female; no patients with existing heart disease (excluded); TLoC history: mean 3.7 (2) episodes in last 6 months. Comorbidities: not stated.

**Other study comments:** 126 patients with recurrent neurocardiogenic syncope + 54 healthy controls (nonspecific symptoms, no history of syncope or structural heart disease). All had 2 tests in random order with 24 hours between

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**Zeng 2001**

- **RCT; study held in China.**

**Setting:** Cardiology.

**Funding:** Third

**Military Medical University of PR China**

**Participant**

TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. Recurrent unexplained syncope after neurological assessment, routine laboratory tests, BP, 12 lead ECG, bilateral bedside and upright carotid sinus massage, 24 hour Holter, echo (exercise test, EPS, angiography, EEG, Doppler, CT head when indicated)

**Definition:** TLoC: syncope: sudden transient loss of consciousness with inability to maintain postural tone and spontaneous recovery; presyncope: prodrome (severe lightheadedness, severe weakness, transient graying of vision, hearing loss) and difficulty maintaining tone.

**Inclusion criteria:** recurrent unexplained syncope.

**Exclusion criteria:** not stated.

**Patient characteristics:** age: patients: mean age 36.8 (21.3) years, range 12 to 60 years; controls: 35 (16.4) years, 14 to 52 years; sex: patients: 51% female; controls 50% female; Unclear/not stated with existing heart disease (not stated); history of TLoC: TLoC history: mean around 7 episodes per year

**Comorbidities:** not stated.

**Other study comments:** randomised crossover study; 37 patients + 20 healthy volunteers (no history of syncope or presyncope; recruited from medical outpatient, matched on age, gender and weight); all had both tests with 1-14 day interval

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**Diagnostic tests**

**Index test:** basic: fasting at least 12 hours; between 8am and 1pm; supine 10 minutes; 60 degrees for 30 minutes; if negative, supine 10 minutes; IV isoproterenol 2microg/min, increased to heart rate130 beats/min, and tilt for 15 minutes; time: maximum duration 65 minutes (n=77)

**Reference standard:** patients versus controls Comparator test: clomipramine test: 10 minutes supine; clomipramine IV 5mg over 5 minutes while tilted at 60 degrees and further 15 minutes tilt; time: maximum duration 30 minutes (n=77).

for Target Condition/Outcome: vasovagal syncope

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**Index test:** fasting at least 12 hours; between 8am and 1pm; supine 10 minutes; 60 degrees for 30 minutes; if negative, supine 10 minutes; IV isoproterenol 2microg/min, increased to heart rate130 beats/min, and tilt for 15 minutes; time: maximum duration 65 minutes (n=77)

**Reference standard:** patients versus controls Comparator test: clomipramine test: 10 minutes supine; clomipramine IV 5mg over 5 minutes while tilted at 60 degrees and further 15 minutes tilt; time: maximum duration 30 minutes (n=77).

for Target Condition/Outcome: vasovagal syncope

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**Index test:** fasting at least 12 hours; between 9 and 11am; nitroglycerin 1.72microg/kg/hr for 5 minutes supine and 10 minutes at 80 degrees; repeated with increments of 0.86microg/kg/hr for 5 stages up to 5.16microg/kg/hr at stage 5; time: maximum duration 75 minutes (n=57)

**Reference standard:** patients versus controls Comparator test: HUT-GTN single stage: fasting; between 9 and 11am; nitroglycerin 3.44microg/kg/hr for 5 minutes supine; 3.44microg/kg/hr for 15 minutes at 80 degrees; time: maximum duration 20 minutes (n=57).

for Target Condition/Outcome: vasovagal syncope

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3.6.2 Proportions of cardioinhibitory response to tilt testing

We calculated the proportion of ‘cases’ with a cardioinhibitory response to tilt testing. This could be the sum of the cardioinhibitory and ‘mixed’ responses, but studies varied in their definitions of ‘mixed’. For example, the VASIS classification (see below) had a definition of ‘mixed’ that did not include a cardioinhibitory response. Other studies had different definitions of ‘mixed’. The various meanings of ‘mixed’ are given in the table.

VASIS classification:

- Type 1 (mixed): heart rate rises initially then falls, ventricular rate does not fall below 40bpm, or falls to below 40 bpm for less than 10s with or without asystole for less than 3s, BP rises then falls before heart rate falls;

- Type 2 (cardioinhibitory):
  - type 2A: heart rate rises initially then falls to a ventricular rate of less than 40bpm for longer than 10s, or asystole occurs for more than 3s; BP change as for type 1;
  - type 2B: heart rate rises initially then falls to a ventricular rate of less than 40bpm for longer than 10s, or asystole occurs for more than 3s; BP rises initially and only falls to hypotensive levels below 80mmHg systolic at or after onset of rapid and severe heart rate fall;

- Type 3 (vasodepressor): heart rate rises progressively and does not fall to more than 10% from peak at time of syncope; BP falls to cause syncope.

Where the study uses the VASIS classification, the proportion of all positive responses that were cardioinhibitory is based only on the pure cardioinhibitory figures. In other studies, in which the ‘mixed’ category could include people with both cardioinhibition and vasodepression, the proportion with a cardioinhibitory response includes those with pure cardioinhibitory plus the mixed response category.
<table>
<thead>
<tr>
<th>Study name</th>
<th>Definition of mixed CI</th>
<th>Vaso-depressor</th>
<th>Mixed CI</th>
<th>not separated out</th>
<th>n=No. of cases; % of cases with CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerts 1997</td>
<td>increase in heart rate 10% or more vs. baseline + bradycardia 60 bpm or less or decrease heart rate of 20bpm or more vs. 1 min before presyncope, or asystole 3s or more + hypotension (systolic BP 90mmHg or less or decrease 20mmHg or more vs. 1 min before presyncope</td>
<td>0</td>
<td>3 (11%)</td>
<td>25 (89%) including 7 (25%) asystole (4-15s)</td>
<td>n=32 altogether; 28 positive 7 definitely had asystole (22% of cases)</td>
</tr>
<tr>
<td>Aerts 1999</td>
<td>decrease heart rate of 20bpm or more and decrease of systolic BP 20mmHg or more</td>
<td>4 (21%) all asystole (8-41s)</td>
<td>4 (21%)</td>
<td>11 (58%)</td>
<td>n=20 : 19 positive 4 CI (20%)</td>
</tr>
<tr>
<td>Aerts 2005</td>
<td>decrease heart rate of 20bpm or more and decrease of systolic BP 20mmHg or more</td>
<td>3 (8%) all asystole (7-20s)</td>
<td>8 (22%)</td>
<td>26 (70%)</td>
<td>n=43 ; 37 positive 3 CI (7%)</td>
</tr>
<tr>
<td>Aerts 2005b</td>
<td>decrease heart rate of 20bpm or more and decrease of systolic BP 20mmHg or more</td>
<td>3 (10%) all asystole (4-28s)</td>
<td>2 (6%)</td>
<td>26 (84%)</td>
<td>n=38; 31 positive 3 CI (8%)</td>
</tr>
<tr>
<td>Almquist 1989</td>
<td>Profound bradycardia &amp; hypotension</td>
<td></td>
<td>15 patients positive, all mixed response</td>
<td></td>
<td>n=24; 15 positives no CI / asystole (0%)</td>
</tr>
<tr>
<td>Aslan 2002</td>
<td>VASIS</td>
<td>2 (25%)</td>
<td>2 (25%)</td>
<td>4 (50%)</td>
<td>n=43; 8 positives 2 CI (5%)</td>
</tr>
<tr>
<td>Athanas 2003</td>
<td>Hypotension and bradycardia</td>
<td></td>
<td>6 (100%)</td>
<td></td>
<td>n=13 none CI/asystole</td>
</tr>
<tr>
<td>Bartoletti 1999</td>
<td>VASIS</td>
<td>conventional: 8 (19%) accelerated: 4 (14%)</td>
<td>conventional: 4 (9%) accelerated: 0</td>
<td>conventional: 31 (72%) accelerated: 25 (86%)</td>
<td>n=84 conventional: 8/84 CI (10%) accelerated: 4/84 (5%)</td>
</tr>
<tr>
<td>Benchimol 2008</td>
<td>not defined</td>
<td></td>
<td></td>
<td>169/259 tests positive</td>
<td>n=259</td>
</tr>
<tr>
<td>Study name</td>
<td>Definition of mixed</td>
<td>CI</td>
<td>Vasodepressor</td>
<td>Mixed</td>
<td>not separated out</td>
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<tr>
<td>Brignole 1991</td>
<td>symptoms plus bradycardia (asystole 3s or more or heart rate 45bpm or less during passive test, or rate 60bpm or less with isoproterenol) and hypotension (fall in systolic BP to 80mmHg or less)</td>
<td></td>
<td></td>
<td>passive: 32/100 positive (including 7 asystole); isoproterenol: 11 additional patients positive (no asystole)</td>
<td>n=100; 43 positives CI or mixed in 17 with passive test + 6 with isoproterenol (23 overall out of; 23%)</td>
</tr>
<tr>
<td>Brignole 2000</td>
<td>mixed included hypotension without pause over 3s</td>
<td>92 (28%)</td>
<td>74 (72%) vasodepressor or mixed</td>
<td>n=175; 103 positives 29 CI (17%)</td>
<td></td>
</tr>
<tr>
<td>Brooks 1993</td>
<td>only vasodepressor response (hypotension and relative bradycardia) counted as positive test</td>
<td>30 (100%)</td>
<td></td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Carlioz 1997</td>
<td>hypotension and bradycardia, or asystole 3s or more</td>
<td>passive: 4 (40%) isoproterenol: not stated</td>
<td>passive: 1 (10%) isoproterenol: not stated</td>
<td>passive: 5 (50%) isoproterenol: 19/24 positives (79%)</td>
<td>n=48; 10 positive passive: CI 4 (8%); with mixed (might not have had asystole) 9 (19%) isoproterenol: NS</td>
</tr>
<tr>
<td>Del Rosso 1998</td>
<td>VASIS</td>
<td>passive: 11 (50%) GTN: 38 (32%)</td>
<td>passive: 1 (5%) GTN: 11 (9%)</td>
<td>passive: 10 (45%) GTN: 70 (59%)</td>
<td>n=202; 22 positive responses Passive: CI 11(5%) of whom 9 had asystole (4%); n=179 had GTN test CI 49 overall (24%) of whom 38 overall had asystole (19%) Asystole 3-38s</td>
</tr>
<tr>
<td>Del Rosso 2002</td>
<td>VASIS</td>
<td>64 (37%)</td>
<td>18 (10%)</td>
<td>92 (53%)</td>
<td>n=324; 174 positives CI 64 (20%) of whom 49 had asystole (15%)</td>
</tr>
<tr>
<td>Doi 2002</td>
<td>Sutton; mixed = bradycardia &lt;40bpm and marked hypotension (systolic BP below 80mmHg)</td>
<td>1 (5%)</td>
<td>7 (35%)</td>
<td>12 (60%)</td>
<td>n=26; 20 positive; exercise-unrelated syncope group CI 1 (4%)</td>
</tr>
<tr>
<td>Study name</td>
<td>Definition of mixed</td>
<td>CI</td>
<td>Vaso-depressor</td>
<td>Mixed not separated out</td>
<td>n=No. of cases; % of cases with CI</td>
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<td>-----------------------------------</td>
</tr>
<tr>
<td>Fitzpatrick 1991</td>
<td>Category not defined (positive test = “vasovagal syncope”)</td>
<td>40 (78%) bradycardia below 60bpm</td>
<td>13 (22%) profound hypotension but rate did not fall below 60bpm</td>
<td>0</td>
<td>n=71; 53 positives CI 40 (56%)</td>
</tr>
<tr>
<td>Fouad 1993</td>
<td>Hypotension + bradycardia</td>
<td>19 (76%); heart rate below 50bpm in 5 and 50-65bpm in 7; complete asystole not observed in any other subjects</td>
<td>6 (24%); BP reduced significantly</td>
<td></td>
<td>n=44; 25 positives CI 19 (43%)</td>
</tr>
<tr>
<td>Gielerak 2002</td>
<td>VASIS</td>
<td>1 (5%)</td>
<td>10 (43%)</td>
<td>12 (52%)</td>
<td>n=40; 23 positives CI 1 (3%)</td>
</tr>
<tr>
<td>Graham 2001</td>
<td>not defined</td>
<td>passive: 31/88 positive isoprenaline: 10/48 positive GTN: 23/48 positive</td>
<td></td>
<td>n=88 had passive tilt</td>
<td></td>
</tr>
<tr>
<td>Grubb 1991b</td>
<td>bradycardia and hypotension</td>
<td>passive: 6/25 positive isoproterenol: 9/19 (passive negative)</td>
<td></td>
<td>n=25 had passive tilt</td>
<td></td>
</tr>
<tr>
<td>Grubb 1992b</td>
<td>bradycardia (abrupt fall in heart rate) and hypotension (abrupt fall in BP)</td>
<td>isoproterenol: 0</td>
<td>isoproterenol: 3 (43%)</td>
<td>n=25 had passive tilt CI not stated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>isoproterenol: 4 (57%)</td>
<td></td>
<td>n=16 passive negative had isoproterenol tilt CI/mixed 3 (19%)</td>
<td></td>
</tr>
<tr>
<td>Study name</td>
<td>Definition of mixed</td>
<td>CI</td>
<td>Vaso-depressor</td>
<td>Mixed</td>
<td>not separated out</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------</td>
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<td>-------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Hermosillo 2000</td>
<td>passive defined as positive if hypotension or bradycardia or both; with drugs, positive only if both hypotension and bradycardia (i.e. all mixed)</td>
<td>isoproterenol: 0 ISDN: 0</td>
<td>isoproterenol: 0 ISDN: 0</td>
<td>isoproterenol: 36 (100%) ISDN: 49 (100%)</td>
<td>passive: 50/120 positive</td>
</tr>
<tr>
<td>Lagi 1992</td>
<td>not defined</td>
<td>asystole + symptoms 2 (6%)</td>
<td></td>
<td></td>
<td>35/72 positive</td>
</tr>
<tr>
<td>Lazzeri 2000</td>
<td>syncope or presyncope plus systolic BP below 80mmHg and heart rate below 40bpm</td>
<td>12 (52%)</td>
<td>11 (48%)</td>
<td>0</td>
<td>n=44; 23 positives; CI 12 (27%)</td>
</tr>
<tr>
<td>Micieli 1999</td>
<td>positive test defined as hypotension with or without bradycardia (i.e. not CI)</td>
<td>0 by definition</td>
<td>9 (50%) hypotension only</td>
<td>9 (50%) bradycardia plus hypotension</td>
<td>n=23; 18 positives; mixed 9 (39%) but not necessarily asystole (not mentioned)</td>
</tr>
<tr>
<td>Mittal 2004</td>
<td>positive response defined as bradycardia and hypotension</td>
<td></td>
<td></td>
<td></td>
<td>23/129 positive</td>
</tr>
<tr>
<td>Morillo 1995</td>
<td>hypotension, systolic BP 70mmHg or below and heart rate 40bpm or below</td>
<td>25 (35%) of whom 5 had asystole over 3s (4-45s)</td>
<td>17 (23%)</td>
<td>31 (42%)</td>
<td>passive: 30/120 positive; isoproterenol of further 43 patients</td>
</tr>
<tr>
<td>Mussi 2001</td>
<td>VASIS</td>
<td>passive: 3 (12%) GTN: 6 (11%)</td>
<td>passive: 13 (50%) GTN: 39 (74%)</td>
<td>passive: 10 (38%) GTN: 8 (15%)</td>
<td>passive: 26/128 positive; GTN: further 53 positive</td>
</tr>
<tr>
<td>Study name</td>
<td>Definition of mixed</td>
<td>CI</td>
<td>Vaso-depressor</td>
<td>Mixed</td>
<td>not separated out</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------</td>
<td>----</td>
<td>----------------</td>
<td>--------</td>
<td>------------------</td>
</tr>
<tr>
<td>Orai 1999</td>
<td>VASIS</td>
<td>passive: 6 (30%) isoprenaline: 4 (15%) GTN: 9 (36%)</td>
<td>passive: 1 (5%) isoprenaline: 2 (8%) GTN: 3 (12%)</td>
<td>passive: 13 (65%) isoprenaline: 20 (77%) GTN: 13 (52%)</td>
<td>74/201 positive 100%</td>
</tr>
<tr>
<td>Oribe 1997</td>
<td>positive test defined as hypotension plus bradycardia plus symptoms (i.e. all mixed type)</td>
<td>passive: 0 GTN: 8 (15%)</td>
<td>passive: 12 (71%) GTN: 28 (52%)</td>
<td>passive: 5 (29%) GTN: 18 (33%)</td>
<td>n=201 100% mixed type (by definition); asystole not stated</td>
</tr>
<tr>
<td>Parry 2008</td>
<td>VASIS</td>
<td>overall 8 (14%)</td>
<td>overall 22 (38%)</td>
<td>overall 28 (48%)</td>
<td>passive positive in 25; GTN positive in 33</td>
</tr>
<tr>
<td>Podolea nu 2004</td>
<td>heart rate rises initially then falls, ventricular rate does not fall below 40 bpm, or falls to below 40 bpm for less than 10s with or without asystole for less than 3s, BP rises then falls before heart rate falls</td>
<td>overall 8 (14%)</td>
<td>overall 22 (38%)</td>
<td>overall 28 (48%)</td>
<td>passive positive in 25; GTN positive in 33</td>
</tr>
<tr>
<td>Prakash 2004</td>
<td>hypotension and bradycardia and symptoms</td>
<td>6 CI with asystole over 3s (26%)</td>
<td>7 (30%)</td>
<td>10 (44%)</td>
<td>23/86 positive</td>
</tr>
<tr>
<td>Shen 1999</td>
<td>syncope or presyncope and bradycardia (decrease in heart rate at least 20% from baseline) and hypotension decrease in systolic BP 30mmHg or more</td>
<td>passive: 35/111; isoproterenol: 62/111 positive</td>
<td>n=111 CI not stated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study name</td>
<td>Definition of mixed</td>
<td>CI</td>
<td>Vaso-depressor</td>
<td>Mixed</td>
<td>not separated out</td>
</tr>
<tr>
<td>------------</td>
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<td>---------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Theodorakis 2000</td>
<td>Hypotension followed by bradycardia</td>
<td>passive/ isoproterenol: 8 (28%) clomipramine: 9 (20%)</td>
<td>passive/ isoproterenol: 8 (28%) clomipramine: 13 (30%)</td>
<td>passive/ isoproterenol: 13 (45%) clomipramine: 22 (50%)</td>
<td>passive: 19 positive; isoproterenol: 10 further positive; clomipramine 44 positive</td>
</tr>
<tr>
<td>Theodorakis 2003</td>
<td>Hypotension followed by bradycardia</td>
<td>isoproterenol: 14 (27%) clomipramine: 21 (20%)</td>
<td>isoproterenol: 12 (23%) clomipramine: 41 (39%)</td>
<td>isoproterenol: 26 (50%) clomipramine: 43 (41%)</td>
<td>passive: 34 positive; isoproterenol: 18 further positive; clomipramine 105 positive</td>
</tr>
<tr>
<td>Zeng 2001</td>
<td>Hypotension (decrease in systolic BP over 50%) and bradycardia (decrease in heart rate over 30%)</td>
<td>convention al GTN: 23/37 single stage GTN: 24/37 positive</td>
<td>convention al GTN: 23/37 single stage GTN: 24/37 positive</td>
<td>convention al GTN: 23/37 single stage GTN: 24/37 positive</td>
<td>n=37 had single stage GTN test and conventional multistage test in random order 1-14 days apart</td>
</tr>
</tbody>
</table>
### 3.7 Carotid sinus massage for NMS review

#### Study

<table>
<thead>
<tr>
<th>Description</th>
<th>TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal.</th>
<th>Prior tests: All patients had at least 1 prior test.</th>
<th>Diagnostic tests: Index test: carotid sinus massage at 60 degrees of tilt; time: 5 seconds (n=259)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benckimol 2008</td>
<td>Definition of TLoC: non-convulsive faints or unexplained falls (drop attacks).</td>
<td>EC and echo normal or showed no association with symptoms</td>
<td>Reference standard: patients versus controls</td>
</tr>
<tr>
<td>Case control study; study held in Brazil.</td>
<td>Inclusion criteria: patients referred for investigation of non-convulsive faints or unexplained falls of which 1st episode several months before.</td>
<td>Definition of TLoC: not defined.</td>
<td>Comparator test: carotid sinus massage at 60 degrees of tilt in controls; time: 5 seconds (n=55), for Target Condition/Outcome: CSM induces asystole for more than 3s (cardioinhibitory type) or systolic pressure decrease above 50mmHg (vasodepressor type).</td>
</tr>
<tr>
<td>Setting: unclear.</td>
<td>Exclusion criteria: carotid murmur, CVA or acute MI in previous 6 months or history of severe ventricular arrhythmia.</td>
<td>Exclusion criteria: postural hypotension, conversion reaction, seizure, TIA, subclavian steal, drug-induced syncope, aortic stenosis, pulmonary HT, hypertrophic cardiomyopathy, dysrhythmia.</td>
<td></td>
</tr>
<tr>
<td>University hospital, department not stated.</td>
<td>Patient characteristics: age: mean 50 (24) years (range 10-96 years); sex: 66% female; Unclear/not stated with existing heart disease (not stated); TLoC history: 1st episode mean of 53 (100) months before</td>
<td>Patient characteristics: age: patients: mean age 60 (18); controls 60 (17); sex: patients: 54% men; controls 57% male; some patients with existing heart disease (39% had structural heart disease); TLoC history: not stated</td>
<td></td>
</tr>
<tr>
<td>Funding: none</td>
<td>Comorbidities: not stated.</td>
<td>Comorbidities: not stated.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other study comments: 55 “controls” no history of seizures, faints or falls; mean age 57 (21) years, range 16-88 years. 2nd part: CSM at 60 degrees patients versus controls diagnostic test accuracy</td>
<td>Other study comments: 100 patients + 25 healthy controls without syncope or presyncope matched on age and gender</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description</th>
<th>TLoC population: unclear/not stated.</th>
<th>Prior tests: All patients had at least 1 prior test; syncope of uncertain origin despite neurological examination, laboratory tests, 12 lead ECG, 24 hour monitoring, chest x-ray, echo (+ where indicated stress test, EEG, Doppler, CT, cardiac catheter, EP, arteriography)</th>
<th>Diagnostic tests: Index test: CSM left and right sides supine and standing for 10 seconds; time: 10 seconds (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brignone 1991</td>
<td>Definition of TLoC: not defined.</td>
<td>Inclusion criteria: syncope of uncertain origin.</td>
<td>Reference standard: patients versus controls</td>
</tr>
<tr>
<td>Case control study; study held in Italy.</td>
<td>Exclusion criteria: postural hypotension, conversion reaction, seizure, TIA, subclavian steal, drug-induced syncope, aortic stenosis, pulmonary HT, hypertrophic cardiomyopathy, dysrhythmia.</td>
<td>Exclusion criteria: postural hypotension, conversion reaction, seizure, TIA, subclavian steal, drug-induced syncope, aortic stenosis, pulmonary HT, hypertrophic cardiomyopathy, dysrhythmia.</td>
<td>for Target Condition/Outcome: vasovagal syncope</td>
</tr>
<tr>
<td>Setting: Cardiology. referred from ER or inpatient service or ambulatory program.</td>
<td>Patient characteristics: age: patients: mean age 60 (18); controls 60 (17); sex: patients: 54% men; controls 57% male; some patients with existing heart disease (39% had structural heart disease); TLoC history: not stated</td>
<td>Patient characteristics: age: patients: mean age 60 (18); controls 60 (17); sex: patients: 54% men; controls 57% male; some patients with existing heart disease (39% had structural heart disease); TLoC history: not stated</td>
<td></td>
</tr>
<tr>
<td>Funding: not stated</td>
<td>Comorbidities: not stated.</td>
<td>Comorbidities: not stated.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other study comments: 100 patients + 25 healthy controls without syncope or presyncope matched on age and gender</td>
<td>Other study comments: 100 patients + 25 healthy controls without syncope or presyncope matched on age and gender</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description</th>
<th>TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal.</th>
<th>Prior tests: Unclear or Not stated.</th>
<th>Diagnostic tests: Index test: carotid sinus massage supine and at 70 degree tilt; both sinuses massaged for 10 seconds with interval of 2 minutes; time: maximum 3 minutes (n=494)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freitas 2004</td>
<td>Definition of TLoC: not defined.</td>
<td>Patients with unexplained syncope, presyncope or falls aged over 42 years</td>
<td>Reference standard: patients versus controls</td>
</tr>
<tr>
<td>Case control study; study held in Portugal.</td>
<td>Inclusion criteria: 380 patients with unexplained syncope, presyncope or falls aged over 42 years plus 108 controls (healthy) aged over 40.</td>
<td>Exclusion criteria: age under 42 years; contraindication to CSM (e.g. carotid bruises or carotid ctenosis of over 70% from previous echo Doppler or history of stroke or TIA).</td>
<td>for Target Condition/Outcome: carotid sinus hypersensitivity</td>
</tr>
<tr>
<td>Setting: Cardiology. Centre for study of autonomic function.</td>
<td>Exclusion criteria: age under 42 years; contraindication to CSM (e.g. carotid bruises or carotid ctenosis of over 70% from previous echo Doppler or history of stroke or TIA).</td>
<td>Patient characteristics: age: not stated; sex: not stated; Unclear/not stated with existing heart disease (not stated); history of TLoC: not stated</td>
<td></td>
</tr>
<tr>
<td>Funding: not stated</td>
<td>Comorbidities: not stated.</td>
<td>Comorbidities: not stated.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other details: patients with unexplained syncope, presyncope or falls aged over 42 years</td>
<td>Other details: patients with unexplained syncope, presyncope or falls aged over 42 years</td>
<td></td>
</tr>
</tbody>
</table>
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3.8 **Comparison of different tests**

3.8.1 **Implantable event recorder versus usual care**

<table>
<thead>
<tr>
<th>Study</th>
<th>Participant</th>
<th>Diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farwell 2006</td>
<td>TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. Basic workup plus Holter/tilt test as indicated. Definition of TLoC: not defined apart from &quot;syncope&quot;. Inclusion criteria: 16 yr or over; acute syncope; 2 or more unexplained syncopes in last 12 months; no pacing indication after basic clinical workup (tilt test &amp; Holter if clinically indicated). Exclusion criteria: see above. Patient characteristics: age: median 74 yr (IQR 61 to 81 yr); sex: 54% female; some patients with existing heart disease (around 50% had prior IHD); TLoC history: mean 1.5 TLOC per year. Comorbidities: not stated. Other details: adults presenting with syncope. Other study comments: Eastbourne Syncope Assessment Study (EsSyAS)</td>
<td>Index test: Reveal Plus set to record 3 patient activations + 5 automatic activations; time: median 17 months (IQR 9-23 months); maximum 34 months (n=103). Comparator test: conventional investigation and management; time: median 17 months (n=98). for Target Condition/Outcome: set to record ventricular pasuses more than 3 seconds; ventricular rate less than 40 bpm or more than 165 bpm; events recorded were bradycardia, SVT or VT (no further details and not prespecified)</td>
</tr>
<tr>
<td>Krahn 2001</td>
<td>TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. Had had clinical assessment, postural BP, 24 hour ambulatory monitoring or telemetry, echocardiogram; could have had other neurological or cardiovascular testing, tilt test or loop recorder. Definition of TLoC: unexplained syncope not further defined. Inclusion criteria: referred to arrhythmia clinic; those with typical history for neurally mediated syncope excluded. Exclusion criteria: Left ventricular ejection fraction below 35%; unlikely to survive 1 year; unable to provide follow up or consent; typical presentation of neurally mediated syncope (upright; prodrome including warmth and diaphoresis; postepisode fatigue). Patient characteristics: age: mean age 66 yr (14 yr); sex: 55% male; some patients with existing heart disease (38% had heart disease); TLoC history: recurrent in 53 patients; 7 had single episode judged to warrant cardiovascular testing. Comorbidities: not stated. Other details: referred to arrhythmia clinic; those with typical history for neurally mediated syncope excluded. Other study comments: If undiagnosed after 1st strategy, pts offered crossover to other strategy: diagnosis in 1/6 (17%) conventional and 8/13 (62%) ILR (p=0.069). Conventional gp only had 2-4 weeks ELR &amp; if tilt &amp; EP negative, immediately offered ILR (diff follow up times)</td>
<td>Index test: Reveal ILR; patient activated; time: follow up at 1 week, 1, 2, 3, 6, 9 and 12 months and after event (aimed for full 1 year monitoring) (n=30). Comparator test: conventional plus external recorder plus tilt and electrophysiological testing; time: ELR 2-4 weeks; pts offered ILR immediately if tilt &amp; EP negative (n=30). for Target Condition/Outcome: symptom/rhythm correlation (not prespecified): found bradycardia, tachycardia</td>
</tr>
</tbody>
</table>
3.8.2 External event recorder versus 24-hour Holter monitoring

**Study**
Krahn 2000
non-randomised comparative study; study held in Canada.

**Setting**
Cardiology.

**Funding**
Ontario Heart and Stroke Foundation

**Participant**
TLoC population: unclear/not stated. Prior tests: Unclear or Not stated. Not stated: retrospective study; no evidence of prior tests
Definition of TLoC: syncope or presyncope (drop attacks, L, fainting or weak spells, blackouts, lightheadedness, dizziness).

**Other study comments**
Patient characteristics: age: 59.8 (21) years for Holter and 52.2 (19.9) for ILR; sex: 53% male; Unclear/not stated with existing heart disease (not stated); TLoC history: not stated
Comorbidities: not stated.

**Diagnostic tests**
Index test: loop recorder (King of Hearts, Instromedix); patient activated; transmission of recordings via telephone; time: median 30 days; range 5-96 days (retrospective - no further details) (n=81)
Comparator test: Holter 24 or 48 hours and symptom diary; time: 24 or 48 hours (n=232), for Target Condition/Outcome: prespecified: sinus pause over 3s; complete heart block; Mobitz type II 2nd degree block; AF with slow ventricular response RR above 3s; sinus brady below 40bpm; SVT over190bpm; VT over 10s; asymptomatic abnormal rhythms; asymptomatic and no arrhythmia

---

3.8.3 External event recorder versus 48-hour Holter monitoring

**Study**
Rockx 2005
RCT; study held in Canada.

**Setting**
Cardiology.

**Funding**
Physician Services Inc, Toronto

**Participant**
TLoC population: patients with a history of recurrent syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.
referred for ambulatory monitoring; 41 had had prior Holter; 31 echo; 13 tilt test
Definition of TLoC: patients had diagnosis of syncope, presyncope or both.
Inclusion criteria: patients had diagnosis of syncope, presyncope or both, referred for ambulatory monitoring.
Exclusion criteria: none.
Patient characteristics: age: mean age 56 (20) years; sex: 44% male; some patients with existing heart disease (33% had heart disease);
TLoC history: median 1 prior episode (mean 50+/12); symptoms for a median of 6.5 months (mean 41 +/-94 months)
Comorbidities: not stated. Other details: see below

**Other study comments**
Same study as Sivakumaran 2003 (number 821) - additional data added in here from that paper (otherwise patients counted twice)

**Diagnostic tests**
Index test: external event recorder; time: worn until 2 clinical episodes occurred or 1 month elapsed (n=49)
Comparator test: Holter monitoring 48 hours; time: 48 hours (n=51).
for Target Condition/Outcome: prespecified: sinus pause over 3s; complete heart block; Mobitz type II 2nd degree block; AF with slow ventricular response (RR over 3s); symptomatic sinus brady below 40bpmSVT over 10s or symptomatic; VT
3.8.4 **Exercise test versus 24-hour Holter monitoring**

<table>
<thead>
<tr>
<th><strong>Study</strong></th>
<th><strong>Participant</strong></th>
<th><strong>Diagnosis tests</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Boudoulas 1979</td>
<td>TLoC population: patients with a suspected cardiac cause. Prior tests: All</td>
<td>Index test: 24 hour ambulatory heart rate recording (Avionics Electrocardiorder</td>
</tr>
<tr>
<td>non-randomised</td>
<td>patients had at least 1 prior test.</td>
<td>Model 400); automatic recording of all ECG; diary for symptoms; time: 24 hours</td>
</tr>
<tr>
<td>comparative</td>
<td>Definition of TLoC: syncope or presyncope (dizziness or lightheadedness).</td>
<td>(n=119) Comparator test: maximum multistage treadmill exercise test Bruce protocol;</td>
</tr>
<tr>
<td>study held in</td>
<td>Inclusion criteria: patients with syncope or presyncope (dizziness or</td>
<td>time: 1 day (n=119). for Target Condition/Outcome: sinus brady below 40 bpm</td>
</tr>
<tr>
<td>USA.</td>
<td>lightheadedness). Exclusion criteria: obvious cause of syncope on</td>
<td>awake; paroxysmal SVT (170 bpm); high grade AV block; frequent ventricular</td>
</tr>
<tr>
<td>Setting:</td>
<td>resting ECG. Patient characteristics: age: mean around 51 years; sex</td>
<td>premature contractions, effective rate less than 40 bpm; repetitive pairs</td>
</tr>
<tr>
<td>Cardiology</td>
<td>53% male; All patients with existing heart disease (all had cardiovascular</td>
<td>PVCs; VT</td>
</tr>
<tr>
<td>and sports</td>
<td>disorders); TLoC history: not stated</td>
<td></td>
</tr>
<tr>
<td>Science.</td>
<td>Comorbidities: not stated. Other details: patients with syncope or</td>
<td></td>
</tr>
<tr>
<td>Heart Chapter</td>
<td>or presyncope (dizziness or lightheadedness);</td>
<td></td>
</tr>
<tr>
<td>fo the</td>
<td>Other study comments: 2 tests within 1 week</td>
<td></td>
</tr>
<tr>
<td>American Heart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Association</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.8.5 **Exercise test versus tilt table**

<table>
<thead>
<tr>
<th><strong>Study</strong></th>
<th><strong>Participant</strong></th>
<th><strong>Diagnosis tests</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Colivicchi 2002</td>
<td>TLoC population: ---. Prior tests: All patients had at least 1 prior test.</td>
<td>Index test: Exercise tolerance testing; Bruce protocol; time: 1 day (n=33)</td>
</tr>
<tr>
<td>non-randomised</td>
<td>echo, 24 hour ECG, exercise test, EPS tilt test.</td>
<td>Comparator test: morning; fasting; 60 degrees for 30 minutes; if negative, 1.25mg</td>
</tr>
<tr>
<td>comparative study</td>
<td>Definition of TLoC: exercise-related syncope: sudden transient loss of</td>
<td>isosorbide dinitrate sublingually and tilt for 15 minutes; time: 1 day (n=33).</td>
</tr>
<tr>
<td>study held in Italy.</td>
<td>consciousness with inability to maintain postural tone and spontaneous</td>
<td></td>
</tr>
<tr>
<td>Setting: Syncpoe</td>
<td>recovery. Inclusion criteria: highly trained athletes with at least 2</td>
<td></td>
</tr>
<tr>
<td>Cardiology/sports</td>
<td>witnessed episodes of syncope during or immediately after exercise in last 6</td>
<td></td>
</tr>
<tr>
<td>Science.</td>
<td>months. Exclusion criteria: none.</td>
<td></td>
</tr>
<tr>
<td>Funding: not stated</td>
<td>Patient characteristics: age: mean age 21.4 (3.2) years; sex: 61% female; no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>patients with existing heart disease (no major cardiac abnormality on 12 lead</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ECG or echo); TLoC history: mean 4.66 seconds before evaluation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comorbidities: none stated. Other details: athletes referred for recurrent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>unexplained episodes of exercise-related syncope</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other study comments: case series</td>
<td></td>
</tr>
</tbody>
</table>

3.8.6 **48-hour Holter monitoring versus tilt table**

<table>
<thead>
<tr>
<th><strong>Study</strong></th>
<th><strong>Participant</strong></th>
<th><strong>Diagnosis tests</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitchet 2003</td>
<td>TLoC population: patients with suspected neurally mediated syncope but 12-</td>
<td>Index test: Holter monitor (no further details); time: 48 hours (n=118)</td>
</tr>
<tr>
<td>case series; study</td>
<td>lead ECG normal. Prior tests: Unclear or Not stated.</td>
<td>Comparator test: fasting 2 to 4 hours; supine 20 min; tilt to 60 degrees for 45</td>
</tr>
<tr>
<td>held in UK.</td>
<td>blackouts suggestive of vasovagal syncope.</td>
<td>minutes; if negative at 30 minutes, GTN 400 microg sublingually or isoproterenol</td>
</tr>
<tr>
<td>Setting: Cardiology.</td>
<td>Definition of TLoC: blackouts suggestive of vasovagal syncope.</td>
<td>IV 1 microg/min, increasing according to heart rate response to a maximum of 5</td>
</tr>
<tr>
<td>cardiologist-run</td>
<td>Inclusion criteria: blackouts suggestive of vasovagal syncope.</td>
<td>microg/min for 15 minutes; time: Maximum duration 65 minutes (n=118). for</td>
</tr>
<tr>
<td>syncope clinic or</td>
<td>Exclusion criteria: contraindications to HUT test.</td>
<td>Target Condition/Outcome: events recorded during TLOC were sinus tachy, sinus</td>
</tr>
<tr>
<td>cardiologists of 2</td>
<td>Patient characteristics: age: mean 50 (20) years, range 16-88 years; sex: 58%</td>
<td>rhythm, AF; major arrhythmia not during TLOC were nonsustained VT or SVT; AF;</td>
</tr>
<tr>
<td>tertiary referral</td>
<td>female; some patients with existing heart disease (7% had IHD and 1% impaired</td>
<td>sinus brady; minor ones were isolated vent ectopics / bigeminy / trigeminy/couples;</td>
</tr>
<tr>
<td>centres.</td>
<td>left ventricle function); TLoC history: previous syncope burden 22 (20) range</td>
<td>1st degree heart block (not prespecified)</td>
</tr>
<tr>
<td>Funding: not stated</td>
<td>1-50 episodes over 8.8 (10.9) years (range 0.02 to 60.0). Comorbidities: not</td>
<td></td>
</tr>
<tr>
<td></td>
<td>stated. Other study comments: case series</td>
<td></td>
</tr>
</tbody>
</table>
3.8.7 24-hour Holter monitoring versus electrophysiological study

**Study**
Boudoulas 1983
non-randomised
comparative study;
study held in USA.
Setting: Cardiology.
Funding: not stated

**Participant**
TLoC population: unclear/not stated. Prior tests: All patients had at least 1 prior test.
syncope or presyncope; had had EEG (some also had CT or cerebral angiography).
Definition of TLoC: not defined.
Inclusion criteria: syncope or presyncope.
Exclusion criteria: obvious cause of syncope or significant arrhythmia on resting ECG.
Patient characteristics: age: not stated; sex: not stated; some patients with existing heart disease (75% had heart disease); TLoC history: not stated. Comorbidities: not stated.
Other study comments: case series; 24 hour monitoring and electrophysiological study within 1 week

**Diagnostic tests**
Index test: 24 hour ambulatory ECG (Avionics model 660-A); whole rhythm analysed; symptom diary; time: 24 hours (n=65)
Comparator test: referenced but not described in this paper; time: 1 day (n=65).
for Target Condition/Outcome: sinus brady less than 40 bpm awake; sinoatrial exit block; paroxysmal SVT (rate over 170 bpm); VT; repetitive pairs premature ventricular beats;

3.8.8 External event recorder versus telemetry

**Study**
Rothman 2007
RCT; study held in USA.
Setting: Cardiology.
Multicentre.
Funding: Cardionet Inc

**Participant**
TLoC population: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test.
high clinical suspicion of malignant arrhythmia; syncope or presyncope; non-diagnostic 24 hour Holter or telemetry in last 45 days
Definition of TLoC: syncope or presyncope (transient dizziness, lightheadedness, unsteadiness or weak spells without LOC).
Inclusion criteria: high clinical suspicion of malignant arrhythmia; syncope or presyncope; non-diagnostic 24 hour Holter or telemetry in last 45 days.
Exclusion criteria: NYHA Class IV heart failure, MI in last 3 months, unstable angina, candidate for or recent valve surgery, sustained VT or VF, complex ectopy, below 18 years, other condition prohibiting completion of or compliance with protocol.
Patient characteristics: age: mean age 56 years; sex: around 30% male; some patients with existing heart disease (around 49% hypertension; 20% coronary artery disease; 5% MI, 5% congestive heart failure); TLoC history: not stated
Comorbidities: not stated. Other details: non-diagnostic 24 hour Holter or telemetry in last 45 days. Other study comments: RCT

**Diagnostic tests**
Index test: external loop event monitoring; patient or automatically activated; time: up to 30 days (minimum 25 days) (n=52)
Comparator test: mobile cardiac outpatient telemetry (MCOT; CardioNet): continual recording; time: up to 30 days (n=62).
for Target Condition/Outcome: prespecified: pauses; complete AV block; Mobitz type 2 2nd deg block; AF/flutter; rate over 120bpm + symptoms; over 150 - symptoms; brady below 40bpm + symptoms; sustained (over 10s)/symptomatic SVT over 120bpm; VT over 100bpm over 3 beats
### 3.9 Tilt table for NMS - cardioinhibitory response review

<table>
<thead>
<tr>
<th><strong>Study</strong></th>
<th><strong>Participant</strong></th>
<th><strong>Diagnostic tests</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gatzoulis 2003 case series; study held in Greece.</td>
<td>TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. Unexplained syncope, neurological assessment, standard laboratory tests, BP, 12 lead ECG, bedside and upright carotid sinus massage, 24 hour Holter, echo (exercise test, EPS, cardiac catheterisation, EEG, Doppler, CT or MRI brain as indicated)</td>
<td>Index test: supine 10 minutes; 80 degrees tilt for 20 minutes; if negative, isoproterenol 1 microg/min for 10 minutes; 5 minutes supine; 2mcg/min for 10 minutes; 5 minutes supine; 3mcg/min for 10 minutes; 5 minutes supine; time: maximum 75 minutes (n=123) for Target Condition/Outcome: vasovagal syncope</td>
</tr>
<tr>
<td>Setting: Cardiology.</td>
<td>Definition of TLoC: not defined. Inclusion criteria: recurrent syncope and negative initial cardiovascular and neurological evaluation. Exclusion criteria: abnormal 12 lead ECG, complex ventricular atopy, runs of supraventricular tachycardia on Holter. Patient characteristics: age: mean age 44 (18) years, range 20 to 70 years; sex: 52% male; no patients with existing heart disease (excluded); TLoC history: mean 4 (3) episodes (range 2 to 8); last episode in last 6 months Comorbidities: not stated. Other details: see below</td>
<td></td>
</tr>
<tr>
<td>Funding: not stated</td>
<td>Other study comments: case series; followed up 24 (7) months</td>
<td></td>
</tr>
</tbody>
</table>

### 3.10 Carotid sinus massage - cardioinhibitory response review

<table>
<thead>
<tr>
<th><strong>Study</strong></th>
<th><strong>Participant</strong></th>
<th><strong>Diagnostic tests</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lagi 1991 diagnostic test accuracy study; study held in Italy.</td>
<td>TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test. Patients with unexplained syncope after history, examination, 12 lead ECG, chest x-ray, blood and urine chemistry, 24 hour Holter, EEG; some time: 1 minute patients also had exercise test, echo, cardiac catheter, CT head, 24 hour EEG</td>
<td>Index test: massage to each right and left carotid sinus for about 5 seconds with the neck hyperextended, supine; (n=56)</td>
</tr>
<tr>
<td>Setting: internal medicine.</td>
<td>Definition of TLoC: not defined. Inclusion criteria: patients with unexplained syncope after history, examination 12 lead ECG, chest x-ray, blood and urine chemistry, 24 hour Holter, EEG; some patients also had exercise test, echo, cardiac catheter, CT head, 24 hour EEG. Exclusion criteria: epileptic; vasodepressive (prodrome; short LOC and complete recovery after lying down for less than 5 minutes without neurological sequelae); carotid artery disease, history of cerebrovascular accident. Patient characteristics: age: mean age 66 (12) years, range 47 to 82 years; sex: not stated; some patients with existing heart disease (75% had heart disease); TLoC history: at least 1 episode of syncope (isolated or recurrent; not stated how many patients in each category) Comorbidities: not stated. Other details: unexplained syncope; epilepsy and vasodepressor syncope excluded</td>
<td>Reference standard: no recurrent syncope after permanent pacemaker; time 11(8) months (n=37) for Target Condition/Outcome: cardioinhibitory carotid sinus hypersensitivity: variation of the cardiac rhythm or ventricular asystole over 3s with or without decrease in BP</td>
</tr>
<tr>
<td>Funding: not stated</td>
<td>Other study comments: case series; mean follow up 11 (8) months</td>
<td></td>
</tr>
</tbody>
</table>
3.11 **Ambulatory ECG - cardioinhibitory response review**

**Study**  
Brignole 2006b  
non-randomised comparative study; study held in Multinational.  
Setting: Cardiology. multinational.  
Funding: Medtronic Europe

**Participant**  
TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had at least 1 prior test.  
causes other than neurally mediated excluded (e.g. by carotid sinus massage, ECG)  
Definition of TLoC: not defined.  
Inclusion criteria: 3 or more clinically severe syncopal episodes in last 2 years without significant ECG or cardiac abnormalities (severe=high number of episodes or high risk of physical injury due to unpredictability).  
Exclusion criteria: orthostatic hypotension, carotid sinus syncope; high likelihood of cardiac syncope; non-syncopal LOC, subclavian steal.  
Patient characteristics: age: mean age 66 (14) years; sex: 55% female; some patients with existing heart disease (14% had heart disease); TLoC history: median 6 events  
Comorbidities: neurological disease 9%, diabetes 8%. Other details: see below  
Other study comments: case series; same patients as Brignole 2006 (number 780); only comparative diagnostic yield given here versus tilt table

**Diagnostic tests**  
Index test: Reveal Plus (Medtronic); patient and automatic activation; time: mean 12 (8) months; device interrogated every 3 months or after event to maximum of 24 months (n=392)  
Comparator test: no details given; time: 1 day (n=348).  
for Target Condition/Outcome: suspected neurally mediated syncope; symptom/rhythm correlation: asystolic pause over 3 seconds (AV block or sinus arrest); bradycardia; tachyarrhythmia (paroxysmal AF; paroxysmal SVT; VT)

## 4 Pacemaker reviews

### 4.1 Pacemakers for Tilt testing

**Study**  
Amirariti 2001 (SYDIT)  
RCT; study held in Italy. Funding: None stated

**Participants**  
TLoC population: selected patients with NM syncope. Prior tests: All patients had 1 prior test. Extensive prior tests to exclude other causes (12-lead ECG, exercise, echo, 24h ECG, CSM, EEG plus CT, MRI, EP as necessary) and positive tilt test. Tilt test: all positive on head up tilt; 60 deg for 30 min; then isosorbide dinitrate 1.25mg for 15 min; 56% had ISD. All patients had TLoC during tilt test.  
Patient characteristics:  
• age: Pacemaker 61(SD 13) years; drug 55 (SD 15) years; age >35 years  
• sex: 43% and 37% male;  
• cardioinhibitory NM syncope: some patients (60.2% patients had syncope in association with > asystole 3s (mean 16 (SD18) pace); 18 (11) drug))  
• comorbidities: not stated, but study excluded cardiac, neurological or metabolic disease and no-one had need for concomitant chronic pharmacological treatment.  
History of TLoC: median 7 (range 3-130) events; median 2 (1-20) and 2(1-12) in 6 months prior to enrollment  
Other study comments: Trial terminated early. Syncope witnessed in 57% of events and 29% other events associated with minor injuries (i.e.86% independently verified). Inclusion criteria: Recurrent vasovagal syncope plus age > 35 y + at least 3 syncopal spells in previous 2 years, with last episode within 6 mo of enrollment. Plus positive response to tilt test with syncope in association with relative bradycardia (< 60 bpm).  
Exclusion criteria: Syncope of cause other than vasovagal known or suspected.  
Any historical, clinical, laboratory evidence of cardiac, neurological or metabolic disease. Need for concomitant chronic pharmacological treatment for any cause.  
Definition of TLoC: Sudden transient loss of consciousness with inability to maintain postural tone and spontaneous recovery.

**Interventions**  
Intervention 1: Dual chamber pacemaker (DDD) with rate drop response pacing: (syncope + trough heart rate < 60 bpm) programmed on basis of heart rate behaviour on tilt test plus lower rate 40bps and minimum AV delay of 200 ms; time: median 390 days (IQR 360-420) time to 1st recurrence (n=46)  
Comparator: Atenolol 50 mg once per day, then titrated up to 100 mg/day within 2-3 days; time: median 135 days (IQR 15-250) time to 1st recurrence (n=47)
**Study**  
Connolly 2003 (VPS II)  
RCT; study held in Canada, Australia, US, Colombia.  
Funding: study co-funded by Medtronic Inc (pacemaker manufacturer) and lead author had honorarium from them.

**Participants**  
TLoC population: selected patients with NM syncope.  
Prior tests: Unclear or Not stated. Typical history of recurrent vasovagal syncope and positive tilt test: syncope/presyncope + heart rate x bp < 6000 mm Hg/min  
All positive on head up tilt; 60-80 deg for 15-30 min; then isoproterenol 1-5 mcg for 5-15 min (44% DDD & 56% ODO IPN). 60% DDD & 71% for ODO had TLoC during tilt test. Patient characteristics:  
• age: 50.8 (SD 17.6) years DDD and 47.8 (SD 17.7) ODO  
• sex: 27.1% men (DDD) 52% men (ODO) - significantly diff;  
• cardioinhibitory NM syncope: some patients (15% DDD and 23% ODO had <40 bpm)  
• comorbidities: diabetes mellitus (8%), cardiac disease (10%), hypertension (25%), chronic lung disease (12%)  
History of TLoC: median 15 (IQR 8-50) DDD and 20 (8-50); median 4 (3-12) DDD and 4 (2-15) events in past year; median 1 month since last event  
Other study comments: Concomitant pharmacological therapy used during follow up: beta-blockers 12% ODO, 19% DDD; fludrocortisone 10% vs 2%; SSRI 12% vs 13%. Syncope witnessed in 12/16 (75%) (DDD) and 12/22 (55%) (ODO).  
Inclusion criteria: Older than 19 years; typical history of recurrent vasovagal syncope with at least 6 episodes ever or 3 in 2 years before enrollment.  
Positive head up tilt result with heart rate < 6000 mm Hg/min  
Exclusion criteria:  
• Any other cause of syncope; patients with important valvular, coronary artery, or myocardial disease; ECG abnormality; any major noncardiovascular disease.  
Definition of TLoC: Transient loss of consciousness with prompt spontaneous recovery.

---

**interventions**  
Intervention 1: Dual chamber pacemaker (DDD) with rate drop response pacing; drop size 20 beats, drop rate 70/min and intervention rate of 100/min for 2 min; time: 6 months (n=48)  
Comparator: Dual chamber pacemaker set to sensing only (ODO); time: 6 months (n=52).

---

Connolly 1999 (VPS)  
RCT; study held in Canada and USA.  
Funding: none stated.

TLoC population: selected patients with NM syncope.  
Prior tests: All patients had 1 prior test. History of recurrent syncope and positive tilt test (syncope/presyncope + trough heart rate <60 bpm or see inclusion criteria) . Other causes of TLoC excluded (arrhythmias, carotid sinus syndrome, seizures)  
Tilt test: all positive on head up tilt; passive then isoproterenol phase; 78% pacemaker and 67% no PM had IPN. 77% in the pacemaker group and 63% in the no PM group had TLoC during tilt test; rest had presyncope  
Patient characteristics:  
• age: 43 years (SD 18)  
• sex: 30% male;  
• cardioinhibitory NM syncope: some patients (19% pacemaker & 26% no pacemaker had <40 bpm)  
• comorbidities: low incidence of diabetes mellitus (3%), hypertension on therapy (13%) & lung disease (6%). Excluded if important valvular, coronary, myocardial/conduction abnormality.  
History of TLoC: TLoC history: median 14 (IQR 8-35) PM and 35 (20-100) lifetime events; median 3 (2-12) and 6 (3-40) in previous year; mean 92 days (SD 126) and 63 (SD 130) from most recent episode to randomisation.  
Other study comments: Trial terminated early. Syncope witnessed in 50% of PM events & 32% no PM; 0% & 21% events associated with minor injuries. 7% in each group received a beta-blocker and 1/27 in the no PM group had disopyramide.  
Adjusted analysis same.  
Inclusion criteria: At least 6 lifetime syncopal spells plus positive tilt test with syncope or presyncope and with relative bradycardia (trough heart rate of <60 bpm if no isoproterenol used, <70 if up to 2 mcg/min IPN used or <80 if over 2 mcg/min used).  
Exclusion criteria: Important valvular, coronary, myocardial/conduction abnormality; previous pacemaker therapy; contraindication to insertion of pacemaker, a major chronic noncardiovascular disease.  
Definition of TLoC: Transient state of unconsciousness characterised by spontaneous recovery.
### 4.2 Pacemakers for CSM

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brigolle 1992c</td>
<td>TLoC population: selected patients with TLoC of mixed known causes. Prior tests: All patients had at least 1 prior test. &quot;severe carotid sinus syndrome&quot;; 97% had syncope; history, exam, 12 lead ECG, ECG at least 24 hours (ambulatory/ telemetry) in CCU CXR, echo, EPS 40/60 had heart disease; CSM: right and left side 10 s; supine and erect; repeated after atropine 0.02mg/kg; for 1 min. Patient characteristics: • age: mean around 70 years (10 years) • sex: 80% male; • cardioinhibitory NM syncope: All patients () • comorbidities: not stated. History of TLoC: mean around 3.3 episodes per patient; 2 in last year. Other study comments: all patients advised against drugs affecting carotid reflex (e.g. beta blockers, digitalis, antiarrhythmic drugs). Inclusion criteria: recurrent syncope/presyncope + major trauma/risk of trauma (sudden onset/activity of patient) or interfered with daily activity (frequency/intensity). CSM reproduced symptoms + asystole at least 3s; reproducible within few days. No other cause. Exclusion criteria: persistent diurnal sinus brady (&lt;50bpm); intermittent mild brady &lt;60bpm with abnormal EPS; AV block; HV interval 70ms or more. Definition of TLoC: syncope: sudden unexplained loss of consciousness.</td>
</tr>
<tr>
<td>Claesson 2007</td>
<td>TLoC population: ---. Prior tests: All patients had at least 1 prior test. syncope or presyncope and induced cardioinhibitory carotid sinus syndrome; history, exam, 12 lead ECG, orthostatic test, HUT, 24 hour ambulatory Holter. CSM consisted of firm pressure to the carotid sinus without any movement of the fingertips for 5 seconds in the supine position, first on the right then on the left if needed. Patient characteristics: • age: mean age around 75 years • sex: 42/60 male; • cardioinhibitory NM syncope: All patients () • comorbidities: 34/60 on cardiovascular drugs (beta-blockers, calcium inhibitors, nitrates). History of TLoC: at least 1 episode. Other study comments: Inclusion criteria: syncope or presyncope and induced cardioinhibitory carotid sinus syndrome. Exclusion criteria: diminished cognitive function; geographical reasons. Definition of TLoC: transient self-terminating loss of consciousness usually leading to falling; onset rapid; recovery spontaneous, complete and prompt. Presyncope: pt feels syncope is imminent; premonitory symptoms of syncope.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention 1: 18 patients received a ventricular inhibited (VVI) pacemaker, while 14 had a dual chamber (DDD) pacemaker; time: 34 months (SD 10) (n=28) Comparator: no pacemaker; 19 (68%) patients however received a pacemaker after a mean of 8.2 months (SD 10) follow up; in 15 cases this was because of TLoC recurrence; time: 36 months (SD 10) (n=28).</td>
<td></td>
</tr>
<tr>
<td>Intervention 1: 24 patients had a pacemaker operating in DDDR mode, 5 in VVIR mode and 1 in AAIR mode; time: 12 months (n=30) Comparator: no pacemaker; patients allowed to cross to pacemaker after they had had syncope or pre-syncope (1/3rd did crossover); time: 12 months (n=30).</td>
<td></td>
</tr>
</tbody>
</table>
Study Participants
Kenny 2001 TLoC population: selected patients with TLoC of mixed known causes. Prior tests: All patients had at least 1 prior test. Cohort that had non-accidental falls and were attending the ED, not necessarily had TLoC. Patients had history, examination including neurological, cardiovascular, gait and balance assessment

Interventions
Kenny 2001 Intervention 1: rate drop response dual-chamber pacemaker implant; paced if heart rate below 50bpm; diaries kept by patients (85% completion); time: 12 months (n=88)

Comparator: usual care; diaries kept by patients (92% completion); time: 12 months (n=88).

Participant characteristics:
- age: mean age 73 (10) years
- sex: 40% male
- cardioinhibitory NM syncope: All patients
- comorbidities: 26% HY; 15% stroke; 9% diabetes; 25% abnormal visual acuity; 45% abnormal gait; 79% abnormal balance

History of TLoC: TLoC history: median 2 falls (mean 9.3; range 0 to >100); 30% had LOC during CSM but 80% had amnesia for this (i.e. previous falls might have been TLOC)

Other study comments: likely to be an indirect population. CSM: supine 5 min; CSM right then left side; 5 seconds each; 1 minute interval between; if no response, tilted to 70 degrees and repeated

Inclusion criteria: patients over 50 years attending A&E with non-accidental fall, with cardioinhibitory or mixed CSH.

Exclusion criteria: cognitive impairment; medical explanation of event within 10 days of presentation; accidental fall; blindness; lived >15 miles from A&E; contraindication to CSM; drugs affecting CSM response.

Definition of TLoC: not defined. Patients had to have had a non-accidental fall, defined as coming to rest on the ground or a lower level, not explained by accidental event and not medical causes such as epilepsy, stroke, alcohol excess, Orthostatic hypotension, bradycardias and tachycardias.