APPENDIX D1 - CHARACTERISTICS OF INCLUDED STUDIES

1 Initial Assessment – included studies table

1.1 Initial symptoms for diagnosis review

Study	Participants	Diagnostic tests
Alboni 2001 prospective cohort study; study held in Italy. Setting: Syncope unit. 'Syncope unit' of the Cardiology Division of 3 hospitals; referrals from ED, inpatients and outpatients.	TLoC population: unclear/not stated. Prior tests: Unclear or Not stated. Population details: 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. Inclusion criteria: Age 18 and over; TLoC referred to Syncope unit. Patient characteristics: age: mean age 61 (SD 20) years; sex: 184/341 (54%) male; Unclear/not stated with existing heart disease (); history of TLoC: median number of episodes 2-3 (range 1-6) Comorbidities: not stated. Other details: referrals from ED, inpatients and outpatients. Cardiac syncope 23%, NM syncope 58% (comprised 10% typical vasovagal, 13% situational, 47% tilt-induced; 24% carotid sinus; 3% OHT; 3.5% adenosine sensitive); 1% neurologic/psychiatric; 18% unexplained Other study comments: Unexplained cause 60/341 (18%)	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) 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) For target condition/outcome: cardiac or NM syncope cause
Benbadis 1995 case control study; study held in USA. Setting: Hospital several departments. Selected patients admitted to epilepsy monitoring unit (prospective; 63/106 eligible) and 82 patients from syncope unit with syncope known cause (retrospective; 45 eligible). Nov 1993-Apr 1994 for both. Funding: None stated	TLoC population: selected patients with TLoC of mixed known causes. Prior tests: Unclear or Not stated. Population details: secondary care population highly selected - patients had to have stiffening (tonic) or shaking (clonic) movements or both or TLoC; monitored over 1 to 17 days; mean 7 seizures per person in epilepsy group; 1 to >50 events per patient in syncope group Definition of TLoC: Epilepsy: bilateral motor activity/TLoC/both; syncope: full loss of consciousness (not near syncope). Inclusion criteria: Epilepsy unit patients: bilateral motor phenomena/LoC/both recorded during EEG monitoring. Syncope patients with a well documented cause and at least one episode of complete LoC. Exclusion criteria: Epilepsy group: no events during monitoring. Syncope group: near syncope. Patient characteristics: age: epilepsy patients: mean 26y (3-57); non-epilepsy patients: 32y (1-57); syncope patients: 63y (23-89); sex: M:F epilepsy 13:21; NES 10:19; syncope 24:21; some patients with existing heart disease (28 syncope patients had cardiac arrhythmia); history of TLoC: not stated, but patients admitted to epilepsy unit and syncope patients had had 1to more than 50 episodes. Comorbidities: not stated. Other details: Final diagnoses were: 31% epileptic seizures (10% generalised, 21% localisation related); 25% pseudoseizures; 2% other and 42% syncope (26% arrhythmic; 6% vasovagal; 10% OHT) Other study comments: Epilepsy unit patients divided into 34 with epilepsy and 29 with non-epileptic seizures. Both groups included children.	Index test: tongue biting and lateral tongue biting signs and symptoms; epilepsy patients examined for signs of tongue biting. Syncope patients asked if they had ever sustained injury from biting and if so they were examined for scars; time: 1-17 days monitoring for epilepsy group; syncope group retrospectively (n=108) Reference standard: prolonged EEG video monitoring, using both interictal and ictal data; 12-lead ECG and Holter monitoring, tilt test and autonomic reflex examination.; time 1-17 days monitoring for epilepsy group; syncope group retrospectively (n=108) For target condition/outcome: different causes of TLoC (epilepsy, psychogenic seizures, Arrhythmic causes, vasovagal syncope and postural hypotension

Study	Participants	Diagnostic tests
del Rosso 2008 prospective cohort study; study held in Italy. Setting: Emergency Department. ED of 14 general hospitals in Italy from Oct 2004 to Nov 2004. Funding: 1 author is employee of Medtronic; organisational support funded by Medtronic	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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-syncopal 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-syncopal attacks; 3% unexplained Other study comments: Validation cohort. Prospective	Index test: Signs and symptoms from 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: initial ECG + ECG monitoring or 24h Holter or during electrophysiological study; time not stated (n=256) For target condition/outcome: Mechanical: severe valvular stenosis or other flow obstruction, or acute myocardial ischaemia. Arrhythmias: bradycardia <40bpm/repetitive sinoatrial blocks/sinus pause >3s. 2nd or 3rd AV block; SVT or VT, etc.
Graf 2008 prospective cohort study; study held in Switzerland. Setting: Syncope unit. Syncope clinic to which patients were referred if they had unexplained syncope or presyncope. Funding: Academic funding	TLoC population: selected patients with unexplained syncope or presyncope. Prior tests: All patients had at least 1 prior test. Population details: 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. Inclusion criteria: patients with unexplained syncope or presyncope. Exclusion criteria: patients with symptoms compatible with: seizure disorders, vertigo, dizziness or coma. Patient characteristics: age: mean 53 years (SD 20); sex: 46% female; some patients with existing heart disease (17% coronary artery disease); history of TLoC: Time elapsed since first episode: mean 5 years (SD 8) Comorbidities: 35% hypertension; 28% hypercholesterolaemia; 29% CV disease; 6% diabetes type II. Other details: Final diagnosis: 9% cardiac arrhythmias (7% tachyarrhythmia, 2% AV block); 18% cardioinhibitory CSS - included with 'rhythmic'; 23% vasovagal syncope; 17% psychogenic; 3% orthostatic hypotension; 2% miscellaneous; 21% unexplained Other study comments: Derivation cohort. Arrhythmias included cardioinhibitory CSS.	Index test: initial symptoms determined from patient history, physical exam, 12-lead ECG; time: initial (n=317) 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; 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 & psychogenic pseudosyncope; orthostatic hypotension and vasodilative CSS

Study	Participants	Diagnostic tests
Hoefnagels 1991 prospective cohort study; study held in The Netherlands. Setting: Neurology. consecutive patients presenting to neurology dept from March 1987-March 1988. Funding: :none stated	TLoC population: selected patients with partly unexplained cause after Initial stage. Prior tests: Unclear or Not stated. Population details: referrals from GPs and the ED; probably selected Definition of TLoC: an episode of less than 1 hour, with inability to maintain posture, loss of contact with the environment, and amnesia for the events which occurred during the episode. Inclusion criteria: Age 15 years and older with one or more episodes of TLoC. Exclusion criteria: LoC due to trauma or subarachnoid haemorrhage; patients with known epilepsy. Patient characteristics: age: 45 years (SD 22 years), with an eye witness account of their TLoC; sex: 51% male; Unclear/not stated with existing heart disease (appears to be none; no-seizure group mixture of vasovagal and hyperventilation syncope); history of TLoC: not stated: one or more episodes Comorbidities: not stated. Other details: final diagnosis: seizure group - 17% generalised epilepsy; 34% partial epilepsy; 49% single seizure. No-seizure group 21% vasovagal; 26% hyperventilation; unexplained 36%	Index test: questionnaire for patients and eye witnesses; initial signs and symptoms; time: initial (n=94) Reference standard: interviews of patients and eye witnesses; follow up; general and neurological exams, routine lab tests, EEG and ECG; CT scan and 24h cardiac monitoring as appropriate; time 14.7 months (mean); 8-21 months range (n=94) For target condition/outcome: Seizure: classified on basis of eyewitness observation (more than a few movements and clonic movements identified from range imitated by the interviewer; clear automatism (e.g. chewing/lip smacking); if motionless, and the patient later described an unequivocal aura (e.g. funny smell)). And if follow up gave no reason for change in diagnosis
Romme 2009 (subset of van Dijk 2008) prospective cohort study; study held in The Netherlands. Setting: Hospital several departments. subset (380/503) of consecutive patients presenting to neurology, cardiology, internal medicine, cardiac emergency room (up to 100 each); non consecutive to ED (only 22% included); 173 excluded. Funding: unrestricted educational grant	TLoC population: selected patients with TLoC of mixed known causes. Prior tests: Some patients had 1 prior test. Population details: Population from van Dijk 2008; 123 patients excluded to correspond to Sheldon 2006 population (55 with cardiomyopathy or MI, 18 with epileptic seizures; 50 with unknown cause after 2y) Definition of TLoC: Self limited TLoC not due to head trauma. Inclusion criteria: TLoC patients from van Dijk 2008, then exclusions to align with Sheldon 2006 population in these respects (55 with cardiomyopathy or MI, 18 with epileptic seizures; 50 with no diagnosis after 2y). Exclusion criteria: head trauma causing TLoC; patients with a known disorder causing TLoC who experienced typical recurrence; younger than 18 years. Patient characteristics: age: mean 53 years (SD 19) for full cohort; sex: 56% male for full cohort; some patients with existing heart disease (3% heart failure; 13% rhythm disturbances; 22% hypertension (may be in >1 category)); history of TLoC: (for this cohort) previous episodes in year before presentation: VVS group 29% <1, 20% 1-3, 51% ≥4; other TLoC diagnoses 46% <1; 10% 1-3; 17% ≥4 Comorbidities: 3% heart failure; 13% rhythm disturbances; 22% hypertension; 7% cerebrovascular accident; 7% diabetes (may be in >1 category). Other details: (this cohort) 55% diagnosed with vasovagal syncope, 11% other forms of NM syncope, 12% OHT; 7% cardiac syncope; psychogenic pseudosyncope 6%	Index test: initial evaluation based on ESC guidelines: standardised history taking (ESC); physical exam (pulse; bp supine & after 3min upright; cardiac auscultation) in 97% patients; 12 lead ECG (84% patients); time: initially (n=380) Reference standard: questionnaire after at least 2 y on recurrence & additional tests (echo, 24h Holter, exercise test, tilt test, CSM) or treatment. Final diagnosis using these, the initial presentation + expert panel if disagree; time 2 year follow up (n=380) For target condition/outcome: vasovagal syncope

Study	Participants	Diagnostic tests
Sarasin 2003 prospective cohort study; study held in Switzerland. Setting: Emergency Department. ED in primary and tertiary care main teaching hospital between 1989 and 1991.	TLoC population: selected patients with partly unexplained cause after initial stage. Prior tests: All patients had at least 1 prior test. Population details: 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. Definition of TLoC: Sudden transient loss of consciousness with an inability to maintain postural tone and with spontaneous recovery. Inclusion criteria: 18 years and older with syncope. Exclusion criteria: patients with symptoms clearly compatible with seizure disorder, vertigo, dizziness, coma, shock or other states of altered consciousness. Those with a cause of syncope strongly suspected based on history and physical exam.. Patient characteristics: age: 65.6 years (SD 17' range 19-90; 47% 65y and older; 42% 75y and older); sex: 54% male; some patients with existing heart disease (27% coronary artery disease; 14% previous MI; 16% congestive HF; 44% hypertension); history of TLoC: 56% with first episode; 24% one prior episode; 20% with ≥ 2 episodes Comorbidities: also 13% with diabetes mellitus. Other details: patients who did not have a definite diagnosis after initial stage; cardiac arrhythmias 17%; organic heart disease 9%; vasovagal syncope 6%; seizures/psychiatric 13%; unknown 50% Other study comments: 30/175 (17%) patients with arrhythmias. 617 patients recruited; 442 had diagnosis by non-invasive assessment. Derivation cohort - cross validation carried out.	Index test: initial symptoms derived from age >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, including: AF, sinus pause ≥2 & <3s; bradycardia >35bpm & ≤45; conduction disorders; signs of old MI or VH; multiple premature ventricular beats; prolonged corrected sinus node recovery time (≥550ms); prolonged H-T interval (≥100ms); SVT 180bpm
Sheldon 2002 case control 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. Population details: 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 patients 35 (SD 12 years) syncope 53 (SD20) p<0.001; sex: seizure patients 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=270) 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 time (n=270) 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=270). For target condition/outcome: Seizure diagnosis if patients had diagnostically positive EEGs

Study	Participants	Diagnostic tests
Sheldon 2006 case control 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. Population details: diagnosis established; not if had >1 plausible cause of TLoC; syncope in apparent absence of structural heart disease and epileptic seizures Definition of TLoC: Loss of consciousness and loss of control of posture. Inclusion criteria: loss of consciousness; diagnosis established according to preset criteria, or if there was no reasonable diagnostic confusion or if reasonable investigations failed to elicit a diagnosis. Exclusion criteria: patients with more than 1 plausible cause of syncope; patients with a history of known/suspected cardiomyopathy or prior MI (with diagnosis confirmed by echo, gated angiography or cardiac catheterisation); patients with structural HD & epileptic seizures. Patient characteristics: age: 42 (SD 18) tilt positive; 49 (SD 21) tilt negative; 63 (SD 16) other syncope; sex: 39% male tilt positive; 46% tilt negative; 55% other; some patients with existing heart disease (10% had valvular heart disease; 18% hypertension); history of TLoC: some patients; some had >30 Comorbidities: not stated. Other details: 3 patient groups: 235/418 tilt positive + no other diagnosis; 95/418 tilt negative + no other diagnosis and 88/41 with complete heart block, SVT, idiopathic VT, aortic stenosis, Toursades-de Pointe VT, cough syncope, hypertensive carotid sinus syncope Other study comments: Tertiary referral clinics / acute care facilities only. Univariate & multivariate analyses. Validation on same sample as derivation, but bootstrap analysis to allow for lack of independent sample.	Index test: Initial symptoms; time: initially (n=418) 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 time (n=418) 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=418). For target condition/outcome: Vasovagal syncope - positive tilt test result using a currently acceptable method

1.2 Decision rules for diagnosis review

Diagnostic Test: ACEP guidelines

Study	Participants	Diagnostic tests
Elseber 2005 retrospective cohort study; study held in USA. Setting: Emergency Department. ED in tertiary care teaching hospital between Jan 1996 and Dec 1998. Funding: 1 author had grant from Medtronic	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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 sates of altered mentation.. Patient characteristics: age: 63 years (SD 20); sex: 101 men 99 women; some patients with existing heart disease (26.0% had history of CAD, 9.5% had history of congestive HF); history of TLoC: 37/200 (19%) had ≥2 syncopal events in the past month Comorbidities: 75/200 had hypertension; 27/200 had cerebrovascular disease, 18/200 had diabetes mellitus.. Other details: 24/200 patients diagnosed with cardiac syncope; 83 had vasovagal syncope; 1 had carotid sinus hypersensitivity, 2 had seizure, 1 had cerebrovascular accident, 35 had situational or orthostatic hypotension (or both); 39 had unknown cause 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%	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: EGSYS score

Study	Participants	Diagnostic tests
del Rosso 2008 prospective cohort study; study held in Italy. Setting: Emergency Department. ED of 14 general hospitals in Italy from Oct 2004 to Nov 2004. Funding: 1 author is employee of Medtronic; organisational support funded by Medtronic	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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-syncopal 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-syncopal attacks; 3% unexplained Other study comments: Validation cohort. Prospective	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: 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 <40bpm/repetitive sinoatrial blocks/sinus pause >3s. 2nd or 3rd AV block; SVT or VT, etc.

Diagnostic Test: ESC guidelines

Study	Participants	Diagnostic tests
van Dijk 2008 prospective cohort study; study held in The Netherlands. Setting: Hospital several departments. consecutive patients presenting to neurology, cardiology, internal medicine, cardiac emergency room (up to 100 each); non consecutive to ED (only 22% included). Funding: unrestricted educational grant from Medtronic Europe and Netherlands Heart Foundation	TLoC population: unselected patients. Prior tests: Some patients had 1 prior test. Population details: consecutive adult patients presenting with TLoC to any department of University hospital Definition of TLoC: Self limited TLoC not due to head trauma. Inclusion criteria: TLoC. Exclusion criteria: head trauma causing TLoC; patients with a known disorder causing TLoC who experienced typical recurrence; younger than 18 years. 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 patients 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	Index test: initial evaluation based on ESC guidelines: standardised history taking (ESC); physical exam (pulse; bp supine & after 3min upright; cardiac auscultation) in 97% patients; 12 lead ECG (84% patients); 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 patients); time 2 year follow up (mean 31.6 months) (n=458) For target condition/outcome: all causes; diagnosis obtained from initial evaluation, follow up outcomes and additional diagnostic tests; cardiac syncope (arrhythmias + structural cardiopulmonary conditions; reflex syncope; orthostatic hypotension; neurological diagnosis (epilepsy, brain tumour, stroke, vascular steal); psychiatric diagnosis

Diagnostic Test: Initial symptoms decision rule

Study	Participants	Diagnostic tests
Graf 2008 prospective cohort study; study held in Switzerland. Setting: Syncope unit. Syncope clinic to which patients were referred if they had unexplained syncope or presyncope. Funding: Academic funding	TLoC population: selected patients with unexplained syncope or presyncope. Prior tests: All patients had at least 1 prior test. Population details: consecutive outpatients with unexplained syncope 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. 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); 18% cardioinhibitory CSS - included with 'rhythmic'; 23% vasovagal syncope; 17% psychogenic; 3% orthostatic hypotension; 2% miscellaneous; 21% unexplained Other study comments: Validation cohort. Arrhythmias included cardioinhibitory CSS.	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; time (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

Study	Participants	Diagnostic tests
Romme 2009 (subset of van Dijk 2008) prospective cohort study; study held in The Netherlands. Setting: Hospital several departments. subset (380/503 = 75%) of consecutive patients presenting to neurology, cardiology, internal medicine, cardiac emergency room (up to 100 each); non consecutive to ED (only 22% included); 173 excluded. Funding: unrestricted educational grant	TLoC population: selected patients with TLoC of mixed known causes. Prior tests: Some patients had 1 prior test. Population details: Population from van Dijk 2008; 123 patients excluded to correspond to Sheldon 2006 population (55 with cardiomyopathy or MI, 18 with epileptic seizures; 50 with unknown cause after 2y) Definition of TLoC: Self limited TLoC not due to head trauma. Inclusion criteria: TLoC patients from van Dijk 2008, then exclusions to align with Sheldon 2006 population in these respects (55 with cardiomyopathy or MI, 18 with epileptic seizures; 50 with no diagnosis after 2y). Exclusion criteria: head trauma causing TLoC; patients with a known disorder causing TLoC who experienced typical recurrence; younger than 18 years. Patient characteristics: age: mean 53 years (SD 19) for full cohort; sex: 56% male for full cohort; some patients with existing heart disease (3% heart failure; 13% rhythm disturbances; 22% hypertension (may be in >1 category)); history of TLoC: (for this cohort) previous episodes in year before presentation: VVS group 29% <1, 20% 1-3, 51% ≥4; other TLoC diagnoses 46% <1; 10% 1-3; 17% ≥4 Comorbidities: 3% heart failure; 13% rhythm disturbances; 22% hypertension; 7% cerebrovascular accident; 7% diabetes (may be in >1 category). Other details: (this cohort) 55% diagnosed with vasovagal syncope, 11% other forms of NM syncope, 12% OHT; 7% cardiac syncope; psychogenic pseudosyncope 6%	Index test: initial evaluation based Sheldon 2006 score (positive and negative scoring items; patients classified as having VVS if points score ≥1); time: initially (n=380) Reference standard: questionnaire after at least 2 y on recurrence & additional tests (echo, 24h Holter, exercise test, tilt test, CSM) or treatment. Final diagnosis using these, the initial presentation + expert panel if disagree; time 2 year follow up (n=380) For target condition/outcome: vasovagal syncope
Sarasin 2003 cross sectional study index 1st; study held in USA. Setting: Emergency Department. ED in primary and tertiary care main teaching hospital between 1989 and 1991.	TLoC population: selected patients with partly unexplained cause after initial stage. Prior tests: All patients had at least 1 prior test. Population details: 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. Definition of TLoC: Sudden transient loss of consciousness with an inability to maintain postural tone and with spontaneous recovery. Inclusion criteria: 18 years and older with syncope. Exclusion criteria: patients with symptoms clearly compatible with seizure disorder, vertigo, dizziness, coma, shock or other states of altered consciousness. Those with a cause of syncope strongly suspected based on history and physical exam.. Patient characteristics: age: 56.1 years (SD 21 range 17-94; 41% 65y and older; 23% 75y and older); sex: 41% male; some patients with existing heart disease (29% coronary artery disease; 8% previous MI; 12% congestive HF; 31% hypertension); history of TLoC: 34% with first episode; 22% one prior episode; 44% with ≥ 2 episodes Comorbidities: also 12% with diabetes mellitus. Other details: patients who did not have a definite diagnosis after initial stage; arrhythmias 17%; organic heart disease 9%; vasovagal syncope 6%; seizures/psychiatric 13%; unknown 50% Other study comments: 48/267 (18%) patients with arrhythmias. 668 patients recruited; 267 considered to have 'unexplained syncope'. Validation cohort – but carried out 10 years before derivation cohort , although appears to be prospective.	Index test: risk score derived from age >65y , history of congestive heart failure, abnormal ECG; time: initially (n=267) 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) For target condition/outcome: Arrhythmias, including: AF, sinus pause ≥2 & <3s; bradycardia >35bpm & ≤45; conduction disorders; signs of old MI or VH; multiple premature ventricular beats; prolonged corrected sinus node recovery time (≥550ms); prolonged H-T interval (≥100ms); SVT 180bpm

Study	Participants	Diagnostic tests
Sheldon 2002 case control 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. Population details: 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 patients 35 (SD 12 years) syncope 53 (SD20) p<0.001; sex: seizure patients 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: Validation sample. 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: Decision rule based on symptoms alone with positive and negative scoring items; patients classified as having seizures if points score ≥1; 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 time (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
Sheldon 2006 case control 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. Population details: diagnosis established; not if had >1 plausible cause of TLoC; syncope in apparent absence of structural heart disease and epileptic seizures Definition of TLoC: Loss of consciousness and loss of control of posture. Inclusion criteria: loss of consciousness; diagnosis established according to preset criteria, or if there was no reasonable diagnostic confusion or if reasonable investigations failed to elicit a diagnosis. Exclusion criteria: patients with more than 1 plausible cause of syncope; patients with a history of known/suspected cardiomyopathy or prior MI (with diagnosis confirmed by echo, gated angiography or cardiac catheterisation); patients with structural HD & epileptic seizures. Patient characteristics: age: 42 (SD 18) tilt positive; 49 (SD 21) tilt negative; 63 (SD 16) other syncope; sex: 39% male tilt positive; 46% tilt negative; 55% other; some patients with existing heart disease (10% had valvular heart disease; 18% hypertension); history of TLoC: some patients; some had >30 Comorbidities: not stated. Other details: 3 patient groups: 235/418 tilt positive + no other diagnosis; 95/418 tilt negative + no other diagnosis and 88/418 with complete heart block, SVT, idiopathic VT, aortic stenosis, T-de-P VT, cough syncope, hypertensive carotid sinus syncope Other study comments: Tertiary referral clinics / acute care facilities. Univariate & multivariate analyses. Validation on same sample as derivation, but bootstrap analysis to allow for lack of independent sample. About 84% of 'controls' had cardiac syncope.	Index test: Decision rule based on symptoms alone with positive and negative scoring items; patients classified as having VV syncope if points score ≥1; time: initially (n=418) 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 time (n=418) 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=418). For target condition/outcome: Vasovagal syncope - positive tilt test result using a currently acceptable method

1.3 Initial symptoms for risk stratification (death) review

Study	Participants	Diagnostic tests
Colivicchi 2003 prospective cohort study; study held in Italy. Setting: Emergency Department. EDs of 6 general community hospitals in 1 region [Nov 1997-Jan 1998). Funding: none stated, but derivation cohort used so likely to be biased	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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. 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 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 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: initial symptoms determined from patient history, physical exam, 12-lead ECG, haemoglobin count, blood glucose: score based on age >65 y, clinical 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
Quinn 2008 prospective cohort study; study held in USA. Setting: Emergency Department. ED of large university teaching hospital. Funding: 1st author received an NIH grant. Same authors developed SFSR - some potential for conflict of interest.	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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: 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: Age over 65 years; 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) Other comparator tests: Physician decision to admit patient (n=684). For target condition/outcome: Death that was possibly related to TLoC; 3, 6 and 12 months reported

1.4 Decision rules for risk stratification (death) review

Diagnostic Test: ACP guidelines

Study	Participants	Diagnostic tests
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. Funding: None	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: Records retrieved for all patients with presenting complaint of 'collapse', 'collapse query cause', 'faint', 'vasovagal', 'syncope', 'fit', 'seizure', 'fall'. Then included if had clear history of TLoC. 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'. 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 cardioactive or psychotropic drugs	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

Diagnostic Test: EGSYS score

Study	Participants	Diagnostic tests
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. Funding: 1 author is employee of Medtronic; organisational support funded by Medtronic	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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-syncopal 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-syncopal attacks; 3% unexplained Other study comments: Validation cohort. Prospective	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 outpatients visit; time 21-24 months (mean 614 days) (n=195) For target condition/outcome: Death from any cause

Diagnostic Test: OESIL score

Study	Participants	Diagnostic tests
Colivicchi 2003 prospective cohort study; study held in Italy. Setting: Emergency Department. EDs of 6 general community hospitals in 1 region [Nov 1997-Jan 1998). Funding: none stated, but derivation cohort used so likely to be biased	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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. 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 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 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, clinical 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

Study	Participants	Diagnostic tests
Quinn 2008 prospective cohort study; study held in USA. Setting: Emergency Department. ED of large university teaching hospital. Funding: 1st author received an NIH grant. Same authors developed SFSR - some potential for conflict of interest.	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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: 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) Other comparator tests: Physician decision to admit patient (n=684). For target condition/outcome: Death that was possibly related to TLoC; 6 and 12 months reported

1.5 Initial symptoms for risk stratification review

Diagnostic Test: Initial symptoms

Study	Participants	Diagnostic tests
Birnbaum 2008 prospective cohort study; study held in USA. Setting: Emergency Department. ED of large urban, academic centre (80,000 visits per year). Funding: None that would create a conflict of interest	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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	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. For target condition/outcome: Short term serious o/c: death, MI, arrhythmia, PE, stroke, SAH, sig haemorrhage needing transfusion; procedural intervention to treat syncope cause; any condition likely to/ causing return to ED; hospitalisation for related event

Study	Participants	Diagnostic tests
Costantino 2008 (STePS) prospective cohort study; study held in Italy. Setting: Emergency Department. EDs of 4 general hospitals in the Milan area; [Jan 2004-July 2004). Funding: Study supported by a donation from Autogrill S.p.A.	TLoC population: unselected patients. Prior tests: unclear/not stated. Population details: 2775 consecutive adult patients who presented with syncope within the previous 48h to ED (syncope, pre-syncope, seizures, falls, head injuries etc). Then exclusion criteria applied - 676/2775 enrolled. Definition of TLoC: Syncope: a sudden and transient loss of consciousness associated with inability to maintain postural tone with spontaneous recovery; presyncope and seizures excluded. Inclusion criteria: Patients presenting with syncope in the previous 48h, aged 18 years and older.. Exclusion criteria: Head injury pre-LoC; non-spontaneous return to consciousness; pre-syncope, coma, shock, seizure; associated diseases with prognosis < 6mo; recent alcohol/drug abuse; non-consent; unfeasible follow-up. Patient characteristics: age: mean 59 years (SD 22); 18-44y 29%, 45-65y 23%, >65y 48%; sex: 43.9% male; some patients with existing heart disease (some had history of structural HD (25%), hypertension (40%), heart failure (4%), ventricular arrhythmias (2%)); history of TLoC: not stated Comorbidities: some with heart disease; also cerebrovascular disease (13%), neurological disease (10%), diabetes (10%), COPD (8%), neoplasm (8%). Other details: additionally, 24% had trauma, 2% had exercise induced syncope. 67% directly discharged from ED. Within 10 days: 36 had major therapeutic procedures & 5 died. At 1 year there were 40 deaths. Other study comments: Also excluded if patients had clinical conditions primarily confirmed in the ED that would have led to hospital admission independently of TLoC (e.g. MI, acute PE, SAH, stroke, cardiac arrest, sustained bradycardia	Index test: Signs and symptoms, history, ECG results; time: initially (n=676) Reference standard: Participating physicians evaluated admitted patients. Discharged patients - directly evaluated before discharge or surveyed within 2 d by phone & then within 10 days of TLoC using 10 item questionnaire. At 1y, phone interview / regional database for death; time 10 days and 1 year (11-365 d) after TLoC (n=670; 667 at 1y) For target condition/outcome: Death and severe outcomes - need for major therapeutic procedures (cardiopulmonary resuscitation, pacemaker or ICD insertion, ICU admittance, acute antiarrhythmic therapy) - not in ED. Readmission to hospital (within 10 days).
Grossman 2007 prospective cohort study; study held in USA. Setting: Emergency Department. large urban teaching hospital ED; consecutive patients with syncope. Funding: none reported	TLoC population: unselected patients. Prior tests: No patients had a prior test. Population details: 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 1episode 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. 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.	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 (>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

Study	Participants	Diagnostic tests
Hing 2005 prospective cohort study; study held in Australia. Setting: Emergency Department. ED of tertiary referral urban hospital (42,000 emergency presentations per annum) [April 2002-Aoril 2003). Funding: none declared	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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	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, including medication changes, admission to hospital, angiogram; significant arrhythmia requiring treatment; death as a result of presumed cardiac causes
Quinn 2004 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.	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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.	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 & 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 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, significant haemorrhage; any condition causing return to ED and hospitalisation for related event

Study	Participants	Diagnostic tests
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	TLoC population: unselected patients. Prior tests: No patients had a prior test. Population details: 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. 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 group skewed towards more serious risk. Admission = >12 h in ED. Scores for SFSR & OESIL determined by study team from data forms.	Index test: signs and symptoms 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 & ACEP guidelines: 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, cerebrovascular accident/SAH, significant haemorrhage needing blood transfusion; acute surgical procedure/endoscopic intervention. 5 died and 6 had serious outcome by 3 mo.
Reed 2010 (derivation) prospective cohort study; study held in UK. Setting: Emergency Department. ED of large urban tertiary centre (100,000 adult attendances per annum) [March - Oct 2007). Funding: none for main study, equipment supplied by Biosite for the pilot (Reed 2007)	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: adult presenting with acute syncope to ED; identified by ED staff. Further group identified from daily search of electronic patient records with appropriate key words, then eligibility assessed. 2 cohorts (derivation and validation) March-Oct 2007 Definition of TLoC: Syncope: a transient, self limited loss of consciousness, usually leading to falling. Onset is relatively rapid and recovery is spontaneous, complete and relatively prompt. Inclusion criteria: people presenting with syncope aged 16 years and older. Exclusion criteria: previously recruited into the study; persistent neurological deficit suggesting stroke, alcohol related, hypoglycaemia, trauma, history of seizure with >15min witnessed post-ictal phase; unable to give written or verbal informed consent. Patient characteristics: age: mean 63.8 years (SD 21.2); sex: 44.4% male; some patients with existing heart disease (IHD 23%, acute MI 10%, valvular HD 6%, heart failure history 5%); history of TLoC: 43% had previous history Comorbidities: hypertension 39%. Other details: 575/890 (65%) potentially eligible patients screened; 550 recruited; 40 had primary outcome (serious outcome/all cause death) Other study comments: Secondary end points (separate) were: cardiovascular serious outcomes (acute MI, arrhythmia, pacemaker/ICD, cardiac procedure) and syncope-related death	Index test: standardised assessment with 32 historical variables (9 clinical features, 10 med history, 13 current meds); 14 exam; 24 ECG; 23 biochemical/haematological variables (incl. characteristics In other decision rules); BNP test (2.7ml ETDA); time: initially (n=548) Reference standard: review of electronic records, hospital pacemaker records, radiology reports, direct contact with patient or GP. Cardiologist & emergency physician independently reviewed ECG. 2 investigators reviewed clinical data & assigned end points; 3 others if disagreed; time 1 month (n=529) For target condition/outcome: Serious o/c: all-cause death, acute MI, life threatening arrhythmia (VF, SVT > 120bpm, ventricular pause > 3s, standstill or asystole), decision for pacemaker or ICD within 1mo, PE, cerebrovascular accident/intracranial haemorrhage/SAH, significant haemorrhage needing blood transfusion; acute surgical procedure/endoscopic intervention. 5 died and 6 had a serious outcome by 1 month

Study	Participants	Diagnostic tests
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)	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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-resuscitate/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)	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/non-trauma haemorrhage, aortic dissection, new SHD, sig haemorrhage/anaemia needing transfusion; procedure to treat syncope cause; readmission for related event

1.6 Decision rules for risk stratification review

Diagnostic Test: Boston Syncope Criteria

Study	Participants	Diagnostic tests
Grossman 2007 prospective cohort study; study held in USA. Setting: Emergency Department. large urban teaching hospital ED; consecutive patients with syncope. Funding: none reported	TLoC population: unselected patients. Prior tests: No patients had a prior test. Population details: 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 1episode 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. 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.	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	Participants	Diagnostic tests
Hing 2005 prospective cohort study; study held in Australia. Setting: Emergency Department. ED of tertiary referral urban hospital (42,000 emergency presentations per annum) [April 2002-Aoril 2003). Funding: none declared	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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	Index test: OESIL score determined from data collection by study team: based on age >65 y, clinical 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, including medication changes, admission to hospital, angiogram; significant arrhythmia requiring treatment; death as a result of presumed cardiac causes
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	TLoC population: unselected patients. Prior tests: No patients had a prior test. Population details: 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. 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 group skewed towards more serious risk. Admission = >12 h in ED. Scores for SFSR & OESIL determined by study team from data forms.	Index test: OESIL score determined from data collection by study team: based on age >65 y, clinical 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 Francisco Syncope Rule; time: initially (n=99). Other comparator tests: 3)initial assessment based on ESC, AAP & ACEP guidelines: standardised assessment with 75 variables (11 clinical features, 9 medical 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, cerebrovascular accident/SAH, significant haemorrhage needing blood transfusion; acute surgical procedure/endoscopic intervention. 5 died and 6 had serious outcome by 3 mo.

Diagnostic Test: ROSE rule

Study	Participants	Diagnostic tests
Reed 2010 (validation) prospective cohort study; study held in UK. Setting: Emergency Department. ED of large urban tertiary centre (100,000 adult attendances per annum) [Oct 2007-July 2008). Funding: none for main study, equipment supplied by Biosite for the pilot (Reed 2007)	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: adults presenting with acute syncope to ED; identified by ED staff. Further group identified from daily search of electronic patient records with appropriate key words, then eligibility assessed. 2 cohorts (derivation and validation) March-Oct 2007 Definition of TLoC: Syncope: a transient, self limited loss of consciousness, usually leading to falling. Onset is relatively rapid and recovery is spontaneous, complete and relatively prompt. Inclusion criteria: people presenting with syncope aged 16 years and older. Exclusion criteria: previously recruited into the study; persistent neurological deficit suggesting stroke, alcohol related, hypoglycaemia, trauma, history of seizure with >15min witnessed post-ictal phase; unable to give written or verbal informed consent. Patient characteristics: age: mean 62.4 years (SD 21.9); sex: 45.5% male; some patients with existing heart disease (IHD 20%, acute MI 11%, valvular HD 6%, heart failure history 4%); history of TLoC: 40% had previous history Comorbidities: hypertension 38%. Other details: 579/951 (61%) potentially eligible patients screened; 550 recruited; 39 had primary outcome (serious outcome/all cause death) Other study comments: Secondary end points (separate) were: cardiovascular serious outcomes (acute MI, arrhythmia, pacemaker/ICD implantation, cardiac procedure) and syncope-related death. Rule from regression + recursive partitioning; 3 multivariables omitted, 2 factors added	Index test: ROSE rule from standardised patient assessment (BNP level ≥300pg/ml; bradycardia ≤ 50bpm, faecal occult blood on rectal exam, anaemia (Hb ≤90g/l), chest pain associated with syncope, ECG: Q wave not in lead III; O2 sats ≤94% room air); time: initially (n=549) Reference standard: review of electronic records, hospital pacemaker records, radiology reports, direct contact with patient or GP. Cardiologist & emergency physician independently reviewed ECG. 2 investigators reviewed clinical data & assigned end points; 3 others if disagreed; time 1 month (n=538) For target condition/outcome: Serious o/c: all-cause death, acute MI, life threatening arrhythmia (VF, SVT > 120bpm, ventricular pause > 3s, standstill or asystole), decision for pacemaker or ICD within 1mo, PE, cerebrovascular accident/intracranial haemorrhage/SAH, significant haemorrhage needing blood transfusion; acute surgical procedure/endoscopic intervention. 5 died and 6 had serious outcome by 3 mo.

Diagnostic Test: San Francisco Syncope Rule

Study	Participants	Diagnostic tests
Birnbaum 2008 prospective cohort study; study held in USA. Setting: Emergency Department. ED of large urban, academic centre (80,000 visits per year). Funding: None that would create a conflict of interest	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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	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 haemorrhage needing transfusion; procedural intervention to treat syncope cause; any condition likely to/ causing return to ED; hospitalisation for related event
Cosgriff 2007 prospective cohort study; study held in Australia. Setting: Emergency Department. ED of large adult teaching hospital (32,000 visits per year). Funding: No conflicts of interest	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: Non-consecutive ED patients 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 interpretation. Diagnosis at ED discharge including: vasovagal 16%, dehydration 10% and hypotension 10%, unknown 32%. Serious outcomes not indicated by rule: 1 sick sinus syndrome who needed pacemaker insertion	Index test: San Francisco Syncope Rule: data on history of congestive heart failure; haemocrit < 30%; patient complaint of shortness of breath; systolic bp < 90 mm Hg. abnormal ECG (any non-sinus rhythm or any new changes) determined separately; time: in ED (n=113) Reference standard: Follow up determined by researcher who was not part of clinical team (probably same person as index test) by phone using scripted interview; time 7 days; not more than 9 days (n=89) Comparator test: Decision to admit patient by ED physicians who were not informed that study was taking place and had relatively low awareness of SFSR; time: ED (n=113). For target condition/outcome: Short term serious o/c: death, MI, arrhythmia, PE, stroke, SAH, significant haemorrhage; acute intervention for inpatient to treat syncope cause; any causing return to ED; hospitalisation for related event

Study	Participants	Diagnostic tests
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.	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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)	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 with in 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, significant haemorrhage; any condition causing return to ED and hospitalisation for related event
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.	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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.	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 some for same patients) Reference standard: Follow up determined by trained research nurse and study investigators; following investigations; 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 diagnosed/present in ED: death, MI, arrhythmia, PE, stroke, SAH, sig haemorrhage/anaemia needing transfusion; procedural intervention to treat syncope cause; any condition likely to/ causing return to ED; hospitalisation for related event

Study	Participants	Diagnostic tests
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	TLoC population: unselected patients. Prior tests: No patients had a prior test. Population details: 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. 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 group skewed towards more serious risk. Admission = >12 h in ED. Scores for SFSR & OESIL determined by study team from data forms.	Index test: San Francisco syncope rule presence of history of congestive heart failure; anaemia (haemocrit < 30%); abnormal ECG result (any non-sinus rhythm or any new changes); patient complaint of shortness of breath; systolic bp < 90 mm Hg; 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: OESIL score; time: initially (n=99). Other comparator tests: 3)initial assessment based on ESC, AAP & ACEP guidelines: standardised assessment with 75 variables (11 clinical features, 9 medical 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, cerebrovascular accident/SAH, significant haemorrhage needing blood transfusion; acute surgical procedure/endoscopic intervention. 5 died and 6 had serious outcome by 3 mo.
Schladenhaufen 2008 retrospective cohort study; study held in USA. 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	TLoC population: patients with syncope or near syncope. Prior tests: Unclear or Not stated. Population details: retrospective study sample from all entries in ED database; 122 excluded because of incomplete ED data or no follow up Definition of TLoC: Keywords of: syncope, near syncope, faint or passed out. ICD 9 code for syncope and near syncope. 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 (47/639 =7%) or uncertain outcomes (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	Index test: retrospectively determined SFSR items (ECG in comparison with previous ECG); time: (n=592) Reference standard: death by documentation in medical record, discharge summary notes if hospital stay >7 days; subsequent inpatient and outpatient visits records if <7days (if no subsequent visits then excluded); 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 haemorrhage needing transfusion; any condition likely to/ causing return to ED; hospitalisation for related event

Study	Participants	Diagnostic tests
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)	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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-resuscitate/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)	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/non-trauma haemorrhage, aortic dissection, new SHD, sig haemorrhage/anaemia needing transfusion; procedure to treat syncope cause; readmission for related event

1.7 Decision rules for recurrence of TLoC review

Diagnostic Test: OESIL score

Study	Participants	Diagnostic tests
Hing 2005 prospective cohort study; study held in Australia. Setting: Emergency Department. ED of tertiary referral urban hospital (42,000 emergency presentations per annum) [April 2002-Aoril 2003). Funding: none declared	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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	Index test: OESIL score determined from data collection by study team: based on age >65 y, clinical 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

Study	Participants	Diagnostic tests
Birnbaum 2008 prospective cohort study; study held in USA. Setting: Emergency Department. ED of large urban, academic centre (80,000 visits per year). Funding: None that would create a conflict of interest	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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	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 haemorrhage needing transfusion; procedural intervention to treat syncope cause; any condition likely to/ causing return to ED; hospitalisation for related event
Colivicchi 2003 prospective cohort study; study held in Italy. Setting: Emergency Department. EDs of 6 general community hospitals in 1 region [Nov 1997-Jan 1998). Funding: none stated, but derivation cohort used so likely to be biased	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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. 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 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 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: 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

Study	Participants	Diagnostic tests
Grossman 2007 prospective cohort study; study held in USA. Setting: Emergency Department. large urban teaching hospital ED; consecutive patients with syncope. Funding: none reported	TLoC population: unselected patients. Prior tests: No patients had a prior test. Population details: 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 1episode 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.	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
Hing 2005 prospective cohort study; study held in Australia. Setting: Emergency Department. ED of tertiary referral urban hospital (42,000 emergency presentations per annum) [April 2002-Aoril 2003). Funding: none declared	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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 Other study comments: Derivation cohort	Index test: 12-lead 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, including medication changes, admission to hospital, angiogram; significant arrhythmia requiring treatment; death as a result of presumed cardiac causes

Study	Participants	Diagnostic tests
Quinn 2004 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.	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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.	Index test: 12 lead ECG results 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 & 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 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, significant haemorrhage; any condition causing return to ED and hospitalisation for related event
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	TLoC population: unselected patients. Prior tests: No patients had a prior test. Population details: 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. 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 group skewed towards more serious risk. Admission = >12 h in ED. Scores for SFSR & OESIL determined by study team from data forms.	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 & ACEP guidelines: standardised assessment with 75 variables (11 clinical features, 9 medical 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, cerebrovascular accident/SAH, significant haemorrhage needing blood transfusion; acute surgical procedure/endoscopic intervention. 5 died and 6 had serious outcome by 3 mo.

Study	Participants	Diagnostic tests
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: university funding and American Geriatrics Society award (1st author)	TLoC population: unselected patients. Prior tests: Unclear or Not stated. Population details: 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-resuscitate/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 patients as SUN 2007; diagnostic ECG = ECG abnormality related to cardiac event. Inter-rater reliability also checked in convenience sample (subgroup)	Index test: 12-lead ECG and history of cardiac comorbidities structured form (abnormal changes including 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 asst; then 2 independent emergency physicians reviewed ED docs (including 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	Participant	Diagnostic tests
Charbit 2006 Study held in France Setting: recovery room after anaesthesia Funding :solely from institution/ department	Population: postoperative patients. Prior tests: Unclear or Not stated. Inclusion criteria: patients admitted to recovery room after anaesthesia (92% general 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)	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)
Christov 2001 Study held in Bulgaria and Italy Setting: Cardiology Funding :CNR-NATO Individual Fellowship	Population: routine ECGs from department of cardiology. Prior tests: unclear or not stated. patients from an annotated atrial flutter-fibrillation database: ECGs collected routinely in cardiology dept; >80% abnormal 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	Index test: algorithm to calculate atrial flutter/fibrillation parameter (mean value of differentiated filtered and rectified signal); threshold of 0.35% as cut-off value; instrument not specified; time: not stated (n=329) Reference standard: atrial flutter-fibrillation records diagnosed and annotated by a group of cardiologists (no further details); time not stated (n=329) for Target Condition/Outcome: either atrial flutter or fibrillation versus normal ECG
Denny 2007 Study held in USA Setting: Hospital several departments (departments of biomedical informatics and medicine) Funding :National Library of Medicine grants	Population: database of ECGs from all inpatients all inpatients admitted for 2-30 days from 1999-2003 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	Index test: machine calculated QT intervals and heart rate (automated QT and QTc) from an ECG management system (no further details); time: not stated (n=44808) Reference standard: ardiologist-generated free text impression (selected from stock phrases or stock phrase edited or typed free text); time not stated (n=44808) for Target Condition/Outcome: QTc over 450ms versus probable or possible QT prolongation identified by cardiologist

Study	Participant	Diagnostic tests
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	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. 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.	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) for Target Condition/Outcome: ischaemic (acute MI/IHD); arrhythmia (premature atrial/ventricular contractions, atrial fibrillation, paroxysmal supraventricular tachycardia); structural (enlarged atrium, ventricular hypertrophy); conduction (AV/bundle branch/sinoatrial block)
Kaneko 2005 Study held in Japan Setting: Hospital several departments (several hospitals in Japan) Funding :not stated	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: 25 male + 2 female patients Comorbidities: not stated 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)	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) for Target Condition/Outcome: Brugada syndrome (type 1 or 2 or 3) or suspected Brugada type
Taha 2000 Study held in USA Setting: unclear Funding: lead author employed by GE Marquette Medical Systems	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 Other study comments: database of 4172 ECGs; frequency domain measures of QRST- subtracted signlas to differentiate between atrial flutter and fibrillation versus neither of these	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) for Target Condition/Outcome: atrial flutter or fibrillation (each correctly classified)

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

Study	**cardiopulmonary cause**	
	arrhythmia	structural heart disease
Boston Syncope Criteria (Grossman 2007)	**Signs and symptoms of acute coronary syndrome**: ● ECG changes VT, VF, SVT, rapid AF or new STT wave change **Worrying cardiac history**: ● history of VT, VF ● history of pacemaker ● history of ICD ● prehospital use of antidysrhythmic medication excluding beta blockers or calcium channel blockers **Family history:** ● 1st degree relative with Brugada's or long QT syndromes **Signs of conduction disease:** ● multiple syncopal episodes within the last 6 months ● rapid heart beat by patient history ● syncope during exercise ● QT interval > 500 ms ● 2nd or 3rd degree heart block or intraventricular block **Persistent (> 15 min) abnormal vital signs in ED**: ● sinus rate < 50 beats/min or > 100 beats/min	**Signs and symptoms of acute coronary syndrome**: ● chest pain of possible cardiac origin ● ischaemic ECG changes (ST elevation or deep (>0.1mV) ST depression) ● complaint of shortness of breath **Worrying cardiac history**: ● history of CAD, incl deep q waves, hypertrophic/ dilatated cardiomyopathy ● history of congestive heart failure or LV dysfunction **Family history:** ● 1st degree relative with sudden death, HOCM **Valvular heart disease:** ● heart murmur noted in history or on ED examination
San Francisco Syncope Rule (Quinn 2005)	● abnormal ECG result (any non-sinus rhythm or any new changes)	● history of congestive heart failure ● complaint of shortness of breath

Study	**cardiopulmonary cause**	
	arrhythmia	structural heart disease
Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL) score (Covicchi 2004; Reed 2007)	History findings: ● age > 65 years ● no prodromal symptoms ECG findings ● Atrial fibrillation or flutter ● Supraventricular tachycardia ● multifocal atrial tachycardia ● frequent or repetitive premature supraventricular or ventricular complexes ● sustained or non-sustained ventricular tachycardia ● paced rhythms ● complete atrioventricular block ● Mobitz I or II atrioventricular block ● bundle branch block ● Intraventricular conduction delay	History findings: ● age > 65 years ● no prodromal symptoms ● clinical history of structural heart disease (incl ischaemic heart disease; valvular dysfunction; primary myocardial disease) ● clinical history of congestive heart failure ● clinical history of peripheral arterial disease ECG findings ● left axis deviation ● left or right ventricular hypertrophy ● old myocardial infarction ● T wave/ST segment abnormalities consistent with or possibly related to myocardial ischaemia
initial evaluation (but unclear which was index test) (Alboni 2001)	● sinus bradycardia < 40 beats per minute ● repetitive sinoatrial blocks ● sinus pauses > 3sec ● Mobitz II or advanced 2nd or 3rd degree atrioventricular block ● atrial fibrillation with a slow ventricular response)(mean heart rate < 50 beats/min) ● sustained supraventricular tachycardia or ventricular tachycardia	
Initial evaluation (ESC guidelines) certain diagnosis (van Dijk 2008)	● sinus bradycardia < 40 beats per minute ● repetitive sinoatrial blocks ● sinus pauses > 3sec in absence of negatively chronotropic medications ● Mobitz II 2nd or 3rd degree atrioventricular block ● alternating left and right bundle branch block ● rapid paroxysmal supraventricular tachycardia or ventricular tachycardia ● pacemaker malfunction with cardiac pauses	● symptoms present with ECG evidence of acute ischaemia with or without myocardial infarction, independently of its mechanism
Initial evaluation (ESC guidelines) highly likely diagnosis (van Dijk 2008)		● presence of severe structural heart disease ● syncope during exertion, or supine ● preceded by palpitation or accompanied by chest pain ● family history of sudden death

Study	**cardiopulmonary cause**	
	arrhythmia	structural heart disease
Initial evaluation symptoms only (Sheldon 2003)	● any presyncope	● any presyncope
Initial evaluation symptoms + history (Sheldon 2003)	● any presyncope	● any presyncope
12-lead ECG (Sun 2008)	**History findings:** ● history of ventricular arrhythmia, supraventricular rhythms incl AF or flutter, bradycardia, sick sinus syndrome, implanted pacemaker or defibrillator) **ECG findings**: ● any non-sinus rhythm ● left or right bundle branch block ● sinus bradycardia < 50 beats per minute ● abnormal conduction interval excluding 1st degree block	**History findings:** ● coronary artery disease ● congestive heart failure ● aortic stenosis ● pulmonary heart disease **ECG findings:** ● Q/ST/T changes consistent with acute or chronic ischaemia ● left axis deviation ● left or right ventricular hypertrophy
ACP guidelines for admission; high risk (Crane 2002)	**History findings:** ● history of VT **ECG findings**: ● serious bradycardia ● serious tachycardia ● long QT interval ● Bundle branch block	**History findings:** ● history of coronary artery disease ● history of congestive cardiac failure ● symptoms of chest pain ● physical signs of CCF ● physical signs of significant valve disease **ECG findings:** ● ischaemia
ACP guidelines for admission; moderate risk (Crane 2002)	● suspicion of arrhythmia ● age over 70 years	● suspicion of coronary heart disease ● syncope during exertion or with injury ● TLoC with rapid heart action

Study	**cardiopulmonary cause**	
	arrhythmia	structural heart disease
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 **ECG findings**: ● arrhythmia ● long QT interval ● Bundle branch block	**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
Sarasin risk score - strongly suspected cause of syncope (Sarasin 2003)	**ECG findings**: ● 3rd degree atrioventricular block	
Sarasin risk score - suspected arrhythmia cause (Sarasin 2003)	**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 infarctionI or ventricular hypertrophy ● multiple premature ventricular beats	**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)	
Graf risk score for vasovagal and psychogenic pseudosyncope (Graf 2008)	● P wave duration longer (≥120 ms or non-sinus rhythm)	

2.2 Vascular cause

study	----------vascular cause----------			
	neurally mediated	vasovagal	situational	orthostatic hypotension
Boston Syncope Criteria (Grossman 2007)	None	None	None	**Volume depletion:** ● GI bleeding by haemoccult or history ● haematocrit < 30 ● Dehydation 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
San Francisco Syncope Rule (Quinn 2005)	None	None	None	● Haematocrit < 30 ● triage systolic bp < 90 mm Hg
Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL) score (Covicchi 2004; Reed 2007)	None	None	None	None
initial evaluation (but unclear which was index test) (Alboni 2001)		● precipitating events (such as fear, severe pain, strong emotional, instrumentation) identified in the absence of another competing diagnosis	● syncope during or immediately after urination, defacation, cough or swallowing	● decrease in systolic bp of at least 20 mm Hg during 5 min after the patient assumed the upright position

study	----------vascular cause----------			
	neurally mediated	vasovagal	situational	orthostatic hypotension
ED guidelines: high risk (admit) (Reed 2007)				Clinical examination: ● systolic bp < 90 mm Hg
ED guidelines: medium risk (consider discharge with early outpatient review) (Reed 2007)				● decrease in bp of 20 mm Hg on standing
Initial evaluation (ESC guidelines) certain diagnosis (van Dijk 2008)		● precipitating events (such as fear, severe pain, emotional distress, instrumentation, or prolonged standing) which are associated with typical prodromal symptoms	● syncope during or immediately after urination, defacation, cough or swallowing	● documentation of orthostatic hypotension associated with syncope or presyncope ● decrease in systolic bp of 20 mm Hg or a decrease of systolic bp to <90 mm Hg is defined as orthostatic hypotension regardless of whether or not symptoms occur
Initial evaluation (ESC guidelines) highly likely diagnosis (van Dijk 2008)	● 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			● 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

study	----------vascular cause----------			
	neurally mediated	vasovagal	situational	orthostatic hypotension
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

study	hypovolaemia	neurological	cerebrovascular	other
Boston Syncope Criteria (Grossman 2007)	none	none	Primary CNS event (i.e. subarachnoid haemorrhage; stroke)	none
San Francisco Syncope Rule (Quinn 2005)	none	none	none	none
Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL) score (Covicchi 2004; Reed 2007)	none	none	**History findings:** ● clinical history of stroke or transient ischaemic attack	none
initial evaluation (but unclear which was index test) (Alboni 2001)	none	none	none	● 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
ED guidelines: high risk (admit) (Reed 2007)	**Clinical examination:** ● Faecal occult blood present on rectal exam ● other suspicions of GI bleed	**Clinical examination:** ● new neurological signs on examination	**Clinical examination:** ● suspicion of cerebrovascular accident or subarachnoid haemorrhage ● syncope associated with headache	
ED guidelines: medium risk (consider discharge with early outpatient review) (Reed 2007)	none	none	none	● trauma associated with collapse

study	hypovolaemia	neurological	cerebrovascular	other
Initial evaluation (ESC guidelines) certain diagnosis (van Dijk 2008)		(Not necessarily 'certain diagnosis') ● Confusion after attack for more than 5 min ● Tonic-clonic movements, automatism, tonguebiting, blue face, epileptic aura	none	none
Initial evaluation (ESC guidelines) highly likely diagnosis (van Dijk 2008)	none	none	● with arm exercise ● differences in blood pressure or pulse in the 2 arms	none
Initial evaluation symptoms only (Sheldon 2003)	● any presyncope	● 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	none	none
Initial evaluation symptoms + history (Sheldon 2003)	● any presyncope	● LoC with emotional stress ● head turning to one side during LoC ● Unresponsiveness during LoC **History findings:** ● number of spells >30	none	none
ACP guidelines for admission; high risk (Crane 2002)	none	**History findings:** ● physical signs of stroke or focal neurology	none	none
ACP guidelines for admission; moderate risk (Crane 2002)	none	none	none	none

study	hypovolaemia	neurological	cerebrovascular	other
ACEP guidelines for cardiac syncope (admission); level B (Elesber 2005)	none	none	none	none
ACEP guidelines for cardiac syncope (admission); level C (Elesber 2005)	none	none	none	none
Sarasin risk score - strongly suspected cause of syncope (Sarasin 2003)	none	none	none	none
Sarasin risk score - suspected arrhythmia cause (Sarasin 2003)	none	none	none	none
Graf risk score for rhythmic syncope (Graf 2008)	none	none	none	none
Graf risk score for vasovagal and psychogenic pseudosyncope (Graf 2008)	none	none	none	none

3 Second stage tests – included studies tables

3.1 Ambulatory ECG - suspect arrhythmia review

3.1.1 Diagnostic Test: Holter monitoring 24-hour

Study	Participant	Diagnostic tests
Boudoulas 1979 non-randomised comparative study; study held in USA. Setting: Cardiology. cardiology. Funding: National Institutes of Health and Central Ohio Heart Chapter of the American Heart Association	TLoC population: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test. syncope or presyncope (dizziness ot lightheadedness) Definition of TLoC: syncope or presyncope (dizziness ot lightheadedness). Inclusion criteria: patients with syncope or presyncope (dizziness ot 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 ot lightheadedness) Other study comments: 2 tests within 1 week	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 SVT (170 bpm); high grade AV block; frequent ventricular premature contractions, effective rate less than 40 bpm; repetitive pairs PVCs; VT
Boudoulas 1983 case series; study held in USA. Setting: Cardiology. Funding: not stated	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 details: see below Other study comments: case series; 24 hour monitoring and electrophysiological study within 1 week	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 bracy less than 40 bpm awake; sinoatrial exit block; paroxysmal SVT (rate over 170 bpm); repetitive pairs premature ventricular beats; VT
Brembilla-Perrot 2001 case series; study held in France. Setting: Cardiology. Funding: not stated	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. Inclusion criteria: patients with syncope, MI and complete bundle branch block. 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: mean 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	Index test: Holter monitor analysed with ELATEC system; time: 24 hours (n=130) Comparator test: "performed according to the literature"; 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)

Study	Participant	Diagnostic tests
Brembilla-Perrot 2004 case series; study held in France. Setting: Cardiology. Funding: not stated	TLoC population: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test. coronary disease with history of MI and/or multiple coronary stenoses on angiography and LVEF below 40% 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	Index test: Holter monitoring (Elatec); time: 24 hours (n=119) for Target Condition/Outcome: ventricular arrhythmias (couplets or nonsustained VT)
Brembilla-Perrot 2004 case series; study held in France. Setting: Cardiology. Funding: not stated	TLoC population: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test. idiopathic dilated cardiomyopathy, normal coronary angiogram, LVEF below 40% Definition of TLoC: a short loss of consciousness. Inclusion criteria: idiopathic dilated cardiomyopathy, normal coronary angiogram, 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 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	Index test: Holter monitoring (Elatec); time: 24 hours (n=61) for Target Condition/Outcome: ventricular arrhythmias (couplets or nonsustained VT)
Sarasin 2005 case series; study held in Switzerland. Setting: Hospital several departments. main teaching hospital of Geneva University Medical School; major primary and teriary hospital for the area. Funding: not stated	TLoC population: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test. unexplained syncope and a high likelihood of arrhythmias (neurological examination and tests for orthostatic hypotension negative; typical history of vasovagal/situational syncope excluded) Definition of TLoC: sudden transient loss of consciousness with inability to maintain postural tone with spontaneous recovery. Inclusion criteria: 18 years or older presenting to ED or inpatient services with syncope as main complaint. Exclusion criteria: neurological problem; orthostatic hypotension; typical history of vasovagal/situational syncope. Patient characteristics: age: mean age 68 (15) years; sex: 53% female; some patients with existing heart disease (31% coronary artery disease; 18% old MI; 20% congestive cardiac failure; 9% non-ischaemic cardiomyopathy; 37% hypertension); TLoC history: 52% 1st episode; 25% had had 3 or more episodes (mean at least 1.7 episodes) Comorbidities: 37% hypertension. Other details: see below Other study comments: case series	Index test: ambulatory or in-hospital 24-hour Holter using 3 channels of ECG (Del Mar Avionics); 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 or with hypotension; Mobitz 2 2nd degree/complete AV block; VT 30s or more

3.1.2 Diagnostic Test: Holter monitoring 48-hour

Study	Participant	Diagnostic tests
Arya 2005 case series; study held in Iran. Setting: Cardiology. arrhythmia clinic. Funding: none 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 or presyncope; had had clinical assessment including BP, ECG and echo Definition of TLoC: not defined. Inclusion criteria: recurrent unexplained syncope or 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	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	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 mulitple episodes Comorbidities: hypertension 15 pts. Other details: Clinical examination had ruled out other causes of symptoms than arrhythmia Other study comments: case series	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

3.1.3 Diagnostic Test: external event recorder

Study	Participant	Diagnostic tests
Rothman 2007 RCT; study held in USA. Setting: Cardiology. Multicentre. Funding: Cardionet Inc	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	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	Participant	Diagnostic tests
Brignole 2001 case series; study held in Multinational. Setting: Hospital several departments. multinational. Funding: not stated	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. Exclusion criteria: . Patient characteristics: age: mean age 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	Index test: Reveal; patient activated; time: median 48 days (IQR 16 to 100); seen every 3 month, until an event or until battery ran down (n=52) for 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
Garcia-Civera 2005 case series; study held in Spain. Setting: Cardiology. Funding: not stated	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) Definition of TLoC: not defined. 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 age 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	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) for 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
Krahn 1999 time: case series; study held in multinational. Setting: Hospital several departments. multinational. Funding: supported in part by the Heart and Stroke Foundation of Ontario	TLoC population: patients with 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	Index test: Reveal; patient activated; 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) for 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	Participant	Diagnostic tests
Menozzi 2002 case series; study held in multinational. Setting: Hospital several departments. multinational. Funding: not stated	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 electrophysiolocial 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	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	Participant	Diagnostic tests
Fitchet 2003 case series; study held in UK. Setting: Cardiology. cardiologist-run syncope clinic or cardiologists of 2 tertiary referral centres. Funding: not stated	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% imparied 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	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	Participant	Diagnostic tests
Moya 2001 case series; study Multinational. Setting: Hospital several departments. 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. 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	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	Participant	Diagnostic tests
Brignole 2006 case series; study held in multinational. Setting: Hospital several departments. Multicentre. Funding: supported by grant from Medtronic Europe	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	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)
Deharo 2006 case series; study held in France. Setting: Cardiology. University cardiology department. 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. 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 3 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	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

Study	Participant	Diagnostic tests
Aronow 1993 case series; study held in USA. Setting: geriatrics; chronic care facility. Funding: not stated	TLoC population: unclear/not stated. Prior tests: All patients had at least 1 prior test. elderly patients with unexplained syncope; vasodepressor, drug-induced, carotid sinus, neurological syncope, orthostatic hypotension, valvular heart disease, HCM, acute MI, PE, hypoglycaemia excluded Definition of TLoC: sudden transient loss of consciousness with inability to maintain postural tone; not seizure, vertigo, dizziness, coma, shock or other altered consciousness. 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. 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 Comorbidities: not stated. Other details: elderly patients Other study comments: case series no comparator; additional data added in from Aronow 1992 (same patients) number 823.	Index test: 24 hour ambulatory ECG (Avionics model 445); time: 24 hours (n=148) for Target Condition/Outcome: symptom/rhythm correlation: pauses >3s; sustained VT; AF with ventricular rate >190 beats pre minute; nonsustained VT; other complex ventricular arrhythmias
Comolli 1993 case series; study held in Italy. Setting: Division of Internal Medicine. 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. negative clinical examination, routine haematological tests, chest x-ray, ECG 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; Unclear/not stated with existing heart disease (not stated); TLoC history: not stated Comorbidities: not stated. Other details: little info 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"	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
Lacroix 1981 case series; study held in Canada. Setting: Department of Medicine. Funding: none 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 aetiology (some patients had had exercise tests & 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	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 blcok (Mobitz type I or II)

Study	Participant	Diagnostic tests
Sarasin 2001 case series; study held in Switzerland. Setting: Emergency Department. ED. Funding: not stated	TLoC population: unclear/not stated. Prior tests: All patients had at least 1 prior test. patients presenting to ED with syncope; had had ECG, BP, carotid massage and syncope still unexplained Definition of TLoC: sudden transient loss of consciousness with inability to maintain postural tone and spontaneous recovery. Inclusion criteria: patients aged 18 years or older presenting to ED with syncope. Exclusion criteria: symptoms compatible with seizure vertigo, dizziness, coma or shock. Patient characteristics: age: mean age 60 (23) years in whole group (range 18-93 years); sex: 52% female; some patients with existing heart disease (unclear how many had heart disease in Holter group); TLoC history: not stated Comorbidities: unclear. Other details: see below Other study comments: case series; some of these patients went on to have external loop (see section b number 841) and tilt test (see section c number 842)	Index test: Holter; time: 24 hours (n=122) for Target Condition/Outcome: prespecified: sinus pause 3s or more / symptom+ pause 2s or more; sinus brady 35bpm or less / symptomatic brady 40bpm or less; AF+slow ventricular response (RR 3s/more); SVT 30s or more, 180bpm or more, or systolic BP 90mmHg/less; 2nd deg (Mob 2)/complete AV block; VT

3.3.2 Diagnostic Test: Holter monitoring 48-hour

Study	Participant	Diagnostic tests
Rockx 2005 RCT; study held in Canada. Setting: Cardiology. patients referred from community or ED. Funding: Physician Services Inc, Toronto	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	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	Participant	Diagnostic tests
Kapoor 1991 case series; study held in USA. Setting: Hospital several departments. General internal medicine and 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. 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	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 I heart block; brady 30-39bpm; SVT 10 or more beats over 150bpm; AF

3.3.4 Diagnostic Test: external event recorder

Study	Participant	Diagnostic tests
Fogel 1997 case series; study held in USA. Setting: Cardiology. Funding: not stated	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 Definition of TLoC: syncope or presyncope. Inclusion criteria: patients presenting for evaluation of syncope or presyncope. Exclusion criteria: none. Patient characteristics: age: mean age 57 years; sex: 53% female; some patients with existing heart disease (42% had heart disease); TLoC history: not stated Comorbidities: not stated. Other details: see below Other study comments: case series no comparator	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)
Linzer 1990 case series; study held in USA. Setting: Hospital several departments. General Internal Medicine, Cardiology. Funding: Charles A Dana Foundation, Duke Women's Auxiliary, National Institutes of Health	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 Definition of TLoC: transient loss of consciousness with loss of postural tone. Inclusion criteria: at least 1 episode of syncope unexplained by history, examination, ECG, 24 hour Holter, carotid sinus massage. Exclusion criteria: Prior electrophysiological testing; Holter showing arrhythmic or non-arrhythmic syncope. Patient characteristics: age: median age 54 years; sex: 58% female; some patients with existing heart disease (35% had heart disease); history of TLoC: median duration of symptoms 12 months; median number of prior episodes 10 Other details: at least 1 episode of syncope unexplained by history, examination, ECG, 24 hour Holter, carotid sinus massage Other study comments: case series no comparator	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
Rockx 2005 RCT; study held in Canada. Setting: Cardiology. patients referred from community or ED. Funding: Physician Services Inc, Toronto	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	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

Study	Participant	Diagnostic tests
Sarasin 2001 case series; study held in Switzerland. Setting: Emergency Department. ED. Funding: not stated	TLoC population: unclear/not stated. Prior tests: All patients had at least 1 prior test. patients presenting to ED with syncope; had had ECG, BP, carotid massage and syncope still unexplained Definition of TLoC: sudden transient loss of consciousness with inability to maintain postural tone and spontaneous recovery. Inclusion criteria: patients aged 18 years or older presenting to ED with syncope. Exclusion criteria: symptoms compatible with seizure vertigo, dizziness, coma or shock. Patient characteristics: age: mean age 60 (23) years in whole group (range 18-93 years); sex: 52% female; some patients with existing heart disease (unclear how many had heart disease in Holter group); TLoC history: not stated Comorbidities: unclear. Other details: see below Other study comments: case series; these patients had negative Holter in section a (number 840) and some went on to have tilt test (see section c number 842)	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
Schuchert 2003 case series; study held in Germany. Setting: unclear. "Medical Clinic III". 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 age 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	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

3.3.5 Diagnostic Test: implantable event recorder - patient activated

Donateo 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: Reveal; patient activated; time: mean 18 (9) months; 1st syncopal event analysed; follow up every 3 months to maximum of 36 months (n=36) 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

Study	Participant	Diagnostic tests
Krahn 1998 case series; study held in Canada. Setting: Cardiology. Funding: Ontario Heart and Stroke Foundation	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 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	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)
Krahn 2002 case series; study held in Multinational. Setting: Hospital several departments. multinational. Funding: Ontario Heart and Stroke Foundation	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 origin; pts had had ECG, Holter or telemetry; some had tilt testing and/or EPS 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)	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
Moya 2001 case series; study held in Multinational. Setting: Hospital several departments. multinational. 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. normal ECG, tilt test negative 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	Index test: Reveal; patient activated; time: mean 9 (5) months; seen every 3 months until diagnosis, battery ran down or end of study (maximum 36 months) (n=82) for Target Condition/Outcome: ECG/syncope: findings (not prespecified): asystole; brady below 40bpm; AV block

Study	Participant	Diagnostic tests
Nierop 2000 case series; study held in The Netherlands. 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. history, examination, ECG, echo, routine lab tests 24 hour ECG, assessment of left ventricular ejection fraction, BP 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	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 case series; study held in multinational. Setting: Hospital several departments. multinational. 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. 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	Index test: Reveal; patient activated; time: mean 10.8 (4.3) months; device implanted until syncope/presyncope or patient or investigator wanted to remove it (n=133) for Target Condition/Outcome: recorded (not prespecified): brady below 50bpm; AV nodal re-entry tachycardia; SVT; torsades de pointes; frequent ventricular premature beats; mixed brady + venticular premature beats + nonsustained VT

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

Study	Participant	Diagnostic tests
Boersma 2004 case series; study held in multinational. Setting: Cardiology. multinational. Funding: European Society of Cardiology	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	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 & after an event (n=43) for Target Condition/Outcome: 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
Brignole 2005 case series; study held in Italy. Setting: Cardiology. 2 hospitals receiving referrals (in or outpatients) for assessment of syncope. Funding: none stated	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 "negative workup" Definition of TLoC: not defined; presyncope 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.	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)
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	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	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

Study	Participant	Diagnostic tests
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	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 1.5 TLOC per year Comorbidities: not stated. Other details: adults presenting with syncope Other study comments: Eastbourne Syncope Assessment Study (EaSyAS)	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 pasues 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)
Krahn 2001 RCT; study held in Canada. Setting: Cardiology. Arrhythmia service. Funding: Heart and Stroke Foundation of Ontario	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 & if tilt & EP negative, immediately offered ILR (diff follow up times)	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
Krahn 2004 case series; study held in Canada. Setting: Cardiology. Funding: Heart and Stroke Foundation of Ontario	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	Index test: ILR: Reveal Plus; patient or automatic activation; time: 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) (n=60) for Target Condition/Outcome: ILR 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

Study	Participant	Diagnostic tests
Lombardi 2005 case series; study held in Italy. Setting: Hospital several departments. cardiology or neurology. 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. 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	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.
Pezawas 2007 case series; study held in Austria. Setting: Cardiology. university cardiac centre. 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. 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	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)
Pierre 2008 case series; study held in France. Setting: Cardiology. Funding: funding for open access publication provided by Medtronic	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	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.

Study name	**category of patients**	**population details**
Aronow 1993	unexplained syncope after secondary tests (i)	elderly patients with unexplained syncope; vasodepressor, drug-induced, carotid sinus, neurological syncope, orthostatic hypotension, valvular heart disease, HCM, acute MI, PE, hypoglycaemia excluded
Arya 2005	suspected arrhythmia	syncope or presyncope; had had clinical assessment including BP, ECG and echo
Ashby 2002	unexplained syncope after secondary tests (i)	unexplained syncope (n=41) or presyncope (n=7); tests included echo, EER, EPS, tilt table, EEG
Boersma 2004	unexplained syncope after secondary tests (ii)	recurrent unexplained syncope despite CSM, echo, exercise test, 24 hour Holter, tilt test and EPS. A positive tilt test or abnormal Holter was not a reason for exclusion
Boudoulas 1979	suspected arrhythmia	syncope or presyncope (dizziness ot lightheadedness); prior ECG (Holter not mentioned)
Boudoulas 1983	suspected arrhythmia	syncope or presyncope; had had EEG (some also had CT or cerebral angiography); prior ECG (Holter not mentioned)
Brembilla-Perrot 2001	suspected arrhythmia	referred with syncope or presyncope and myocardial infarction. Prior ECG (Holter not mentioned)
Brembilla-Perrot 2004	suspected arrhythmia	coronary disease with history of MI and/or multiple coronary stenoses on angiography and LVEF below 40%. Prior ECG (Holter not mentioned)
Brembilla-Perrot 2004	suspected arrhythmia	idiopathic dilated cardiomyopathy, normal coronary angiogram, LVEF below 40%
Brignole 2001	suspected arrhythmia	Bundle branch block and negative EPS, carotid sinus massage, echo, 24-hour ECG; tilt test (but not excluded because of this)
Brignole 2005	unexplained syncope after secondary tests (i)	unexplained syncope; all had "negative workup" (likely to include Holter)
Brignole 2006	Ambulatory ECG - suspect NM syncope	patients with suspected neurally mediated syncope. Holter not mentioned; Most patients had a tilt test before IER, but all included

Study name	category of patients	population details
Brignole 2006b	Ambulatory ECG - suspect NM syncope	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
Comolli 1993	unexplained syncope after initial tests	negative clinical examination, routine haematological tests, chest x-ray, ECG (negative ECG = inclusion criterion). Not Holter
Cumbee 1990	unexplained syncope after secondary tests (i)	92% previous Holter; 46% previous EPS; patients excluded if cause of syncope already known
Deharo 2006	Ambulatory ECG - suspect NM syncope	vasovagal syncope, because of history, physical exam, CSM, positive HUT included Prior ECG (Holter not mentioned)
Donateo 2003	unexplained syncope after secondary tests (ii)	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)
Ermis 2003	unexplained syncope after initial tests	patients with syncope who received an IER; prior tests not stated (refers to ESC guidelines 2001)
Farwell 2006	unexplained syncope after secondary tests (i)	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 & CSM in all patients (patients with asystolic tilt/CSM results were excluded)
Fitchet 2003	Ambulatory ECG - suspect NM syncope	blackouts suggestive of vasovagal syncope. Holter vs Tilt test. Not done previously
Fogel 1997	unexplained syncope after secondary tests (i)	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
Garcia-Civera 2005	suspected arrhythmia	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.
Gibson 1984	unexplained syncope after initial tests	referred for syncope of unknown cause; no evidence of prior tests
Kabra 2009	unexplained syncope after secondary tests (i)	unexplained syncope/ palpitations/ presyncope/ dizziness; 35% had had CT head; 27% EEG; 55% Holter or event monitoring; 54% tilt table; 42% EPS;
Kapoor 1991	unexplained syncope after initial tests	unexplained syncope but normal clinical examination findings, history and normal 12-lead ECG

Study name	category of patients	population details
Krahn 1998	unexplained syncope after secondary tests (i)	ambulatory or in-hospital monitoring, tilt table and EPS negative in all patients
Krahn 1999	suspected arrhythmia	undiagnosed after history, examination, ECG and at least 24 hours ambulatory monitoring
Krahn 2000	unexplained syncope after initial tests	not stated: retrospective study; no evidence of prior tests
Krahn 2001	unexplained syncope after secondary tests (i)	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.
Krahn 2002	unexplained syncope after secondary tests (i)	syncope of unknown origin; pts had had ECG, Holter or telemetry; some had tilt testing and/or EPS
Krahn 2004	unexplained syncope after secondary tests (i)	patients referred to arrhythmia service for investigation of syncope; 24 hour Holter negative
Kuhne 2007	unexplained syncope after secondary tests (i)	patients referred with syncope; some patients had had echo; 24 hour Holter negative; other prior tests unclear
Lacroix 1981	unexplained syncope after secondary tests (i)	syncope of unknown aetiology (some patients had had exercise tests & echo); positive test for arrhythmia excluded
Linzer 1990	unexplained syncope after secondary tests (i)	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
Lombardi 2005	unexplained syncope after secondary tests (i)	unexplained syncope: cardiac diagnosis excluded (from history, examination, echo, Holter, telemetry, positive tilt test) and neurological diagnosis excluded (CT/MRI/EEG)
Mason 2003	suspected arrhythmia	recurrent unexplained syncope; patients had had ECG (20), event recorders (16) EPS (17) stress test (19) tilt test (32), cardiac catheterisation (12)
Menozzi 2002	suspected arrhythmia	suspected tachycardia cause; carotid sinus massage, echo, 24-hour ambulatory ECG not diagnostic
Morrison 1997	unexplained syncope after secondary tests (ii)	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
Moya 2001	Ambulatory ECG -	normal ECG, tilt test positive

	suspect NM syncope	

Study name	category of patients	population details
Moya 2001	unexplained syncope after secondary tests (i)	normal ECG, tilt test negative
Nierop 2000	unexplained syncope after secondary tests (ii)	history, examination, ECG, echo, routine lab tests 24 hour ECG, assessment of left ventricular ejection fraction, BP; abnormal Holter did not exclude patients
Pezawas 2007	unexplained syncope after secondary tests (i)	unexplained syncope after neurological investigation, ECG, carotid sinus massage, BP, echo, 24 hour ECG
Pierre 2008	unexplained syncope after secondary tests (i)	cardiac investigations including EPS all normal
Porterfield 1999	unexplained syncope after initial tests	patients who had experienced syncope; selected from national database; prior tests not stated
Ringqvist 1989	suspected arrhythmia	patients referred for investigation of syncope from Department of Internal Medicine or GP
Rockx 2005	unexplained syncope after secondary tests (i)	referred for ambulatory monitoring; 41 had had prior Holter; 31 echo; 13 tilt test (could have had previous investigations provided they had ongoing undiagmosed symptoms)
Rothman 2007	suspected arrhythmia	high clinical suspicion of malignant arrhythmia; syncope or presyncope; non-diagnostic 24 hour Holter or telemetry in last 45 days. No tilt test.
Sarasin 2001	unexplained syncope after secondary tests (i)	patients presenting to ED with syncope; had had ECG, BP, carotid massage and syncope still unexplained
Sarasin 2005	suspected arrhythmia	unexplained syncope and a high likelihood of arrhythmias (neurological examination and tests for orthostatic hypotension negative; typical history of vasovagal/ situational syncope excluded)
Saxon 1990	suspected arrhythmia	dizziness (n=30) or (n=20) syncope and persistent atrial fibrillation
Schernthaner 2008	unexplained syncope after secondary tests (ii)	unexplained recurrent syncope or presyncope; neurological tests (including EEG), 12 lead ECG, 24 hour Holter, echo, exercise stress test, all negative carotid sinus massage, all negative tilt table; AF or previous positive EPS did not exclude patients
Schuchert 2003	unexplained syncope after secondary tests (i)	tilt test negative, ECG and echo negative, no suggestion of vasovagal trigger mechanism
Seidl 2000	unexplained syncope after secondary tests (i)	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)

Zeldis 1980	unexplained syncope after secondary tests (i)	patients had syncope with or without other indications; patients had had coronary angiograms

3.4.2 TLoC frequency (previous episodes), duration of monitoring and time to first syncope, frequency x duration, category for freq x duration

Study name	Frequency of TLoC (number per year)	Duration of monitoring (days) [Time to first syncope]	Frequency x duration	Frequency x duration (a) < 0.1; b) 0.1 to 0.99; c) 1 to 10; d) >10)
Aronow 1993	NS	1 [NA]	NS	NS
Arya 2005	NS	1 1st day + 1 2nd day [NA]	NS	NS
Ashby 2002	NS	168 [mean 2.8 (2.1) months = 84 days]	NS	NS
Boersma 2004	6	540 [NA]	6/365 x 540 = 8.9	c
Boudoulas 1979	NS	1 [NA]	NS	NS
Boudoulas 1983	NS	1 [NA]	NS	NS
Brembilla-Perrot 2001	NS	1 [NA]	NS	NS
Brembilla-Perrot 2004	NS	1 [NA]	NS	NS
Brembilla-Perrot 2004	NS	1	NS	NS
Brignole 2001	1.5	48 [37% had event after median 48 days (range 2–367) days]	1.5/365 x 48 = 0.2	b
Brignole 2005	NS	420 [not stated}	NS	NS
Brignole 2006	3	270 [36% patients had event after median 9 months (IQR 3–17)]	3/365 x 270 = 2.2	c
Brignole 2006b	2	365 [26% of patients had syncope documented after mean of 3 months (90 days)]	2/365 x 365 = 2	c
Comolli 1993	NS	1 [NA]	NS	NS
Cumbee 1990	NS	mean 42d, median 28d, range 3–140 d [diagnostic recorders worn for mean 33d, median 28d, range 3–140 d; non-diagnostic (usually no spells) mean 48 d, median 28 d, range 21–112 d]	NS	NS
Deharo 2006	6.9	510 [12/25 had events; time to 1st event mean 4.8 months (SD 4.7)]	6.9/365 x 510 = 9.6	c
Donateo 2003	1.5	540 [16/36 activated device	1.5/365 x	c

		for syncope: median time 9 months (range 1–36)	540 = 2.2	

Study name	Frequency of TLoC (number per year)	Duration of monitoring (days) [Time to first syncope]	Frequency x duration	Frequency x duration (a) < 0.1; b) 0.1 to 0.99; c) 1 to 10; d) >10)
Ermis 2003	NS	429 [mean time to TLoC was 13.4 months (range 1–23) in 12% patients	NS	NS
Farwell 2006	1.5	510 Time not stated but mean follow up was 276 (SD 134 days) for both groups.	1.5/365 x 510 = 2.1	c
Fitchet 2003	2.5	2 [NA]	2.5/365 x 2 = 0.01	a
Fogel 1997	NS	28 [NA]	NA	NA
Garcia-Civera 2005	3.5	276 [IER documented syncope/pre-syncope occurred in 40% pts in mean of 85 (SD 95) days]	3.5/365 x 276 = 2.6	c
Gibson 1984	NS	1 [NA]	NA	NA
Kabra 2009	NS	10 months (300 days)	NS	NS
Kapoor 1991	NS	3 [NA]	NS	NS
Krahn 1998	3.6	138 [21/24 developed syncope or presyncope at a mean of 5.1 (4.8) months = 153 days]	3.6/365 x 138 = 1.4	c
Krahn 1999	5.1	315 [58/85 (68%) had symptoms a mean of 71 (79) days after ILR]	5.1/365 x 315 = 4.4	c
Krahn 2000	NS	2 Holter; 30 IER [NA]	NS	NS
Krahn 2001	2.6	365 [NA]	2.6/365 x 365 = 2.6	c
Krahn 2002	NS	6 months (180 days) [symptoms recurred in 69% of patients at a mean of 93 (107) days]	NS	NS
Krahn 2004	4.4	365 [NA]	4.4/365 x 365 = 4.4	c
Kuhne 2007	NS	1 [NA]	NS	NS
Lacroix 1981	3	1 [NA]	3/365 x 1 = 0.08	a
Linzer 1990	10	30 [mean duration of monitoring before diagnosis was 1 week (7 days)]	10/365 x 30 = 0.8	b
Lombardi 2005	2	210 [NA]	2/365 x 210 = 1.2	c

Mason 2003	NS	333 [mean time to recurrence of symptoms 7.6 (7.2) months (228 days)]	NS	NS

Study name	Frequency of TLoC (number per year)	Duration of monitoring (days) [Time to first syncope]	Frequency x duration	Frequency x duration (a) < 0.1; b) 0.1 to 0.99; c) 1 to 10; d) >10)
Menozzi 2002	1	480 [syncope occurred in 6/35 (17)5 of patients after a mean of 6 (5) months (180 days)]	1/365 x 480 = 1.3	c
Morrison 1997	NS	1 [NA]	NS	NS
Moya 2001 (tilt positive)	1.5	300 [8/29 (28%) of patients had recurrence at a median of 59 days (range 22–98)]	1.5/365 x 300 = 1.2	c
Moya 2001 (tilt negative)	2	270 [24/82 (29%) of patients had recurrence at a median of 105 days (range 47–226)]	2/365 x 270 = 1.5	c
Nierop 2000	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]]	5.2/365 x 330 = 4.7	c
Pezawas 2007	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]	NS	NS
Pierre 2008	NS	306 [43/95 (45.2%) of patients had recurrence at a mean time of 5.4 (4.6) months = 162 days]	NS	NS
Porterfield 1999	NS	30 [NA]	NS	NS
Ringqvist 1989	NS	2 [NA]	NS	NS
Rockx 2005	1.8	2 for 48 hour Holter; 30 for EER [median time to diagnosis 16 days (mean 17 (13) days for loop)]	Holter: 1.8/365 x 2 = 0.01; 1.8/365 x 30 = 0.15	Holter: a; EER: b
Rothman 2007	NS	NS [median time to diagnosis was 10 and 6 days for EER and telemetry	NS	NS

		respectively. Diagnosis corresponded to TLoC]		
Sarasin 2001 Holter	NS	1 [NA]	NS	NS

Study name	Frequency of TLoC (number per year)	Duration of monitoring (days) [Time to first syncope]	Frequency x duration	Frequency x duration (a) < 0.1; b) 0.1 to 0.99; c) 1 to 10; d) >10)
Sarasin 2001 EER	NS	7 [NA]	NS	NS
Sarasin 2005	NS	1 [NA]	NS	NS
Saxon 1990	NS	1 [NA]	NS	NS
Schernthaner 2008	1	270 [40/55 (73%) of patients had recurrence at a mean time of 7.6 (6.6) months = 228 days]	1/365 x 270 = 0.7	b
Schuchert 2003	6	50 [median time to TLoC 103 days (range 1 to 704 days) after tilt test in 8/24 patients.]	6/365 x 50 = 0.8	b
Seidl 2000	6.3	324 [NA]	6.3/365 x 324 = 5.6	c
Zeldis 1980	NS	1 [NA]	NS	NS

3.4.3 Arrhythmias detected in the studies

Study name Index test (group)	Index test time	Target condition	Arrhythmia detected (% refers to percentage of patients with brady or tachyarrhythmia out of total patients)	Bradyarrhythmias as proportion of a) arrhythmias during TLoC; b) arrhythmias not during TLoC and c) all arrhythmias found
Aronow 1993 Holter 24h (4)	24 hours	symptom/rhythm correlation: pauses >3s; sustained VT; AF with ventricular rate >190 beats pre 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 (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)	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%

Study name (group)	Index test time	Target condition	Arrhythmia detected	Brady propn a) with TLoC; b) not with TLoC; c) all
Boudoulas 1983 Holter 24h (1)	24 hours	sinus brady less than 40 bpm awake; sinoatrial exit block; paroxysmal SVT (rate over 170 bpm); repetitive pairs premature ventricular beats; VT	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%)	a) not stated b) not stated c) 11/31=35%
Brembilla-Perrot 2001 Holter 24h (1)	24 hours	non-sustained ventricular tachycardia (3 consecutive beats or tachycardia less than 10 seconds)	nonsustained VT: 42/130 patients (i.e. tachy 32%)	a) not stated b) not stated c) 0%
Brignole 2006 IER pt & auto activated (2)	up to 24 months; median 9 months; follow up every 3 months or to event or to max 24 months	ECG documented syncope: asystolic pause over 3 seconds (AV block or sinus arrest); bradycardia; tachyarrhythmia (paroxysmal AF; paroxysmal SVT; VT)	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%)	a) 61/77=79% b) 11/15=73% c) 72/92=78%
Comolli 1993 Holter 24h (3)	24 hours	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	During TLoC: 2VT; 1 normal rhythm out of 3 patients with TLoC (i.e. tachy 1%); not during TLoC: VT 23; pause > 2s: 11; bradycardia <30bpm: 13; high-grade AV block: 8 out of 287 patients (i.e. brady 11%, tachy 8%)	a) 0/2=0% b) 32/55=58% c) 32/57=56%

Study name (group)	Index test time	Target condition	Arrhythmia detected	Brady propn a) with TLoC; b) not with TLoC; c) all
Deharo 2006 IER pt & auto activated (2)	planned duration 18 mo; device interrogated after 1 mo + every 3 mo and after event; all followed to 18 mo except 2 explanted (infection/ neoplasia)	severe bradycardia during syncope (less than 40 bpm for at least 10 seconds); asystole (ventricular pause over 3 seconds); tachycardia over 165 bpm	during TLoC: 4 sinus bradycardia + 1 sinus arrest + 1 AV block = 6; sinus tachy: 1 out of 25 patients (i.e.brady 24%; tachy 4%)	a) 6/7=86% b) none c) 6/7=86%
Donateo 2003 IER pt activated (4)	mean 18 (9) months; 1st syncopal event analysed; follow up every 3 months to maximum of 36 months	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	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%)	a) 11/14=79% b) none c) 11/14=79%
Ermis 2003 IER pt & auto activated (3)	mean 14.3 (7.9) months; to extraction of IER or maximum 31 months to end of study	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	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	a) ¼=25% b) not stated c) not stated
Farwell 2006 IER pt & auto activated (4)	median 17 months (IQR 9-23 months); maximum 34 months	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)	bradycardia: 15; tachycardia: 5 (2 VT + 3 SVT) out of 101 patients (i.e. brady 15%, tachy 5%)	a) 15/20=75% b) none c) 15/20=75%

Study name (group)	Index test time	Target condition	Arrhythmia detected	Brady propn a) with TLoC; b) not with TLoC; c) all
Fitchet 2003 Holter 48h (2)	48 hours	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)	during TLoC: AF 2; sinus tachy 8 out of 118 patients (i.e. tachy 7%); not during TLoC: nonsustained VT 7; AF 13; nonsustained SVT 5; sinus brady 4 (i.e. tachy 21%; brady 3%)	a) none b) 4/29=14% c) 4/39=10%
Fogel 1997 EER (4)	usually 4 weeks; less if an event; extended if no event	symptom/rhythm correlation: detected arrhythmias were SVT; paroxysmal AF; prolonged pause following AF (not prespecified)	detected arrhythmias were SVT; paroxysmal AF; prolonged pause following AF (not prespecified)	a) b) c)
Garcia-Civera 2005 IER pt activated (1)	mean 9.2 (5.9) months; seen every 3 months; followed up until diagnosis reached, battery expired or patient died	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	during TLoC: AV block: 12; sinus brady: 5; sinus pause: 4; VT: 6 out of 81 patients (i.e. brady = 26%; tachy = 7%)	a) 21/27 = 78% b) none c) 21/27 = 78%
Kapoor 1991 Holter 72h (4)	72 hours	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	VT: 19; pause >2s: 8; bradycardia: 1; complete heart block: 1 out of 95 patients (i.e. brady 11%, tachy 20%)	a) 1/1=100% b) 6/25=24% c) 7/26=27%
Krahn 1998 IER pt activated (4)	up to 12 months; mean 4.6 (3.8) months; device explanted if diagnosis made or no event in 2 years (battery life)	symptom/rhythm correlation or exclusion of arrhythmia: found: bradycardia; bradytachy; AV block; sinus arrest; SVT; VT (not prespecified)	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%)	a) 8/10=80% b) none c) 8/10=80%

Study name (group)	Index test time	Target condition	Arrhythmia detected	Brady propn a) with TLoC; b) not with TLoC; c) all
Krahn 1999 IER pt activated (1)	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	arrhythmia or exclusion of arrhythmic cause: found: bradycardia below 50bpm; tachycardia (sustained SVT; atrial flutter with rapid ventricular response) not prespecified	bradycardia: 18; tachycardia: 3 out of 85 patients (i.e. brady 21%; tachy 3.5%)	a) 18/21 = 86% b) none c) 18/21 = 86%
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%)	a) 10/11 = 91% b) none c) 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%)	a) 35/47 = 74% b) none c) 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%)	a) 10/14 = 71% b) 7/9 = 78% c) 17/23 = 74%

Study name (group)	Index test time	Target condition	Arrhythmia detected	Brady propn a) with TLoC; b) not with TLoC; c) all
Lacroix 1981 Holter 24h (4)	24 hours	symptom/rhythm correlation: not prespecified; rhythms found were VTAF; wide complex tachy; SVT; atrial flutter; ventricular pause over 3sAV lock (Mobitz type I or II)	3 AV block; 1 ventricular pause >3s; 1 sustained VT; 9 nonsustained VT; 2 AF; nonsustained SVT 2; atrial flutter 2; wide QRS complex tachy 1 out of 100 patients (i.e. brady 4%, tachy 17%); unclear if during TLoC or not	a) unclear b) unclear c) 4/21 = 19%
Linzer 1990 EER (4)	up to 1 month; recording stopped if diagnostic event	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) 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: device set to record heart rate below 40bpm or over 160bpm or asystole over 3s. Rhythms found were bradycardia/asystole or AF.	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) 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: bradycardia + long pause 3 (2 AV block + 1 sinus arrest); 2 sinus tachy; 3 AF; sustained VT 1; 1 post-tachycardia pause (counted as brady) = 10 out of 35 patients (i.e. tachy 17%, brady 11%)	a) 4/10 = 40% b) none c) 4/10 = 40%

Study name (group)	Index test time	Target condition	Arrhythmia detected	Brady propn a) with TLoC; b) not with TLoC; c) all
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 months)	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%
Moya 2001a IER pt activated (4)	mean 9 (5) months; seen every 3 months until diagnosis, battery ran down or end of study (maximum 36 months)	ECG/syncope: findings (not prespecified): asystole; brady below 40bpm; AV block	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%)	a) 13/15 = 87% b) none c) 13/15 = 87%
Nierop 2000 IER pt activated (4)	11 (8) months; seen every 3 months	symptom-rhythm correlation: findings (not prespecified): bradycardia below 40bpm; asystole over 3s; tachycardia 180-220bpm	during TLoC: extreme bradycardia or asystole >5s: 4; tachycardia: 6 out of 35 patients (i.e. brady 11%, tachy 17%)	a) 4/10 = 40% b) none c) 4/10 = 40%
Pezawas 2007 IER pt & auto activated (4)	mean 16 (8) months; seen every 3 months to diagnosis or end of IER life	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)	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%)	a) 18/33 = 54% b) none c) 18/33 = 54%
Pierre 2008 IER pt & auto activated (4)	mean 10.2 (5.2) months; seen every 3 months until diagnosis or end of battery life (14 months)	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	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%)	a) 21/27 = 78% b) none c) 21/27 = 78%

Study name (group)	Index test time	Target condition	Arrhythmia detected	Brady propn a) with TLoC; b) not with TLoC; c) all
Ringqvist 1989 Holter 48h (1)	48 hours	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	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; atrail flutter 1; AF 1 (brady 6%; tachy 6%)	a) 3/4 = 75% b) 4/8 = 50% c) 7/12 = 58%
Rockx 2005 EER (4)	worn until 2 clinical episodes occurred or 1 month elapsed	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	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	a) Loop: 1/1 = 100%; Holter 0 b) none c) Loop: 1/1 = 100%; Holter 0
Rothman 2007 EER (1)	up to 30 days (minimum 25 days)	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	unclear – numbers don't add up between text and table	a) unclear b) unclear c) unclear
Sarasin 2001 EER (4)	mean 6.7 (1.7) days	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	3/113 had arrhythmia (not stated which)	a) unclear b) unclear c) unclear

Study name (group)	Index test time	Target condition	Arrhythmia detected	Brady propn a) with TLoC; b) not with TLoC; c) all
Sarasin 2001 Holter 24h (4)	24 hours	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	9/122 had arrhythmia (not stated which)	a) unclear b) unclear c) unclear
Sarasin 2005 Holter 24h (1)	24 hours	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 or with hypotension; Mobitz 2 2nd degree/complete AV block; VT 30s or more	during TLoC: 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 2003 EER (4)	mean 7 (3) weeks; range 1-10 weeks	symptom/rhythm correlation; recorded (not prespecified): sinus tachycardia (rate not specified); atrial flutter	during TLoC: sinus tachy: 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% b) 0/10 = 0% c) 0/11 = 0%
Seidl 2000 IER pt activated (4)	mean 10.8 (4.3) months; device implanted until syncope/presyncope or patient or investigator wanted to remove it	recorded (not prespecified): brady below 50bpm; AV nodal re-entry tachycardia; SVT; torsades de pointes; frequent ventricular premature beats; mixed brady + venticular 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 non-sustained VT) of 133 patients (i.e. brady 17%, tachy 8%)	a) 22/32 = 69% b) none c) 22/32 = 69%

3.5 Exercise testing for arrhythmia review

3.5.1 Diagnostic Test: exercise test

Study	Participant	Diagnostic tests
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	TLoC population: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test. syncope or presyncope (dizziness ot lightheadedness) Definition of TLoC: syncope or presyncope (dizziness or lightheadedness). Inclusion criteria: patients with syncope or presyncope (dizziness ot 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	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
Colivicchi 2002 non-randomised comparative study; study held in Italy. Setting: Syncope unit. Cardiology/sports science. Funding: not stated	TLoC population: ---. Prior tests: All patients had at least 1 prior test. echo, 24 hour ECG, exercise test, EPS tilt test Definition of 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	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
Doi 2002 diagnostic test accuracy study; study held in Japan. Setting: Department of Internal Medicine. Funding: not stated	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 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: 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	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

3.6 Tilt table for NMS review

3.6.1 Included studies table

Study	Participant	Diagnostic tests
Aerts 1997 case control study; study held in Belgium. Setting: Cardiology. two hospital cardiology departments. 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. 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, overcrowding, 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	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 (n=32) Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope; comparison of classic HUT and HUT-ISO (but only done once)
Aerts 1999 case control study; study held in Belgium. Setting: Cardiology. cardiology departments at 3 hospitals. 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. 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; prodrome of nausea, sweating, visual dimming; precipitating anxiety, 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	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 (n=43) Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope

Study	Participant	Diagnostic tests
Aerts 2005 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. 12-lead ECG, routine laboratory tests, CT, Doppler flow of neck vessels, 24 hour Holter, echo EEG Definition of TLoC: syncope provoked by emotional and orthstatic stress; situational (micturition, defecation, swallowing); prodrome (warmth, nausea, sweating, visual dimming, lightheadedness); symptom relief with recumbence. 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	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
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	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
Almquist 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 isoproterenol. Patient characteristics: age: patients 14 to 80 years; controls 13 tp 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	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

Study	Participant	Diagnostic tests
Aslan 2002 case control study; study held in Turkey. 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. unexplained syncope after CSM, BP, routine biochemical and haematological tests, 12 lead ECG, echo, neurological evaluation, exercise tests, 24 hour Holter, EPS, angiography Definition of TLoC: sudden and transient loss of consciousness and upright posture. Inclusion criteria: unexplained syncope. Exclusion criteria: none. 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) Comorbidities: not stated. Other details: see below Other study comments: 18 controls mean age 45.8 (12) years, no syncope/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	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
Athanasos 2003 case control study; study held in Australia. Setting: Clinical and experimental pharmacology. Funding: not stated	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	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
Bartoletti 1999 RCT; study held in Italy. Setting: Cardiology. cardiology several hospitals. 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. 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	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

Study	Participant	Diagnostic tests
Benchimol 2008 case control study; study held in Brazil. Setting: unclear. University hospital, department not stated. Funding: none	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	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	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 strress 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, dysrhythmia. 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	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	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, lipothymia, cardiopathy or other underlying disease); 1st batch of patients/controls had passive HUT; 2nd batch had HUT-ISO	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	Participant	Diagnostic tests
Del Rosso 1998 case control study; study held in Italy. Setting: Cardiology. Cardiology, internal medicine, Arrhythmology departments at hospitals. 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. 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 Patient 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)	Index test: HUT-GTN: after overnight fast, between 8.30 and 10.30 am; 10 minutes supine; 60 degrees for 20 minutes; if negative, sublingual nitroglycerin 400 microg and 25 more minutes; time: maxumum 55 minutes (n=236) Reference standard: patients versus controls for Target Condition/Outcome: vasovagal 4 syncope
Del Rosso 2002 case control study; study held in Italy. Setting: Syncope unit. syncope units in secondary and tertiary hospitals. 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. 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) yr) + 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	Index test: HUT-GTN: between 8.30 and 10.30 am; supine 10 minutes; 60 degrees for 20 minutes; if negative, sublingual GTN 400 microg and further 15 minutes; time : maximum 45 minutes (n=388) Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope
Doi 2002 diagnostic test accuracy study; study held in Japan. Setting: Department of Internal Medicine. Funding: not stated	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)	Index test: fasting; morning; 10 minutes rest; 80 degrees for 30 minutes; if negative 0.01-0.02microg/kg/min isoproterenol; increased 0.005microg every 5 minutes; total duration 45 minutes; time: maximum 45 minutes (n=44) Reference standard: patients versus controls for Target Condition/Outcome: diagnosis

Study	Participant	Diagnostic tests
Englund 1997 case control study; study held in Sweden. Setting: Hospital several departments. cardiology, medicine. Funding: Swedish Heart and Lung Foundation; Karolinska Institute	TLoC population: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test. patients with bifascicular block and unexplained syncope after extensive invasive and non-invasive EPS investigation; exercise test, echo, 24 hour ambulatory ECG, carotid sinus massage Definition of TLoC: syncope or severe presyncope (lightheadedness plus at least 1 of: partial loss of postural tone, decreased vision, slow response to verbal stimuli, nausea) plus marked hypotension or bradycardia. 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: not stated. Patient characteristics: age: in table not supplied with paper; sex: in table not supplied with paper; All patients with existing heart disease (bifascicular block); TLoC history: not stated Comorbidities: not stated. Other study comments: 25 patients with bifascicular block and unexplained syncope + 25 controls with bifascicular block without syncope or dizzy spells	Index test: after 4 hours fasting; 10 minutes supine; 60 degrees for 45 minutes (Westminster protocol); time: (n=50) Reference standard: patients versus controls for Target Condition/Outcome: vasovagal 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: 71 patients + 27 symptom-free controls (no history of syncope)	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	Participant	Diagnostic tests
Gilligan 1992 case control study; study held in UK. Setting: Cardiology. department of medicine (clinical cardiology). Funding: not stated	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)	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	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, supine and upright carotid sinus massage, 24 hour Holter, 24 hour ambulatory BP (EEG, echo, CT brain an dexercsie 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	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-ISO: 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	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, supine and upright carotid sinus massage, 24 hour Holter, 24 hour ambulatory BP (EEG, echo, CT brain and exercsie 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	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	Participant	Diagnostic tests
Grubb 1991b case control study; study held in USA. Setting: Cardiology. 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 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 details: see below Other study comments: 25 patients + 6 controls (no history of syncope)	Index test: fasting; 80 degrees for 30 minutes; if negative, supine 5 minutes, IV isoproterenol 1microg/min 5 minutes; 80 degrees for 30 minutes; repeated with 2microg/min and 3microg/min; time: maximum duration 150 minutes (n=31) Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope
Grubb 1992b case control study; study held in USA. Setting: Cardiology. electrophysiology laboratory of university hospital. 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. 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	Index test: fasting; HUT 30 minutes at 80 degrees, if negative, 5 minutes supine, isoproterenol 1microg/min and tilt for 30 minutes, repeated at 2microg/min and 3microg/min; time: maximum 135 minutes (n=32) for Target Condition/Outcome: vasovagal syncope: bradycardia and/or hypotension on tilt test associated with LOC
Herrmosillo 2000 case control study; study held in Mexico. Setting: department of electrophysiology and division of clinical research. 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. 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, orthgostatic 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 sycope 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)	Index test: overnight fast; between 9 and 11am; 10 minutes supine; 70 degrees for 30 minutes; if negative, 30 minutes supine; isoproterenol 4microg/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	Participant	Diagnostic tests
Lagi 1992 case control study; study held in Italy. Setting: Hospital several departments. internal medicine and neurology. 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. 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	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
Lazzeri 2000 case control study; study held in Italy. Setting: Hospital several departments. internal medicine 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. unexplained 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 echocardiography. 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 urinalysis 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	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
Micieli 1999 case control study; study held in Italy. Setting: Department of neurology. 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 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	Index test: fasting; 9am; 10 minutes supine; 10 minutes 60 degrees; 10 minutes supine; performed in abseline 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	Participant	Diagnostic tests
Mittal 2004 case control study; study held in USA. Setting: Cardiology. 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	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 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)	Index test: fasting; between 8 and 10am; supine 3 minutes; 60 degrees and immediately IV adenosine 150microg/kg for 3 minutes, if negative, supine 5 minutes; retilted 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
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)	Index test: postabsorptive state; between 8.30am and noon; supine 15 minutes; 60 degrees for 15 minutes; if negative, isoproterenol 1microg/min increased every 5 minutes until decrease in sinus cycle length of 25% (max 3microg/min) to maximum of 15 minutes; time: maximum duration 45 minutes (n=150) Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope
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)	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

Study	Participant	Diagnostic tests
Oraii 1999 RCT; study held in Iran. 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. unexplained syncope after BP, carotid sinus massage, routine laboratory tests, 12lead ECG, echo, 24 hour Holter (and exercise test, EPS, angiography or CT if indicated) Definition of TLoC: syncope: transient loss of consciousness with spontaneous recovery; presyncope: intense dizziness plus 1 or more of: decreased vision, slow response to verbal stimuli, partial loss of tone, nausea, vomiting. Inclusion criteria: outpatients with syncope referred to Shahid Rajaii Heart Hospital. Exclusion criteria: not stated. Patient characteristics: age: patients: mean 34 (11.2) years; range 17 to 56 years; controls: 29 (9.5), 17 to 56 years; sex: patients: 60% female; controls 50% female; Unclear/not stated with existing heart disease (not stated); TLoC history: mean 3.3 (3.8), range 1 to 20 episodes (not stated over what time period) Comorbidities: not stated. Other study comments: 65 patients + 20 controls (no history of syncope or presyncope; no abnormalities on examination, ECG or echo). All had 2 tests on successive days, in random order	Index test: overnight fast; morning; supine 15 minutes; 70 degrees for 45 minutes; if negative, isoprenaline 1microg/min and tilt to 70 degrees for 10 minutes; if negative, dose increased by 1microg/min at 10 minute intervals to max 4microg/min or heart rate>150bpm; time: maximun 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, 400microg sublingual GTN and 70 degrees for 20 minutes; time: maximum duration 80 minutes (n=85). 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 syncopal symptoms)	Index test: supine 20 minutes; 60 degrees 40 minutes; time: maximum duration 60 minutes (n=303) Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope

Study	Participant	Diagnostic tests
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	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	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

Study	Participant	Diagnostic tests
Podoleanu 2004 case control study; study held in Romania. Setting: medical clinic. 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 origin after neurological assessment, routine laboratory tests, supine and orthostatic BP, 12 lead ECG, bedside and upright carotid sinus massage, echo Definition of TLoC: transient self-limited loss of consciousnessrapid onset, duration seconds to a few minutes, loss of postural tone, spontaneous and complete recovery; due to transient global cerebral hypoperfusion; presyncope: sensation of near-fainting. Inclusion criteria: syncope of unknown origin. Exclusion criteria: medication. Patient characteristics: age: patients: mean age 38.5 (15.7) years; controls: 26.0 (6.5) years; sex: patients: 51% female; controls: 56% female; Unclear/not stated with existing heart disease (not stated); TLoC history: mean 2.3 (1.3) episodes, range 1 to 10 episodes; mean duration of symptoms 3.01 (1.9) months Comorbidities: not stated. Other study comments: 72 patients + 16 healthy controls (no history of syncope or presyncope)	Index test: HUT-GTN: overnight fast; morning;supine 15 minutes; 70 degrees for 30 min; ;if negative, 400microg nitroglycerin sublingually and tilt for 20 minutes; time: maximum duration 65 minutes (n=88) Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope
Prakash 2004 case control study; study held in India. Setting: Hospital several departments. physiology, neurology, medicine, paediatrics, cardiology. Funding: Central Council for Research in Yoga and Naturopathy, New Delhi	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	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: vasovagal syncope
Shen 1999 case control study; study held in USA. Setting: Hospital several departments. cardiovascular diseases, internal medicine. Funding: National Institutes of Health	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 comprehnesive 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 abnormailities, 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)	Index test: fasting 6-10 hours; supine 10 minutes; 70 degrees for 45 minutes; 10-20 minutes supine; isoproterenol 0.05microg/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: vasovagal syncope

Study	Participant	Diagnostic tests
Theodorakis 2000 non-randomised comparative study; study held in Greece. Setting: 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. neurocardiogenic syncope; 12 lead ECG, echo (EPS, EEG, CT when needed) Definition of 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 struc tural heart disease). All had 2 tests, 24 hours apart	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
Theodorakis 2003 RCT; study held in Greece. Setting: 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. neurocardiogenic syncope; 12 lead ECG, echo (EPS, EEG, CT when needed) Definition of 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	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=180) 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=180). for Target Condition/Outcome: vasovagal syncope
Zeng 2001 RCT; study held in China. Setting: Cardiology. Funding: Third Military Medical University of PR China	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 of 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 year; 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 outpatients, matched on age, gender and weight); all had both tests with 1-14 day interval	Index test: HUT-GTN: conventional: fasting; 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

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 cardioinbitory 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 cardioinhibition plus the mixed response category.

Study name	Definition of mixed	CI	Vaso-depressor	Mixed	not separated out	n=No. of cases; % of cases with CI
Aerts 1997	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	0	3 (11%)	25 (89%) including 7 (25%) asystole (4-15s)		n=32 altogether; 28 positive 7 definitely had asystole (22% of cases)
Aerts 1999	decrease heart rate of 20bpm or more and decrease of systolic BP 20mmHg or more	4 (21%) all asystole (8-41s)	4 (21%)	11 (58%)		n=20 ; 19 positive 4 CI (20%)
Aerts 2005	decrease heart rate of 20bpm or more and decrease of systolic BP 20mmHg or more	3 (8%) all asystole (7-20s)	8 (22%)	26 (70%)		n=43 ; 37 positive 3 CI (7%)
Aerts 2005b	decrease heart rate of 20bpm or more and decrease of systolic BP 20mmHg or more	3 (10%) all asystole (4-28s)	2 (6%)	26 (84%)		n=38; 31 positive 3 CI (8%)
Almquist 1989	Profound bradycardia & hypotension			15 patients positive, all mixed response		n=24; 15 positives no CI / asystole (0%)
Aslan 2002	VASIS	2 (25%)	2 (25%)	4 (50%)		n=43; 8 positives 2 CI (5%)
Athanasos 2003	Hypotension and bradycardia			6 (100%)		n=13 none CI/asystole
Bartoletti 1999	VASIS	conventional: 8 (19%) accelerated: 4 (14%)	conventional: 4 (9%) accelerated: 0	conventional: 31 (72%) accelerated: 25 (86%)		n=84 conventional: 8/84 CI (10%) accelerated: 4/84 (5%)
Benchi-mol 2008	not defined				169/259 tests positive	n=259

Study name	Definition of mixed	CI	Vaso-depressor	Mixed	not separated out	n=No. of cases; % of cases with CI
Brignole 1991	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)				passive: 32/100 positive (including 7 asystole); isoproterenol: 11 additional patients positive (no asystole)	n=100; 43 positives CI or mixed in 17 with passive test + 6 with isoproterenol (23 overall out of; 23%)
Brignole 2000	mixed included hypotension without pause over 3s	29 (28%)			74 (72%) vasodepressor or mixed	n=175; 103 positives 29 CI (17%)
Brooks 1993	only vasodepressor response (hypotension and relative bradycardia) counted as positive test		30 (100%)			0%
Carlioz 1997	hypotension and bradycardia, or asystole 3s or more	passive: 4 (40%) isoproterenol: not stated	passive: 1 (10%) isoproterenol: not stated	passive: 5 (50%) isoproterenol: 19/24 positives (79%)		n=48; 10 positive passive: CI 4 (8%); with mixed (might not have had asystole) 9 (19%) isoproterenol: NS
Del Rosso 1998	VASIS	passive: 11 (50%) GTN: 38 (32%)	passive: 1 (5%) GTN: 11 (9%)	passive: 10 (45%) GTN: 70 (59%)		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
Del Rosso 2002	VASIS	64 (37%)	18 (10%)	92 (53%)		n=324; 174 positives CI 64 (20%) of whom 49 had asystole (15%)
Doi 2002	Sutton; mixed = bradycardia <40bpm and marked hypotension (systolic BP below 80mmHg)	1 (5%)	7 (35%)	12 (60%)		n=26; 20 positive; exercise-unrelated syncope group CI 1 (4%)

Study name	Definition of mixed	CI	Vaso-depressor	Mixed	not separated out	n=No. of cases; % of cases with CI
Fitz-patrick 1991	Category not defined (positive test = “vasovagal syncope”)	40 (78%) bradycardia below 60bpm	13 (22%) profound hypotension but rate did not fall below 60bpm	0		n=71; 53 positives CI 40 (56%)
Fouad 1993	Hypotension + bradycardia	19 (76%); heart rate below 50bpm in 5 and 50-65bpm in 7; complete asystole not observed in any other subjects	6 (24%); BP reduced significantly			n=44; 25 positives CI 19 (43%)
Gielerak 2002	VASIS	1 (5%)	10 (43%)	12 (52%)		n=40; 23 positives CI 1 (3%)
Graham 2001	not defined				passive: 31/88 positive isoprenaline: 10/48 positive GTN: 23/48 positive	n=88 had passive tilt n=48 (passive tilt negative) had GTN and isoprenaline tilt tests 1 week apart; CI not stated
Grubb 1991b	bradycardia and hypotension				passive: 6/25 positive isoproterenol: 9/19 (passive negative)	n=25 had passive tilt n=19 passive negative had isoproterenol tilt CI not stated
Grubb 1992b	bradycardia (abrupt fall in heart rate) and hypotension (abrupt fall in BP)	isoproterenol: 0	isoproterenol: 4 (57%)	isoproterenol: 3 (43%)	passive: 9/25 (including 2 asystole [8s and 14s]) isoproterenol: 7/16 (passive negative)	n=25 had passive tilt CI not stated n=16 passive negative had isoproterenol tilt CI/mixed 3 (19%)

Study name	Definition of mixed	CI	Vaso-depressor	Mixed	not separated out	n=No. of cases; % of cases with CI
Hermo-sillo 2000	passive defined as positive if hypotension or bradycardia or both; with drugs, positive only if both hypotension and bradycardia (i.e. all mixed)	isoproterenol: 0 ISDN: 0	isoproterenol: 0 ISDN: 0	isoproterenol: 36 (100%) ISDN: 49 (100%)	passive: 50/120 positive	n=120 had passive tilt CI not stated n=70 passive negative had isoprenaline and ISDN tilt CI 0% by definition (not recognised as a positive test); all positive tests mixed
Lagi 1992	not defined	asystole + symptoms 2 (6%)			35/72 positive	n=72; 35 positives CI 2 (3%)
Lazzeri 2000	syncope or presyncope plus systolic BP below 80mmHg and heart rate below 40bpm	12 (52%)	11 (48%)	0		n=44; 23 positives; CI 12 (27%)
Micieli 1999	positive test defined as hypotension with or without bradycardia (i.e. not CI)	0 by definition	9 (50%) hypotension only	9 (50%) bradycardia plus hypotension		n=23; 18 positives; mixed 9 (39%) but not necessarily asystole (not mentioned)
Mittal 2004	positive response defined as bradycardia and hypotension				23/129 positive	n=129 CI not stated
Morillo 1995	hypotension, systolic BP 70mmHg or below and heart rate 40bpm or below	25 (35%) of whom 5 had asystole over 3s (4-45s)	17 (23%)	31 (42%)	passive: 30/120 positive; isoproterenol further 43 patients	n=120 had passive tilt n=90 passive negative had isoproterenol tilt CI 25 (18%)
Mussi 2001	VASIS	passive: 3 (12%) GTN: 6 (11%)	passive: 13 (50%) GTN: 39 (74%)	passive: 10 (38%) GTN: 8 (15%)	passive: 26/128 positive; GTN: further 53 positive	n=128 had passive test; 26 positive CI 3 (2%) n=102 passive negative had GTN test; overall 9 CI (7%)

Study name	Definition of mixed	CI	Vaso-depressor	Mixed	not separated out	n=No. of cases; % of cases with CI
Oraii 1999	VASIS	passive: 6 (30%) isoprenaline: 4 (15%) GTN: 9 (36%)	passive: 1 (5%) isoprenaline: 2 (8%) GTN: 3 (12%)	passive: 13 (65%) isoprenaline: 20 (77%) GTN: 13 (52%)		n=65 had passive test; 20 positives; CI 6 (9%) 45 passive negative had drug tests with GTN or isoprenaline (two successive days in random order) CI isoprenaline 4 (15%) and GTN 9 (36%)
Oribe 1997	positive test defined as hypotension plus bradycardia plus symptoms (i.e. all mixed type)			74 (100%)	74/201 positive	n=201 100% mixed type (by definition); asystole not stated
Parry 2008	VASIS	passive: 0 GTN: 8 (15%)	passive: 12 (71%) GTN: 28 (52%)	passive: 5 (29%) GTN: 18 (33%)	passive: 17/149; GTN: 54/149	n=149 had passive tilt (CI none) and GTN tilt (CI: 8 [9%]) 1 week apart in random order
Podolea nu 2004	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	overall 8 (14%)	overall 22 (38%)	overall 28 (48%)	passive positive in 25; GTN positive in 33	n=72 had passive test if passive negative, 47 had GTN test. Overall CI 8 (11%)
Prakash 2004	hypotension and bradycardia and symptoms	6 CI with asystole over 3s (26%)	7 (30%)	10 (44%)	23/86 positive	n=86; (43 syncope + 43 presyncope) ; 23 positives CI 6 (7%)
Shen 1999	syncope or presyncope and bradycardia (decrease in heart rate at least 20% from baseline) and hypotension decrease in systolic BP 30mmHg or more				passive: 35/111; isoproterenol: 62/111 positive	n=111 CI not stated

Study name	Definition of mixed	CI	Vaso-depressor	Mixed	not separated out	n=No. of cases; % of cases with CI
Theodorakis 2000	Hypotension followed by bradycardia	passive/ isoproterenol: 8 (28%) clomipramine: 9 (20%)	passive/ isoproterenol: 8 (28%) clomipramine: 13 (30%)	passive/ isoproterenol: 13 (45%) clomipramine: 22 (50%)	passive: 19 positive; isoproterenol: 10 further positive; clomipramine 44 positive	n=55 had passive test: if negative, isoproterenol infused CI 8 (15%); and clomipramine tests CI 9 (16%) 24 hours apart
Theodorakis 2003	Hypotension followed by bradycardia	isoproterenol: 14 (27%) clomipramine: 21 (20%)	isoproterenol: 12 (23%) clomipramine: 41 (39%)	isoproterenol: 26 (50%) clomipramine: 43 (41%)	passive: 34 positive; isoproterenol: 18 further positive; clomipramine 105 positive	n=126 passive and if negative isoproterenol: CI 14 (11%) and clomipramine test CI 21 (17%) in random order 24 hours apart
Zeng 2001	hypotension (decrease in systolic BP over 50%) and bradycardia (decrease in heart rate over 30%)				conventional GTN: 23/37 single stage GTN: 24/37 positive	n=37 had single stage GTN test and conventional multistage test in random order 1-14 days apart

3.7 Carotid sinus massage for NMS review

Study	Participant	Diagnostic tests
Benchimol 2008 case control study; study held in Brazil. Setting: unclear. University hospital, department not stated. Funding: none	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. 2nd part: CSM at 60 degrees patients versus controls diagnostic test accuracy	Index test: carotid sinus massage at 60 degrees of tilt; time: 5 seconds (n=259) Reference standard: patients versus controls 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).
Brignole 1991 case control study; study held in Italy. Setting: Cardiology. referrerd from ER or inpatient service or ambulatory program. Funding: not stated	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 strress test, EEG, Doppler, CT, cardiac catheter, EP, arteriography) Definition of TLoC: not defined. Inclusion criteria: syncope of uncertain origin. Exclusion criteria: postural hypotension, conversion reaction, seizure, TIA, subclavian steal, drug-induced syncope, aortic stenosis, pulmonary HT, hypertrophic cardiomyopathy, dysrhythmia. 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 Comorbidities: not stated. Other study comments: 100 patients+ 25 healthy controls without syncope or presyncope matched on age and gender	Index test: CSM left and right sides supine and standing for 10 seconds; time: 10 seconds (n=125) Reference standard: patients versus controls for Target Condition/Outcome: vasovagal syncope
Freitas 2004 case control study; study held in Portugal. Setting: Cardiology. Centre for study of autonomic function. Funding: not stated	TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: Unclear or Not stated. patients with unexplained syncope, presyncope or falls aged over 42 years Definition of TLoC: not defined. Inclusion criteria: 380 patients with unexplained syncope, presyncope or falls aged over 42 years plus 108 controls (healthy) aged over 40. Exclusion criteria: age under 42 years; contraindication to CSM (e.g. carotid bruits or carotid ctenosis of over 70% from previous echo Doppler or history of stroke or TIA). Patient characteristics: age: not stated; sex: not stated; Unclear/not stated with existing heart disease (not stated); history of TLoC: not stated Comorbidities: not stated. Other details: patients with unexplained syncope, presyncope or falls aged over 42 years	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) Reference standard: patients versus controls for Target Condition/Outcome: carotid sinus hgypersensitivity

Study	Participant	Diagnostic tests
Kumar 2003 case control study; study held in UK. Setting: Blackout clinic. falls clinic in clinical gerontology research unit. Funding: not stated	TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had 1 prior test. referred to falls clinic by hospital consultant or GP; history, examination, postural BP, routine blood tests, 12 lead ECG, 24 hour Holter where indicated Definition of TLoC: syncope: falls associated with definite loss of consciousness. Inclusion criteria: 130 patients with syncope plus 44 asymptomatic controls aged 60 or more. Exclusion criteria: significant aortic stenosis, recent myocardial infarction, cerebrovascular events, significant carotis artery disease. Patient characteristics: age: patients: mean 78.8 years (range 60-96 years); controls: mean 71.3 years (range 63-86 years); sex: patients: 64% female; controls 36% female; Unclear/not stated with existing heart disease (not stated); TLoC history: not stated. Comorbidities: not stated. Other details: patients aged over 60 years referred to falls clinic by hospital consultant or GP	Index test: light breakfast, usual medication; test in the morning; supine 5 minutes, CSM for 5 seconds separately each side; 70 degree tilt; repeat CSM each side; time: 5 seconds each side supine and at 70 degrees (n=174) Reference standard: patients versus controls for Target Condition/Outcome: Carotid sinus syndrome (cardioinhibitory: asystole >3s; vasodepressor: fall in systolic BP >50mmHg; or mixed if both)
Morillo 1999 case control study; study held in USA. Setting: Hospital several departments. department of medicine; Veterans Affairs Centre; Department of Cardiology. Funding: National Institutes of Health; Colombian Institute for the Advancement of Science and Technology	TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had 1 prior test. recurrent unexplained syncope; 12 lead ECG; 24-48 hour ambulatory ECG, echo, non-CSS syncope pts also had EPS Definition of TLoC: not defined. Inclusion criteria: 2 or more syncopal episodes in last 6 months. Exclusion criteria: not stated. Patient characteristics: age: pts: mean 63 (12; range 46-85); controls 65 (14; 48-89); other syncope 59 (12; 31-74); sex: pt: 73% male; cont: 83% male; non-CSS: 56% male; some patients with existing heart disease (pts 29% CAD; cont 10%; non-CSS syncope 16%); TLoC history: mean 6 (3) episodes Comorbidities: hypertension: pts 43%; cont 26%; non-CSS syncope 38%. Other details: 80 patients with recurrent unexplained syncope; 30 age-matched controls (no syncope or presyncope) and 16 patients with syncope not related to CSS	Index test: post-absorptive state, between 8.30 and noon; 15 minutes supine; CSM 5 seconds supine repeated at least twice each side, 5 minutes rest; and after 2 minutes at 60 degrees; time: around 25 minutes (n=126) Reference standard: a) asymptomatic controls; b) controls with syncope not related to CSS for Target Condition/Outcome: vasodepressor: fall in systolic BP of 50mmHg or more; cardioinhibitory: asystole 3 s; mixed: bradycardia 40 bpm plus fall in BP; associated with syncope or presyncope that resembled the clinical presentation
Parry 2000 case control study; study held in UK. Setting: Cardiology. Cardiovascular investigation unit and institute for the health of the elderly. Funding: British Heart Foundation; National Cardiovascular Research and Development grant	TLoC population: patients with suspected neurally mediated syncope but 12-lead ECG normal. Prior tests: All patients had 1 prior test. patients with unexplained syncope aged over 55 years, from A&E or syncope facility; prior tests not stated Definition of TLoC: syncope: loss of consciousness with loss of postural tone and collapse. Inclusion criteria: patients with unexplained syncope over 55 years; controls with no history of falls, dizziness or syncope and no cardiovascular comorbidity. (cardioinhibitory or mixed subtypes) Exclusion criteria: contraindications to CSM (carotid bruits, cerebrovascular accident or myocardial infarction in previous 3 months, history of ventricular arrhythmia); cognitive impairment. Patient characteristics: age: not stated; sex: not stated; Unclear/not stated with existing heart disease (not stated); TLoC history: not stated Comorbidities: not stated. Other details: 1149 patients with unexplained syncope aged over 55 years, from A&E or syncope facility plus 25 healthy age-matched controls	Index test: supine CSM for 5 seconds on right side; repeated on left after haemodynamic re-equilibration; repeated after 1 minute at 70 degrees tilt; time: 5 seconds each side supine and tilted (n=1174) Reference standard: patients versus controls for Target Condition/Outcome: Carotid sinus hypersensitivity with asystole over 3 s

3.8 Comparison of different tests

3.8.1 Implantable event recorder versus usual care

Study	Participant	Diagnostic tests
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	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 syncopes 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 1.5 TLOC per year Comorbidities: not stated. Other details: adults presenting with syncope Other study comments: Eastbourne Syncope Assessment Study (EaSyAS)	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 pasues 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)
Krahn 2001 RCT; study held in Canada. Setting: Cardiology. Arrhythmia service. Funding: Heart and Stroke Foundation of Ontario	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 & if tilt & EP negative, immediately offered ILR (diff follow up times)	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

3.8.2 External event recorder versus 24-hour Holter monitoring

Study	Participant	Diagnostic tests
Krahn 2000 non-randomised comparative study; study held in Canada. Setting: Cardiology. Funding: Ontario Heart and Stroke Foundation	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). Inclusion criteria: retrospective review: recordings for assessment of syncope or presyncope. Exclusion criteria: none. 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. Other study comments: case series; retrospective	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	Participant	Diagnostic tests
Rockx 2005 RCT; study held in Canada. Setting: Cardiology. patients referred from community or ED. Funding: Physician Services Inc, Toronto	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)	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

3.8.4 Exercise test versus 24-hour Holter monitoring

Study	Participant	Diagnostic tests
Boudoulas 1979 non-randomised comparative study; study held in USA. Setting: Cardiology. Funding: National Institutes of Health and Central Ohio Heart Chapter fo the American Heart Association	TLoC population: patients with a suspected cardiac cause. Prior tests: All patients had at least 1 prior test. syncope or presyncope (dizziness ot lightheadedness) Definition of TLoC: syncope or presyncope (dizziness ot 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 lightheadednes)s Other study comments: 2 tests within 1 wee k	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 SVT (170 bpm); high grade AV block; frequent ventricular premature contractions, effective rate less than 40 bpm; repetitive pairs PVCs; VT

3.8.5 Exercise test versus tilt table

Colivicchi 2002 non-randomised comparative study; study held in Italy. Setting: Syncope unit. Cardiology/sports science. Funding: not stated	TLoC population: ---. Prior tests: All patients had at least 1 prior test. echo, 24 hour ECG, exercise test, EPS tilt test Definition of 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	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

3.8.6 48-hour Holter monitoring versus tilt table

Study	Participant	Diagnostic tests
Fitchet 2003 case series; study held in UK. Setting: Cardiology. cardiologist-run syncope clinic or cardiologists of 2 tertiary referral centres. Funding: not stated	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% imparied 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 study comments: case series	Index test: Holter monitor (no further details); time: 48 hours (n=118) Comparator test: fasting 2 to 4 hours; supine 20 min; 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 v ent ectopics / bigeminy / trigeminy/couplets; 1st degree heart block (not prespecified)

3.8.7 24-hour Holter monitoring versus electrophysiological study

Study	Participant	Diagnostic tests
Boudoulas 1983 non-randomised comparative study; study held in USA. Setting: Cardiology. cardiology. Funding: not stated	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	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	Participant	Diagnostic tests
Rothman 2007 RCT; study held in USA. Setting: Cardiology. Multicentre. Funding: Cardionet Inc	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	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

Study	Participant	Diagnostic tests
Gatzoulis 2003 case series; study held in Greece. Setting: 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. unexplained syncope, neurological assessment, standard laboratory tests, BP, 12 lead ECG, bedside and upright carotid sinus massage, 24 hour Holter, echo (exercsie test, EPS, cardiac catheterisation, EEG, Doppler, CT or MRI brain as indicated) 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 Other study comments: case series; followed up 24 (7) months	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; 3microg/min for 10 minutes; 5 minutes supine; time: maximum 75 minutes (n=123) for Target Condition/Outcome: vasovagal syncope

3.10 Carotid sinus massage - cardioinhibitory response review

Study	Participant	Diagnostic tests
Lagi 1991 diagnostic test accuracy study; study held in Italy. Setting: internal medicine. 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. 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 Definition of TLoC: . 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 recvoery 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 Other study comments: case series; mean follow up 11 (8) months	Index test: massage to each right and left carotid sinus for about 5 seconds with the neck hyperextended, supine; (n=56) 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

3.11 Ambulatory ECG - cardioinhibitory response review

Study	Participant	Diagnostic tests
Brignole 2006b non-randomised comparative study; study held in Multinational. Setting: Cardiology. multinational. Funding: Medtronic Europe	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	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=343). 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	Participants	interventions
Ammirati 2001 (SYDIT) RCT; study held in Italy. Funding: None stated	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.	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 40bpm 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	Participants	interventions
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.	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 x bp < 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.	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 <60bpm 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.	Intervention 1: Dual chamber pacemaker (DDD) with rate drop response pacing: drop 5 to 15 bpm over 20-40 beats, drop rate 60/min and intervention rate of 100/min for 2 min] + usual care (none required); time: mean 112days (n=27) Comparator: usual care medical or nonmedical at discretion of physician (none required); time: mean 54 days (n=27).

4.2 Pacemakers for CSM

Study	Participants	Interventions
Brignole 1992c RCT; study held in Italy. Funding: not stated	TLoC population: selected patients with TLoC of mixed known causes. Prior tests: All patients had at least 1 prior test. "severe carotid sinus syndrome"; 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 driugs 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 (<50bpm); intermittent mild brady <60bpm with abnormal EPS; AV block; HV interval 70ms or more. Definition of TLoC: syncope: sudden unexplained loss of consciousness.	Intervention 1: 18 patients received a ventricular inhibited (VVI) pacemaker, while 14 had a dual chamber (DDD) pacemaker; time: 34 months (SD 10) (n=32) 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).
Claesson 2007 RCT; study held in Sweden. Funding: Skaraborg Institute for Research and Development	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.	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).

Study	Participants	Interventions
Kenny 2001 RCT; study held in UK. Funding: National Health Service Cardiovascular research and development programme; research into ageing, educational grant from Medtronic	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 12% had ischaemic heart disease; patients over 50 years attending A&E with non-accidental fall, with cardioinhibitory or mixed CSH Patient 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.	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=87) Comparator: usual care; diaries kept by patients (92% completion); time: 12 months (n=88).