APPENDIX D2 – Methodological quality

1 Initial assessment stage

1.1 Initial symptoms for diagnosis review - QUADAS

1.1.1 Diagnostic Test: Initial symptoms

Study	Representative? Selection criteria	Index test / reference standard well described? Reference standard OK? Independent of index test?	Verification bias (partial and differential)	Same Clinical Data? Intermediate tests reported? Withdrawals?	Overall Assessment
Alboni 2001	Representative? unclear; referrals to syncope unit from the ED, inpatients and outpatients Selection Criteria Described? no; didn't say how referrals decided upon	Is index test well described? unclear Is ref std well described? yes Is ref std OK? unclear; consisted of a number of tests; based on suspected cause Is time between tests short enough? yes Is ref standard independent? no; index test part of ref std	All receive ref std? unclear; if the initial evaluation gave a definite diagnosis, further tests were said to be interrupted, but no numbers given; 15 (4%) protocol violations Same ref std? no; received different tests depending on suspected cause.	Same clinical data available? yes Uninterpretable/ Intermediate reported? no Withdrawals explained? yes	-
del Rosso 2008	Representative? no; syncope only, not epileptic seizures or other forms of TLoC Selection Criteria Described? no	Is index test well described? no Is ref std well described? no Is ref std OK? yes Is time between tests short enough? unclear Is ref standard independent? no; initial ECG was part of reference standard	All receive ref std? no; about 95% Same ref std? no.	Same clinical data available? yes Uninterpretable/ Intermediate reported? unclear; data not available for 5% of patients Withdrawals explained? yes	-
Graf 2008	Representative? no; selected patients referred for unexplained syncope Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? no; ECG part of reference standard; but symptoms/history were not	All receive ref std? yes; whole Same ref std? no; varied according to previous tests/history.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? N/A	-

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessement
Sarasin 2003	Representative? no; patients with definite cause of syncope excluded Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes; yes arrhythmias in presence of syncope or near syncope Is time between tests short enough? unclear; not stated, but probably fairly soon Is ref standard independent? yes; 12-lead ECG apparently not included in reference	All receive ref std? yes Same ref std? unclear; reference standard tests were modified according to the suspected diagnosis, but unclear on what this was based.	Same clinical data available? yes Uninterpretable/ Intermediate reported? no Withdrawals explained? yes; no withdrawals	+
Sheldon 2002	Representative? no; tertiary care and acute care settings; selected patients with known diagnosis, pseudoseizures excluded; GDG regarded this as unacceptable Selection Criteria Described? unclear; unclear when patients had their TLoC	Is index test well described? yes Is ref std well described? yes Is ref std OK? unclear; EEG not sufficient for diagnosing seizures; GDG regarded this as unacceptable Is time between tests short enough? unclear; unclear when patients had diagnoses Is ref standard independent? yes	All receive ref std? yes Same ref std? yes; reference standard carried out first.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? yes	-
Sheldon 2006	Representative? no; tertiary care and acute care settings; selected patients with known diagnosis; GDG regarded this as unacceptable Selection Criteria Described? unclear; unclear when patients had their TLoC	Is index test well described? yes Is ref std well described? yes Is ref std OK? no; EEG not sufficient; GDG regarded this as unacceptable Is time between tests short enough? unclear; unclear when patients had diagnoses Is ref standard independent? yes	All receive ref std? yes Same ref std? yes; reference standard carried out first.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? yes	-

1.2   Decision rules for diagnosis review - QUADAS

1.2.1   Diagnostic Test: ESC guidelines

Study	*Representative? Selection criteria described?*	*Are index test and reference standard well described?* *Is Reference standard OK? and independent of index test?*	*Verification bias (partial and differential)*	*Same Clinical Data?* *Intermediate tests reported? Withdrawals explained?*	*Overall Assessment*
van Dijk 2008	Representative? no; combination of ED and referrals, but study population contained more males and middle aged patients than found in typical TLoC population Selection Criteria Described? yes	Is index test well described? yes; but included reference to other work (ESC guidelines) Is ref std well described? yes; a bit vague in places, but ok Is ref std OK? yes Is time between tests short enough? yes; follow up of 2 years considered OK by GDG Is ref standard independent? yes	All receive ref std? yes Same ref std? no; some patients received further testing which informed ref std; those with a certain diagnosis only had follow up.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? yes; 40 died and 5 lost to follow up; assumed not included in results	+

1.2.2   Diagnostic Test: Initial evaluation based on ACEP guidelines

Elseber 2005	Representative? yes Selection Criteria Described? yes; yes, but retrospective study from patient records	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? unclear; interval uncertain Is ref standard independent? no; part of index test (ECG) was the reference standard	All receive ref std? yes Same ref std? unclear; not stated which tests carried out when.	Same clinical data available? unclear; retrospective study Uninterpretable/ Intermediate reported? no Withdrawals explained? yes; only 90% had ECG	-

1.2.3 Diagnostic Test: Initial symptoms decision rule

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessement
Graf 2008	Representative? no; selected patients referred for unexplained syncope Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? no; ECG part of reference standard; but symptoms/history were not	All receive ref std? yes; whole Same ref std? no; varied according to previous tests/history.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? N/A	-
Sarasin 2003	Representative? no; patients with definite cause of syncope excluded Selection Criteria Described? yes	Is index test well described? no; Must have been applied retrospectively - model developed after validation study finished Is ref std well described? yes Is ref std OK? yes; yes arrhythmias in presence of syncope or near syncope Is time between tests short enough? unclear; not stated, but probably fairly soon	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? no Withdrawals explained? yes; no withdrawals	-
Sheldon 2002	Representative? no; tertiary care and acute care settings; selected patients with known diagnosis, pseudoseizures excluded; GDG regarded this as unacceptable Selection Criteria Described? unclear; unclear when patients had their TLoC	Is index test well described? yes Is ref std well described? yes Is ref std OK? no; EEG not sufficient for seizure diagnosis; GDG regarded this as unacceptable Is time between tests short enough? unclear; unclear when patients had diagnoses Is ref standard independent? yes	All receive ref std? yes Same ref std? yes; reference standard carried out first.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? yes	-
Sheldon 2006	Representative? no; tertiary care and acute care settings; selected patients with known diagnosis; GDG regarded this as unacceptable Selection Criteria Described? unclear; unclear when patients had their TLoC	Is index test well described? yes Is ref std well described? yes Is ref std OK? no; tilt table test positive; GDG regarded this as unacceptable Is time between tests short enough? unclear; unclear when patients had diagnoses Is ref standard independent? yes	All receive ref std? yes Same ref std? yes; reference standard carried out first.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? yes	-

1.3 Initial symptoms for risk stratification (death) review - QUADAS

1.3.1 Diagnostic Test: Initial symptoms

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessment
Colivicchi 2003	Representative? yes Selection Criteria Described? no	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes; only all-cause deaths after 12 months; GDG considered this acceptable Is time between tests short enough? yes; within 12 months; GDG considered this acceptable Is ref standard independent? Yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? yes; none	+

1.4 Initial symptoms for risk stratification review - QUADAS

1.4.1 Diagnostic Test: Initial symptoms

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessment
Birnbaum 2008	Representative? no; included large proportion of non-white people; syncope and near syncope; excluded seizures Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes; but complete predictor data and complete follow up data missing for only 2 and 3% respectively Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? yes	+
Grossman 2007	Representative? yes; TLoC, but seizures excluded Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes; structured follow up Is time between tests short enough? unclear; up to 30 days between Is ref standard independent? yes; different assessors	All receive ref std? yes; follow up available for 81%; only these reported Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? no; follow up available for 81%; only these reported Withdrawals explained? yes; rates of adverse events in ED and hospital	+
Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessment

Hing 2005	Representative? no; patients only recruited if investigators present (22%); excludes seizures Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? unclear Is ref std OK? no; follow up predominantly medical records and reliance on patient account; only limited input from HCPs Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? no; but only 5% loss to follow up and 6% excluded because no troponin 4h results Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? no —
Quinn 2004	Representative? no; syncope and near syncope (latter not defined); seizures excluded; single hospital; age range 10 to 102 years (mean 62) Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? unclear; unclear if study nurse was independent of ECG Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? yes +
Reed 2007 (ROSE pilot)	Representative? no; 62% patients missed (younger); study gp skewed towards more serious risk; GDG considered this to be unacceptable Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? unclear; 3 months Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? yes —
Sun 2007	Representative? yes; only during day hours recruited (76%); syncope and near syncope, excludes seizures and people with confusion Selection Criteria Described? yes	Is index test well described? yes; on website Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? no; 14/477 had no follow up data; for index test:153 (32%) did not have haematocrit testing; 7 did not have shortness of breath indicator data; 6 did not have history of CHF data; 33 (7%) did not have an ECG Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes; for 27 (6%) patients inpatient/outpatient data used rather than phone follow up Withdrawals explained? yes +

1.5 Decision rules for risk stratification (death) review -- QUADAS

1.5.1 Diagnostic Test: EGSYS score

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessment
del Rosso 2008	Representative? no; syncope only, not epileptic seizures or other forms of TLoC Selection Criteria Described? no	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes; death as target condition Is time between tests short enough? yes Is ref standard independent? Yes	All receive ref std? no; 76% follow up Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? unclear Withdrawals explained? yes	−

1.5.2 Diagnostic Test: Evaluation based on ACP guidelines

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessment
Crane 2002	Representative? yes Selection Criteria Described? no; yes, but retrospective study from patient records	Is index test well described? no; However, 36% patients did not receive an ECG in ED and 81% did not have postural bp measured, so other clinical data on their record was used. Not necessarily important for high risk group as not one of criteria. Is ref std well described? yes Is ref std OK? yes; death only	All receive ref std? no; Follow up for 90% Same ref std? yes.	Same clinical data available? unclear; retrospective study Uninterpretable/ Intermediate reported? yes; Kaplan Meier plots Withdrawals explained? yes	−

1.5.3 Diagnostic Test: OESIL score

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessment
Colivicchi 2003	Representative? yes Selection Criteria Described? no	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes; only all-cause deaths after 12 months; GDG considered this acceptable Is time between tests short enough? yes; within 12 months; GDG considered this acceptable Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? yes; none	+

1.5.4 Diagnostic Test: San Francisco Syncope Rule

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessment
Quinn 2008	Representative? yes Selection Criteria Described? yes	Is index test well described? no Is ref std well described? yes Is ref std OK? unclear; although not determined if people were alive, only if they had died Is time between tests short enough? yes Is ref standard independent? Yes	All receive ref std? unclear; not determined if people were alive, only if they had died Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? no	**+**

1.6 Decision rules for risk stratification review - QUADAS

1.6.1 Diagnostic Test: Boston Syncope Criteria

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessment
Grossman 2007	Representative? yes; TLoC, but seizures excluded Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes; structured follow up Is time between tests short enough? unclear; up to 30 days between Is ref standard independent? yes; different assessors	All receive ref std? yes; follow up available for 81%; only these reported Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? no; follow up available for 81%; only these reported Withdrawals explained? yes; rates of adverse events in ED and hospital	**+**

1.6.2   Diagnostic Test: OESIL score

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessment
Hing 2005	Representative? no; patients only recruited if investigators present (22%); excludes seizures Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? unclear Is ref std OK? no; follow up predominantly medical records and reliance on patient account; only limited input from HCPs Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? no; but only 5% loss to follow up and 6% excluded because no troponin 4h results Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? no	−
Reed 2007 (ROSE pilot)	Representative? no; 62% patients missed (younger); study gp skewed towards more serious risk; GDG considered this to be unacceptable Selection Criteria Described? Yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? unclear; 3 months Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? yes	−

1.6.3   Diagnostic Test: San Francisco Syncope Rule

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessment
Birnbaum 2008	Representative? no; included large proportion of non-white people; syncope and near syncope; excluded seizures Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes; but complete predictor data and complete follow up data missing for only 2 and 3% respectively Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? yes	+
Cosgriff 2007	Representative? no; TLoC, but seizures excluded; near syncope included; non-English excluded; non-consecutive; 12% from records Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? no; follow up achieved only for 89/113 (79%); GDG considered this unacceptable Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? yes	−

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessment
Quinn 2005	Representative? yes; syncope and near syncope (latter not defined); seizures excluded; single hospital Selection Criteria Described? yes	Index test well described? yes Is ref std well described? unclear; unclear if study nurse was independent of SFSR application Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? yes	+
Quinn 2006	Representative? no; syncope and near syncope (latter not defined); seizures excluded; single hospital but authors state demographics typical; age range 6 to 99 years (mean 61) Selection Criteria Described? yes; although 'near syncope' not defined	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? yes; up to 30 days between Is ref standard independent? yes	All receive ref std? no; 54/767 patients having serious outcomes present or diagnosed within the ED may have been excluded from the analysis, which only included 53 with an outcome Same ref std? yes; but some patients received further testing which informed ref std.	Same clinical data available? yes Uninterpretable/ Intermediate reported? unclear; unclear how many patients in final analysis had >1 TLoC visit Withdrawals explained? yes	+
Reed 2007 (ROSE pilot)	Representative? no; 62% patients missed (younger); study gp skewed towards more serious risk; GDG considered this to be unacceptable Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? unclear; 3 months Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? yes	-
Schladen haufen 2008	Representative? no; retrospective records; 12% patients excluded if no subsequent follow up visits and <7 days in hospital; further 7% excluded for incomplete data Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes; apart from 12% missing data Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? no; 19% missing Withdrawals explained? yes	-
Sun 2007	Representative? yes; only during day hours recruited (76%); syncope and near syncope, excludes seizures and people with confusion Selection Criteria Described? yes	Is index test well described? yes; on website Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? no; 14/477 had no follow up data; for index test:153 (32%) did not have haemocrit testing; 7 did not have shortness of breath indicator data; 6 did not have history of CHF data; 33 (7%) did not have an ECG Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes; for 27 (6%) patients inpatient/outpatient data used rather than phone follow up Withdrawals explained? yes	+

2 12-lead ECG review

2.1 *12-lead ECG for predicting serious events - QUADAS*

Study	Representative? Selection criteria	Index test / reference standard well described? Reference standard OK? Independent of index test?	Verification bias (partial and differential)	Same Clinical Data? Intermediate tests reported? Withdrawals?	Overall Assessment
Quinn 2004	Representative? no; syncope and near syncope (latter not defined); seizures excluded; single hospital; age range 10 to 102 years (mean 62) Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? unclear; unclear if study nurse was independent of ECG Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? yes	**+**
Reed 2007 (ROSE pilot)d	Representative? no; 62% patients missed (younger); study gp skewed towards more serious risk; GDG considered this to be unacceptable Selection Criteria Described? yes	Is index test well described? unclear; unclear who did this Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? unclear; 3 months Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? yes	**–**
Sun 2008	Representative? no; 33 (7%) did not have an ECG; only during day hours recruited (76%); syncope and near syncope, excludes seizures and people with confusion Selection Criteria Described? yes	Is index test well described? unclear; not always clear which was outcome and which was index test Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? yes; 2 weeks Is ref standard independent? yes; though ECGs recorded in the index test were used (but interpreted by different outcome assessors in the ref standard	All receive ref std? yes; 97% follow up; 33 (7%) did not have an ECG Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? yes	**+**

2.2   12-lead ECG: automatic versus clinician read - QUADAS

Study	Representative? Selection criteria	Index test / reference standard well described? Reference standard OK? Independent of index test?	Verification bias (partial and differential)	Same Clinical Data? Intermediate tests reported? Withdrawals?	Overall Assessment
Charbit 2006	Representative? no; postoperative patients; cardiac arrhythmias/bundle branch block excluded Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? unclear; expert clinician (anaesthetist) Is time between tests short enough? yes; 2 ECGs recorded consecutively Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Christov 2001	Representative? no; routine ECGs in cardiology department Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? no Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? yes Withdrawals explained? N/A	-
Denny 2007	Representative? yes Selection Criteria Described? yes	Is index test well described? no Is ref std well described? no Is ref std OK? yes; cardiologist Is time between tests short enough? yes; same ECG read by cardiologist and machine Is ref standard independent? no; cardiologist would be looking at same ECG presumably with machine readout when making diagnosis	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? unclear Withdrawals explained? N/A	-
Fatemi 2008	Representative? no; admitted to CCU/Cardiac emergency ward Selection Criteria Described? no	Is index test well described? no Is ref std well described? no Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessement
Kaneko 2005	Representative? unclear; not TLOC Selection Criteria Described? no	Is index test well described? yes Is ref std well described? no; expert clinician Is ref std OK? yes; expert clinician Is time between tests short enough? yes; same ECGs read by machine and cardiologist Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Taha 2000	Representative? unclear Selection Criteria Described? no	Is index test well described? no Is ref std well described? no Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? unclear Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-

3 Second stage assessment

3.1 *Ambulatory ECG – RCTs*

Study	Sequence Generation and Allocation concealment	Blinding	Baseline Comparability	Attrition, ITT and Power Calculation
Farwell 2006	Sequence Generation: Partial (random number tables). Allocation Concealment: Adequate (sealed envelopes held in study centre).	Patient: no not blinded. Outcome assessor: Unclear; not stated.	Yes; comparable on age, gender, previous ischaemic heart disease, duration of symptoms, previous episodes.	Power calculation: Yes. sample size 200 appropriate to detect 18% improvement in diagnosis with 90% power. Attrition: No (≤ 20% loss to follow up). ITT: Yes (all followed).
Krahn 2001	Sequence Generation: Unclear. Allocation Concealment: Unclear.	Patient: no not blinded. Outcome assessor: Unclear; not stated.	Yes; comparable on age, sex, baseline ECG, heart diseasee, left ventricular ejection fraction, number of syncopal episodes, syncope duration.	Power calculation: No. Attrition: Yes. ITT: Yes (all followed).
Rockx 2005	Sequence Generation: Adequate (computer algorithm). Allocation Concealment: Unclear.	Patient: no not blinded. Outcome assessor: Unclear; not stated.	Yes; comparable on age, gender, duration of symptoms, number of episodes.	Power calculation: Not stated. . Attrition: Yes. ITT: Yes (all followed).
Rothman 2007	Sequence Generation: Adequate (randomisation generated b y independent source (within site randomisation)). Allocation Concealment: Adequate ("Investigators, other study personnel, and the subjects were not able to identify the assignment").	Patient: no not blinded. Outcome assessor: Yes; independent electrophysiologist blind to randomisation.	Yes; comparable on age, gender, ethnicity, cardiac history.	Power calculation: Yes. 300 patients to power the study to detect a 33% deifference to confirm or exclude arrythmia as cause of symptoms. Attrition: Yes. ITT: Yes (all followed).

3.2   Ambulatory ECG – non-randomised studies

3.2.1   Ambulatory ECG - suspect arrhythmia review

Study name	*Prospective? All eligible?*	*Outcome Blinding*	*Attrition*	*Overall Comments*
Arya 2005; case series	Prospective? Yes All eligible included? Unclear	Yes(blinded cardiologist read ECGs)	Yes	
Boudoulas 1979; non-randomised comparative study	Prospective? Yes All eligible included? Unclear	No	Yes	
Boudoulas 1983; case series	Prospective? Yes All eligible included? Unclear	No	Yes	
Brembilla-Perrot 2001; case series	Prospective? Yes All eligible included? Yes	No	Yes	
Brembilla-Perrot 2004; case series	Prospective? All eligible included?			
Brembilla-Perrot 2004; case series	Prospective? Yes All eligible included? Yes	No	Yes	
Brignole 2001; case series	Prospective? Yes All eligible included? Yes	No	Yes	
Garcia-Civera 2005; case series	Prospective? Yes All eligible included? Yes	No	Yes	
Krahn 1999; case series	Prospective? Yes All eligible included? Unclear	No	Yes	
Menozzi 2002; case series	Prospective? Yes All eligible included? Unclear	No	Yes	
Study name	*Prospective? All eligible?*	*Outcome Blinding*	*Attrition*	*Overall Comments*

Ringqvist 1989; case series	Prospective? Yes All eligible included? Yes	No	Yes	
Sarasin 2005; case series	Prospective? Yes All eligible included? No	No	Yes	140/155 (90%) eligible enrolled; non-participants (presumably declined) older (mean 77) than participants (mean 68)

3.2.2 Ambulatory ECG - suspect NM syncope review

Study name	Prospective? All eligible?	Outcome Blinding	Attrition	Overall Comments
Brignole 2006; case series	Prospective? Yes All eligible included? No	----(N/A)	No (≤ 20% loss to follow up); 6% did not comply with follow up	6% of eligible patients declined & 6% had ILR but did not comply with follow up
Deharo 2006; case series	Prospective? Yes All eligible included? Yes	No	No (≤ 20% loss to follow up); 2 patients had device prematurely explanted, 1 due to breast cancer & 1 due to infection	
Fitchet 2003; case series	Prospective? Yes All eligible included? Yes	No	Yes	
Moya 2001; case series	Prospective? All eligible included?			

3.2.3 Ambulatory ECG - unexplained recurrent TLoC review

Study name	Prospective? All eligible?	Outcome Blinding	Attrition	Overall Comments
Aronow 1993; case series	Prospective? Yes All eligible included? Unclear	No	Yes	
Boersma 2004; case series	Prospective? Yes All eligible included? Yes	No	Yes	
Brignole 2005; case series	Prospective? Yes All eligible included? No	Unclear (not stated)	Unclear or Not stated	only 1/3 patients with unexplained syncope had ILR
Comolli 1993; case series	Prospective? Yes All eligible included? Yes	No	Yes	
Donateo 2003; case series	Prospective? Yes All eligible included? Unclear	No	Unclear or Not stated	

Study name	Prospective? All eligible?	Outcome Blinding	Attrition	Overall Comments
Ermis 2003; case series	Prospective? Yes All eligible included? Yes	No	Yes	
Fogel 1997; case series	Prospective? Yes All eligible included? Yes	No	Yes	
Kapoor 1991; case series	Prospective? Yes All eligible included? Yes	No	Yes	
Krahn 1998; case series	Prospective? Yes All eligible included? Unclear	No	Yes	
Krahn 2000; non-randomised comparative study	Prospective? No All eligible included? Yes	No	Yes	
Krahn 2002; case series	Prospective? Yes All eligible included? Unclear	No	Yes	
Krahn 2004; case series	Prospective? Yes All eligible included? Yes	No	Yes	
Lacroix 1981; case series	Prospective? Yes All eligible included? Yes	No	Yes	
Linzer 1990; case series	Prospective? Yes All eligible included? Yes	No	Yes	
Lombardi 2005; case series	Prospective? Yes All eligible included? Yes	No	Yes	
Moya 2001; case series	Prospective? Yes All eligible included? Unclear	No	Yes	
Nierop 2000; case series	Prospective? Yes All eligible included? Unclear	No	Yes	
Study name	**Prospective? All eligible?**	**Outcome Blinding**	**Attrition**	**Overall Comments**
Pezawas	Prospective? Yes	No	Yes	

2007; case series	All eligible included? Unclear			
Pierre 2008; case series	Prospective? Yes All eligible included? Unclear	No	Yes	
Sarasin 2001; case series	Prospective? Yes All eligible included? Yes	No	Yes	
Sarasin 2001; case series	Prospective? All eligible included?			
Schuchert 2003; case series	Prospective? Yes All eligible included? Yes	No	Yes	
Seidl 2000; case series	Prospective? Yes All eligible included? Unclear	No	No (≤ 20% loss to follow up); 3 patients lost to follow up	

3.3   Exercise testing for arrhythmia review

3.3.1   Non-randomised study quality

Study name	Prospective? All eligible?	Outcome Blinding	Attrition	Overall Comments
Boudoulas 1979; non-randomised comparative study	Prospective? Yes All eligible included? Unclear	No	Yes	
Colivicchi 2002; non-randomised comparative study	Prospective? Yes All eligible included? Yes	No	Yes	
Doi 2002; diagnostic test accuracy study	Prospective? Yes All eligible included? Yes	No	Yes	

3.3.2   QUADAS diagnostic test accuracy

Study	Representative? Selection criteria	Index test / reference standard well described? Reference standard OK? Independent of index test?	Verification bias (partial and differential)	Same Clinical Data? Intermediate tests reported? Withdrawals?	Overall Assessment
Boudoulas	Representative? yes	Is index test well described? yes	All receive ref std? yes	Same clinical data	+

1979	Selection Criteria Described? yes	Is ref std well described? yes Is ref std OK? yes; 24 hour ambulatory monitoring Is time between tests short enough? yes; 1 week Is ref standard independent? yes	Same ref std? yes.	available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	
Colivicchi 2002	Representative? no; young competitive athletes Selection Criteria Described? yes	Is index test well described? no Is ref std well described? yes Is ref std OK? yes; tilt test Is time between tests short enough? unclear; not stated Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	**+**
Doi 2002	Representative? yes Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	**+**

3.4 Tilt table for NMS review

3.4.1 Non-randomised study quality

Study name	Prospective? All eligible?	Outcome Blinding	Attrition
Aerts 1997; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Aerts 1999; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Aerts 2005; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Aerts 2005b; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Almquist 1989; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Aslan 2002; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Athanasos 2003; case control study	Prospective? Yes All eligible included? Unclear	No	Yes
Benchimol 2008; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Brignole 1991; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Brignole 1991; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Carlioz 1997; non-randomised comparative study	Prospective? Yes All eligible included? Yes	No	Yes

Study name	Prospective? All eligible?	Outcome Blinding	Attrition
Del Rosso 1998; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Del Rosso 2002; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Doi 2002; diagnostic test accuracy study	Prospective? Yes All eligible included? Yes	No	Yes
Englund 1997; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Fitzpatrick 1991; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Gielerak 2002; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Gilligan 1992; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Graham 2001; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Grubb 1991b; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Grubb 1992b; case control study	Prospective? Yes All eligible included? Unclear	Unclear	Yes
Herrmosillo 2000; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Lagi 1992; case control study	Prospective? Yes All eligible included? Yes	No	Yes

Study name	Prospective? All eligible?	Outcome Blinding	Attrition

Lazzeri 2000; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Micieli 1999; case control study	Prospective? Yes All eligible included? Yes	Yes	Yes
Mittal 2004; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Morillo 1995; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Mussi 2001; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Oribe 1997; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Podoleanu 2004; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Prakash 2004; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Shen 1999; case control study	Prospective? Yes All eligible included? Yes	No	Yes
Theodorakis 2000; non-randomised comparative study	Prospective? Yes All eligible included? Yes	No	Yes

3.5 QUADAS – diagnostic test accuracy

Study	Representative? Selection criteria	Index test / reference standard well described? Reference standard OK? Independent of index test?	Verification bias (partial and differential)	Same Clinical Data? Intermediate tests reported? Withdrawals?	Overall Assessment
Aerts 1997	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? unclear; classic tilt (non-pharmacological) compared with HUT-ISO Is time between tests short enough? yes; only 1 test classic then isosorbide dinitrate if negative	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Aerts 1999	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Aerts 2005	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Aerts 2005b	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Almquist 1989	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessement
Aslan 2002	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Athanasos 2003	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Bartoletti 1999	Representative? no Selection Criteria Described? no	Is index test well described? yes Is ref std well described? yes Is ref std OK? unclear; HUT-NTG conventional not expert clinician Is time between tests short enough? yes; 24-72 hours Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Benchimol 2008	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Brignole 1991	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Carlioz 1997	Representative? no; young patients Selection Criteria Described? yes	Is index test well described? yes; HUT-passive Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessment
Carlioz 1997	Representative? no Selection Criteria Described? yes	Is index test well described? yes; HUT-ISO Is ref std well described? yes Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Del Rosso 1998	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Del Rosso 2002	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Doi 2002	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Fitzpatrick 1991	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Gielerak 2002	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessment
					+
Gilligan 1992	Representative? yes Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	
Graham 2001	Representative? no Selection Criteria Described? yes	Is index test well described? yes; HUT-GTN Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	**-**
Graham 2001	Representative? no Selection Criteria Described? yes	Is index test well described? yes; HUT-ISO Is ref std well described? yes Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	**-**
Grubb 1991b	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	**-**
Grubb 1992b	Representative? no; elderly patients only Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? N/A Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	**-**
Herrmosillo 2000	Representative? no Selection Criteria Described? yes	Is index test well described? yes; HUT_-ISO Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	**-**

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessment
Herrmosillo 2000	Representative? no Selection Criteria Described? yes	Is index test well described? yes; HUT-ISDN Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Herrmosillo 2000	Representative? no Selection Criteria Described? yes	Is index test well described? yes; HUT Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Lagi 1992	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Lazzeri 2000	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Micieli 1999	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Mittal 2004	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? no Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessment
Morillo 1995	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Mussi 2001	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Oraii 1999	Representative? no Selection Criteria Described? yes	Is index test well described? yes; HUT-ISO Is ref std well described? N/A Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Oraii 1999	Representative? no Selection Criteria Described? yes	Is index test well described? yes; HUT-GTN Is ref std well described? N/A Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Oraii 1999	Representative? no Selection Criteria Described? yes	Is index test well described? yes; HUT Is ref std well described? N/A Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessement
Oribe 1997	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Parry 2008	Representative? no Selection Criteria Described? yes	Is index test well described? yes; HUT-GTN Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Parry 2008	Representative? no Selection Criteria Described? yes	Is index test well described? yes; HUT Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Podoleanu 2004	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Prakash 2004	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessement
Shen 1999	Representative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	−
Theodorakis 2000	Representative? no Selection Criteria Described? yes	Is index test well described? yes; HUT-clomipramine Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	−
Theodorakis 2000	Representative? no Selection Criteria Described? yes	Is index test well described? yes; HUT Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	−
Theodorakis 2003	Representative? no Selection Criteria Described? yes	Is index test well described? yes; HUT-ISO Is ref std well described? N/A Is ref std OK? yes; patiernts versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	−
Theodorakis 2003	Representative? no Selection Criteria Described? yes	Is index test well described? yes; HUT-clomipramine Is ref std well described? N/A Is ref std OK? yes; patiernts versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	−

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessement
Zeng 2001	Representative? no Selection Criteria Described? yes	Is index test well described? yes; HUT-GTN conventional Is ref std well described? N/A Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Zeng 2001	Representative? no Selection Criteria Described? yes	Is index test well described? yes; HUT-GTN single stage Is ref std well described? N/A Is ref std OK? yes Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-

3.6 Carotid sinus massage for NMS review

3.6.1 Non-randomised study quality

Study name	*Prospective? All eligible?*	*Outcome Blinding*	*Attrition*	*Overall Comments*
Benchimol 2008; case control study	Prospective? Yes All eligible included? Yes	No	Yes	
Brignole 1991; case control study	Prospective? Yes All eligible included? Yes	No	Yes	
Freitas 2004; case control study	Prospective? Yes All eligible included? Yes	Unclear	Yes	
Kumar 2003; case control study	Prospective? No All eligible included? Yes	No	Yes	retrospective cases; prospective controls
Morillo 1999; case control study	Prospective? Yes All eligible included? Yes	No	Yes	
Parry 2000; case control study	Prospective? Yes All eligible included? Yes	No	Yes	

3.6.2 QUADAS – diagnostic test accuracy

Study	Representative? Selection criteria	Index test / reference standard well described? Reference standard OK? Independent of index test?	Verification bias (partial and differential)	Same Clinical Data? Intermediate tests reported? Withdrawals?	Overall Assessment
Benchimol 2008	Represenatative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? N/A Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? N/A Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessement
Brignole 1991	Represenatative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? unclear Is ref std OK? unclear; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes Same ref std? N/A.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Freitas 2004	Represenatative? no Selection Criteria Described? no	Is index test well described? yes Is ref std well described? no Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Kumar 2003	Represenatative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? no Is ref std OK? yes; patients versus controls Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-
Morillo 1999	Represenatative? no Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? no Is ref std OK? yes; patients versus controls (no syncope) Is time between tests short enough? yes Is ref standard independent? yes	All receive ref std? yes Same ref std? yes.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? N/A	-

4 Second stage Assessment – diagnostic tests to direct pacing therapy

4.1 Pacemaker intervention reviews

4.1.1 Pacemaker for tilt test determined cardioinhibitory NM syncope

Study	Sequence Generation and Allocation concealment	Blinding	Baseline Comparable and early stopping	Attrition, ITT and Power Calculation
Ammirati 2001 (SYDIT)	Sequence Generation: Adequate (computer generated). Allocation Concealment: Partial ('central randomisation').	Patient: no not blinded. Outcome assessor: No; patients were outcome assessors, 57% witnessed and 29% other events associated with minor injuries.	Yes mainly; Comparable for gender, no. of prior syncopal episodes, reported prodromes, asystolic response during tilt testing, but said to be a trend towards pacemaker patients being older (61 vs 55 y) & having more syncope related traumatic injuries (55 v 36). Early stopping? yes, stopped after 93 had been enrolled because of significant effect in pacemaker group	Power calculation: Yes. 80% power at alpha level of 0.05 to detect 5%/y recurrence rate in pacemaker arm and 15% /y in drug arm syncope = 60 patients. Attrition: Yes. ITT: Yes (all followed).
Connolly 1999 (VPS)	Sequence Generation: Unclear. Allocation Concealment: Adequate (Central randomisation by telephone).	Patient: no not blinded. Outcome assessor: No; Patients are assessors, although witnessed in 50% of PM events and 32% no PM events.	Yes mainly; Comparable for age, prior therapy for syncope, baseline tilt results) probably not comparable for median number of lifetime TLoCs (14vs 35 (no PM)) or for median no. events in previous year (3 vs 6). Early stopping? yes, because of significant treatment effect	Power calculation: Yes. 80% power to detect 30% RRR in risk of syncope for rate of 60% in control group = 286 patients; but 54 recruited and trial stopped early. Attrition: Yes. ITT: Yes (all followed).
Connolly 2003 (VPS II)	Sequence Generation: Unclear. Allocation Concealment: Adequate (Person responsible for randomisation not involved in recruitment; telephone randomisation).	Patient: yes double blind. Outcome assessor: Yes; patients were outcome assessors.	Yes mainly; Comparable for age, number of TLoC events, tilt test variables, number with heart rate below 40 bpm, but not comparable for gender (DDD lower proportion men 27% vs 52%). Early stopping? no	Power calculation: Yes. 80% power to detect 50% RRR in risk of syncope for rate of 60% in control group = 80 patients; but 100 recruited. Attrition: Yes. ITT: Yes (all followed).

4.1.2 Pacemaker for CSM determined cardioinhibitory NM syncope

Study	Sequence Generation and Allocation concealment	Blinding	Baseline Comparability	Attrition, ITT and Power Calculation
Brignole 1992c	Sequence Generation: Adequate (table of random numbers). Allocation Concealment: Unclear.	Patient: no not blinded. Outcome assessor: No.	Yes; comparable on age, gender, symptoms, type of CSH.	Power calculation: No. Attrition: Yes. ITT: Yes (all followed).
Claesson 2007	Sequence Generation: Adequate (numbered opaque sealed envelopes, shuffled 21 times and then numbered). Allocation Concealment: Adequate (sequentially numbered, opaque, sealed envelopes).	Patient: no not blinded. Outcome assessor: No.	Yes; comparable on age, gender, ECG findings, duration of asystole with CSM, cardiovascular drugs.	Power calculation: No. Attrition: Yes. ITT: Yes (all followed).
Kenny 2001	Sequence Generation: unclear. Allocation Concealment: unclear.	Patient: no not blinded. Outcome assessor: No.	Yes; comparable on age, gender, type of response, previous injury, co-morbidities.	Power calculation: Yes. sample size based on detecting a 40% difference in number of falls (from 10 to 6 falls per year), assuming SD 8 falls/yr. 85 subjects per group gave 90% power to detect this difference at alpha=0.05. Attrition: No (≤ 20% loss to follow up). ITT: No (available case analysis).

4.2 Tests for a cardioinhibitory response review

4.2.1 Non-randomised quality

Study name	*Prospective? All eligible?*	*Outcome Blinding*	*Attrition*
4.2.1.1 Tilt table			
Gatzoulis 2003	Prospective? Yes All eligible included? Yes	No	Yes
4.2.1.2 Carotid sinus massage			
Lagi 1991;	Prospective? Yes All eligible included? Yes	No	No (≤ 20% loss to follow up); 2 patients lost to follow up out of 56 (4%)
4.2.1.3 Ambulatory ECG - implantable event recorder			
Brignole 2006b	Prospective? Yes All eligible included? Yes	No	Yes

4.2.2 QUADAS – diagnostic test accuracy

Study	Representative? Selection criteria	Index test / reference standard well described? Reference standard OK? Independent of index test?	Verification bias (partial and differential)	Same Clinical Data? Intermediate tests reported? Withdrawals?	Overall Assessment

4.2.2.1 tilt table for NMS

Gatzoulis 2003	Represenatative? yes Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes; reference standard taken as symptom-free after pacing Is time between tests short enough? no; follow up 24 months Is ref standard independent? yes	All receive ref std? no; not all paced; decision on who received pacemaker and why unclear Same ref std? no; pacing dependent on test result and patient preference.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? yes	-

4.2.2.2 Carotid sinus massage

Lagi 1991	Represenatative? no; patients selected: case series: epilepsy and vasodepressor excluded Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes; reference standard taken as symptom-free after pacing Is time between tests short enough? no; follow up 11 (8) months Is ref standard independent? yes	All receive ref std? no; not all paced Same ref std? no; pacing dependent on test result.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? yes	-

4.2.2.3 Ambulatory ECG - implantable event recorder

Brignole 2006b	Represenatative? yes Selection Criteria Described? yes	Is index test well described? yes Is ref std well described? yes Is ref std OK? yes; reference standard taken as symptom-free after pacing Is time between tests short enough? no; follow up 9 months Is ref standard independent? yes	All receive ref std? no; not all paced Same ref std? no; pacing dependent on test result.	Same clinical data available? yes Uninterpretable/ Intermediate reported? N/A Withdrawals explained? yes	-