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1 Initial assessment stage

1.1 Initial symptoms for diagnosis review - QUADAS

1.1.1 Diagnostic Test: Initial symptoms

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	Index test well described? unclear. Ref std well described? yes. Ref std OK? unclear: tests based on suspected cause. Time between tests OK? yes. Ref std independent? no: index test part of ref std	All get ref std? unclear: if index test gave definite diagnosis, no further tests (no numbers given). Same ref std? no: tests depended on suspected cause. Index test blinded? yes. Ref std blinded? no	Same clinical data available? yes. Uninterpretable/ Intermediate reported? no. Withdrawals explained? yes: 15 (4%) protocol violations	Overall assessment: - Reason: Index test integral part of reference standard
Benbadis 1995	Representative? no: Highly selected patients; case control (epilepsy unit and syncope of known cause). Selection Criteria Described? yes	Index test well described? yes. Ref std well described? yes. Ref std OK? yes. Time between tests OK? yes. Ref std independent? yes	All get ref std? yes. Same ref std? no: different tests for epilepsy and syncope patients. Index test blinded? no: reference standard first or simultaneous. Ref std blinded? no: simultaneous for epilepsy unclear.	Same clinical data available? no. Uninterpretable/ Intermediate reported? unclear. Withdrawals explained? N/A	Overall assessment: - Reason: Highly selected patients; case control
del Rosso 2008	Representative? no: syncope only, not epileptic seizures or other forms of TLoC. Selection Criteria Described? no	Index test well described? no. Ref std well described? no. Ref std OK? yes. Time between tests OK? unclear. Ref std independent? no: initial ECG was part of reference standard	All get ref std? no: about 95%. Same ref std? no. Index test blinded? yes. Ref std blinded? no: index test part of reference standard	Same clinical data available? yes. Uninterpretable/ Intermediate reported? unclear: data not available for 5% of patients. Withdrawals explained? yes	Overall assessment: - Reason: index test part of reference standard for ECG
Graf 2008	Representative? no: selected patients referred for unexplained syncope. Selection Criteria Described? yes	Index test well described? yes. Ref std well described? yes. Ref std OK? yes. Time between tests OK? yes. Ref std independent? no: ECG part of reference standard; but symptoms/history were not	All get ref std? yes: whole. Same ref std? no: varied according to previous tests/history. Index test blinded? unclear. Ref std blinded? no.	Same clinical data available? yes. Uninterpretable/ Intermediate reported? yes. Withdrawals explained? N/A	Overall assessment: - Reason: Selected patients; ECG part of reference standard

Hoefnagels 1991	Representative? no: referrals to neurology; eye witness only. Selection Criteria Described? yes	Index test well described? yes. Ref std well described? yes. Ref std OK? yes: no true reference standard. Time between tests OK? yes. Ref std independent? no: symptoms were important part of reference standard	All get ref std? yes. Same ref std? no: some further tests subject to clinician judgement. Index test blinded? yes. Ref std blinded? no: part of reference standard	Same clinical data available? yes. Uninterpretable/ Intermediate reported? N/A. Withdrawals explained? N/A	Overall assessment: - Reason: selected group and index test part of reference standard
Romme 2009 (subset of van Dijk 2008)	Representative? no: combination of ED and referrals; 123/503 (25%) excluded (CMO, MI, epileptic seizures, unknown cause after 2y). Selection Criteria Described? unclear	Index test well described? yes. Ref std well described? yes. Ref std OK? yes. Time between tests OK? yes. Ref std independent? no: index test part of ref std	All get ref std? yes. Same ref std? no: further tests depended on suspected cause. Index test blinded? yes. Ref std blinded? no: index test part of ref std	Same clinical data available? unclear. Uninterpretable/ Intermediate reported? unclear. Withdrawals explained? yes	Overall assessment: - 25% exclusions of some patients; borderline acceptable
Sarasin 2003	Representative? no: patients with definite cause of syncope excluded. Selection Criteria Described? yes	Index test well described? yes. Ref std well described? yes. Ref std OK? yes. Time between tests OK? unclear: not stated. Ref std independent? yes: 12-lead ECG apparently not in ref std	All get ref std? yes. Same ref std? unclear: tests depended on suspected diagnosis - unclear how. Index test blinded? yes: appears to be different people. Ref std blinded? yes	Same clinical data available? yes. Uninterpretable/ Intermediate reported? no. Withdrawals explained? yes: no withdrawals	Overall assessment: + Reason: only unexplained syncope
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	Index test well described? yes. Ref std well described? yes. Ref std OK? unclear: EEG not sufficient for diagnosing seizures; GDG regarded this as unacceptable. Time between tests OK? unclear: unclear when patients had diagnoses. Ref std independent? yes	All get ref std? yes. Same ref std? yes: reference standard carried out first. Index test blinded? unclear: unclear what investigators knew. Ref std blinded? unclear: unclear if any of symptoms known at time of diagnosis	Same clinical data available? yes. Uninterpretable/ Intermediate reported? yes. Withdrawals explained? yes	Overall assessment: - Reason: selected patients (case control); reference standard inadequate
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	Index test well described? yes. Ref std well described? yes. Ref std OK? no: EEG not sufficient; GDG regarded this as unacceptable. Time between tests OK? unclear: unclear when patients had diagnoses. Ref std independent? yes	All get ref std? yes. Same ref std? yes: reference standard carried out first. Index test blinded? unclear: uncertain what investigators knew. Ref std blinded? unclear: uncertain if symptoms known at time of diagnosis	Same clinical data available? yes. Uninterpretable/ Intermediate reported? yes. Withdrawals explained? yes	Overall assessment: - Reason: selected patients with known diagnosis

1.2 Decision rules for diagnosis review - QUADAS

1.2.1 Diagnostic Test: ACEP guidelines

Elseber 2005	Representative? yes. Selection Criteria Described? yes: but retrospective study from patient records	Index test well described? yes. Ref std well described? yes. Ref std OK? yes. Time between tests OK? unclear: interval uncertain. Ref std independent? no: part of index test (ECG) was reference standard.	All get ref std? yes. Same ref std? unclear: not stated which tests carried out when. Index test blinded? unclear: uncertain who assessed records. Ref std blinded? unclear	Same clinical data available? unclear: retrospective study. Uninterpretable/ Intermediate reported? no. Withdrawals explained? yes: only 90% had ECG	Overall assessment: - Reason: retrospective study; ECG part of reference standard
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1.2.2 Diagnostic Test: EGSYS score

del Rosso 2008	Representative? no: syncope only, not epileptic seizures or other forms of TLoC. Selection Criteria Described? no	Index test well described? no. Ref std well described? no. Ref std OK? yes. Time between tests OK? unclear. Ref std independent? no: initial ECG was part of reference standard	All All get ref std? no: about 95%. Same ref std? no. Index test blinded? yes. Ref std blinded? no: index test part of reference standard	Same clinical data available? yes. Uninterpretable/ Intermediate reported? unclear: data not available for 5% of patients. Withdrawals explained? yes	Overall assessment: - Reason: index test part of reference standard for ECG
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1.2.3 Diagnostic Test: ESC guidelines

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	Index test well described? yes: but included reference to other work (ESC guidelines). Ref std well described? yes: a little vague in places. Ref std OK? yes. Time between tests OK? yes: 2 year follow up considered OK by GDG. Ref std independent? no: assessment part of ref std; unclear if different assessors	All get ref std? yes. Same ref std? no: some had further tests; pts with certain diagnosis follow-up only. Index test blinded? unclear: earlier test results may be known. Ref std blinded? yes: 19% expert panel when index test & follow up disagreed	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	Overall assessment: +
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1.2.4 Diagnostic Test: Initial symptoms decision rule

Graf 2008	Representative? no: selected patients referred for unexplained syncope. Selection Criteria Described? yes	Index test well described? yes. Ref std well described? yes. Ref std OK? yes. Time between tests OK? yes. Ref std independent? no: ECG part of reference standard; but symptoms/history were not	All get ref std? yes: whole. Same ref std? no: varied according to previous tests/history. Index test blinded? unclear. Ref std blinded? no	Same clinical data available? yes. Uninterpretable/Intermediate reported? yes. Withdrawals explained? N/A	Overall assessment: - Reason: selected patients; ECG part of reference standard
Romme 2009 (subset of van Dijk 2008)	Representative? no: combination of ED and referrals; 123/503 (25%) excluded (CMO, MI, epileptic seizures, unknown cause after 2y). Selection Criteria Described? unclear	Index test well described? yes. Ref std well described? yes. Ref std OK? yes. Time between tests OK? yes. Ref std independent? no: index test part of ref std	All get ref std? yes. Same ref std? no: further tests depended on suspected cause. Index test blinded? yes. Ref std blinded? unclear: index test part of ref std	Same clinical data available? unclear. Uninterpretable/Intermediate reported? unclear. Withdrawals explained? yes	Overall assessment: + Reason: 25% exclusions of some patients; borderline acceptable
Sarasin 2003	Representative? no: patients with definite cause of syncope excluded. Selection Criteria Described? yes	Index test well described? no: must have been retrospective - rule developed post validation study. Ref std well described? yes. Ref std OK? yes. Time between tests OK? unclear: not stated. Ref std independent? yes	All get ref std? yes. Same ref std? yes. Index test blinded? unclear: not stated how index test analysed. Ref std blinded? unclear	Same clinical data available? yes. Uninterpretable/Intermediate reported? no. Withdrawals explained? yes: no withdrawals	Overall assessment: - Reason: retrospective evaluation
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	Index test well described? yes. Ref std well described? yes. Ref std OK? no: EEG not sufficient for seizure diagnosis; GDG regarded this as unacceptable. Time between tests OK? unclear: uncertain when patients had diagnoses. Ref std independent? yes	All get ref std? yes. Same ref std? yes: reference standard carried out first. Index test blinded? unclear: unclear what investigators knew. Ref std blinded? unclear: unclear if symptoms known at time of diagnosis	Same clinical data available? yes. Uninterpretable/Intermediate reported? yes. Withdrawals explained? yes	Overall assessment: - Reason: selected patients (case control); reference standard inadequate

Sheldon 2006	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	Index test well described? yes. Ref std well described? yes. Ref std OK? no: tilt table test positive; GDG regarded this as unacceptable. Time between tests OK? unclear: unclear when patients had diagnoses. Ref std independent? yes.	All get ref std? yes. Same ref std? yes: reference standard carried out first. Index test blinded? unclear: unclear what investigators knew. Ref std blinded? unclear: uncertain if symptoms known at time of diagnosis	Same clinical data available? yes. Uninterpretable/ Intermediate reported? yes. Withdrawals explained? yes	Overall assessment: - Reason: selected patients with known diagnosis
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1.3 Initial symptoms for risk stratification (death) review - QUADAS

1.3.1 Diagnostic Test: Initial symptoms

Colivicchi 2003	Representative? yes. Selection Criteria Described? no	Index test well described? yes. Ref std well described? yes. Ref std OK? yes: only all-cause deaths after 12 months; GDG considered this acceptable. Time between tests OK? yes: within 12 months; GDG considered this acceptable. Ref std independent? yes	All get ref std? yes. Same ref std? yes. Index test blinded? yes. Ref std blinded? unclear: uncertain who did follow up	Same clinical data available? yes. Uninterpretable/ Intermediate reported? yes. Withdrawals explained? yes: none	Overall assessment: +
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1.4 Decision rules for risk stratification (death) review -- QUADAS

1.4.1 Diagnostic Test: ACP guidelines

Crane 2002	Representative? yes. Selection Criteria Described? yes, but retrospective study from patient records	Index test well described? no: 36% patients did not have ECG in ED and 81% had no postural bp measurement, so data from their records used. Ref std well described? yes. Ref std OK? yes: death only. Time between tests OK? yes: 1 year between; GDG considered this acceptable. Ref std independent? yes	All get ref std? no: Follow up for 90%. Same ref std? yes. Index test blinded? yes: explicitly stated. Ref std blinded? unclear: but unimportant since death was the outcome	Same clinical data available? unclear: retrospective study. Uninterpretable/ Intermediate reported? yes: Kaplan Meier plots. Withdrawals explained? yes	Overall assessment: - Reason: retrospective study
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1.4.2 Diagnostic Test: EGSYS score

del Rosso 2008	Representative? no: syncope only, not epileptic seizures or other forms of TLoC. Selection Criteria Described? no	Index test well described? yes. Ref std well described? yes. Ref std OK? yes: DEATH as target condition. Time between tests OK? yes. Ref std independent? yes	All get ref std? no: 76% follow up. Same ref std? yes. Index test blinded? yes. Ref std blinded? yes	Same clinical data available? yes. Uninterpretable/ Intermediate reported? unclear. Withdrawals explained? yes	Overall assessment: - Reason: only 76% follow up
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1.4.3 Diagnostic Test: OESIL score

Colivicchi 2003	Representative? yes. Selection Criteria Described? no	Index test well described? yes. Ref std well described? yes. Ref std OK? yes: only all-cause deaths after 12 months; GDG considered this acceptable. Time between tests OK? yes: within 12 months; GDG considered this acceptable. Ref std independent? yes	All get ref std? yes. Same ref std? yes. Index test blinded? yes. Ref std blinded? unclear: not clear who did follow up	Same clinical data available? yes. Uninterpretable/ Intermediate reported? yes. Withdrawals explained? yes: none	Overall assessment: +
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1.4.4 Diagnostic Test: San Francisco Syncope Rule

Quinn 2008	Representative? yes. Selection Criteria Described? yes	Index test well described? no. Ref std well described? yes. Ref std OK? unclear: although not determined if people were alive, only if they had died. Time between tests OK? yes. Ref std independent? yes	All get ref std? unclear: not determined if people were alive, only if they had died. Same ref std? yes. Index test blinded? yes. Ref std blinded? yes	Same clinical data available? yes. Uninterpretable/ Intermediate reported? N/A. Withdrawals explained? no	Overall assessment: +
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1.5 Initial symptoms for risk stratification review - QUADAS

1.5.1 Diagnostic Test: Initial symptoms

Birnbaum 2008	Representative? no: included large proportion of non-white people; syncope and near syncope; excluded seizures. Selection Criteria Described? yes	Index test well described? yes. Ref std well described? yes. Ref std OK? yes. Time between tests OK? yes. Ref std independent? yes	All get ref std? yes: but complete predictor data and complete follow up data missing for only 2 and 3% respectively. Same ref std? yes. Index test blinded? yes. Ref std blinded? yes	Same clinical data available? yes. Uninterpretable/ Intermediate reported? yes. Withdrawals explained? yes	Overall assessment: +
Costantino 2008 (STePS)	Representative? no: TLoC, but seizures excluded. Also excluded other concurrent conditions. Selection Criteria Described? yes	Index test well described? no. Ref std well described? yes. Ref std OK? yes. Time between tests OK? yes: especially for 10 day outcomes. Ref std independent? yes	All get ref std? yes. Same ref std? yes. Index test blinded? yes. Ref std blinded? unclear: appears to be same people, but blinding unimportant	Same clinical data available? yes. Uninterpretable/ Intermediate reported? yes: for 1y outcomes. Withdrawals explained? yes: 9/676 (1%) loss to follow up	Overall assessment: + Reason: but more specific population
Grossman 2007	Representative? yes: TLoC, but seizures excluded. Selection Criteria Described? yes	Index test well described? yes. Ref std well described? yes. Ref std OK? yes: structured follow up. Time between tests OK? unclear: up to 30 days between. Ref std independent? yes: different assessors	All get ref std? yes: follow up available for 81%. Same ref std? yes. Index test blinded? yes. Ref std blinded? yes	Same clinical data available? yes. Uninterpretable/ Intermediate reported? no: follow up available for 81%. Withdrawals explained? yes: rates of adverse events in ED and hospital similar for missing data	Overall assessment: +
Hing 2005	Representative? no: patients only recruited if investigators present (22%); excludes seizures. Selection Criteria Described? yes	Index test well described? yes. Ref std well described? unclear. Ref std OK? no: follow up predominantly medical records and reliance on patient account; only limited input from HCPs. Time between tests OK? yes. Ref std independent? yes	All get ref std? no: but only 5% loss to follow up and 6% excluded because no troponin 4h results. Same ref std? yes. Index test blinded? yes. Ref std blinded? unclear: uncertain who obtained reference standard results	Same clinical data available? yes. Uninterpretable/ Intermediate reported? N/A. Withdrawals explained? no	Overall assessment: - Reason: retrospective reference standard and 22% eligible recruited

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	Index test well described? yes. Ref std well described? unclear: unclear if study nurse was independent of ECG. Ref std OK? yes. Time between tests OK? yes. Ref std independent? yes	All get ref std? yes. Same ref std? yes. Index test blinded? yes. Ref std blinded? unclear: unclear if study nurse was independent of ECG	Same clinical data available? yes. Uninterpretable/Intermediate reported? yes. Withdrawals explained? yes	Overall assessment: +
Reed 2007 (ROSE pilot)	Representative? no: 62% patients missed (younger); study group skewed towards more serious risk; GDG considered this to be unacceptable. Selection Criteria Described? yes	Index test well described? yes. Ref std well described? yes. Ref std OK? yes. Time between tests OK? unclear: 3 months. Ref std independent? yes	All get ref std? yes. Same ref std? yes. Index test blinded? yes. Ref std blinded? unclear: unclear who recorded the reference standard outcomes	Same clinical data available? yes. Uninterpretable/Intermediate reported? yes. Withdrawals explained? yes	Overall assessment: - Reason: Spectrum bias
Reed 2010 (derivation)	Representative? yes. Selection Criteria Described? yes	Index test well described? yes. Ref std well described? yes. Ref std OK? yes. Time between tests OK? yes. Ref std independent? no: ECG part of ref std but 1/2 people assessed both tests	All get ref std? yes: 19/548 lost to follow up (3%). Same ref std? yes. Index test blinded? yes. Ref std blinded? unclear: 1/2 people assessed both tests	Same clinical data available? yes. Uninterpretable/Intermediate reported? N/A. Withdrawals explained? yes	Overall assessment: + Reason: not downrated because 1 of outcome assessors was independent
Sun 2007	Representative? yes: only during day hours recruited (76%); syncope and near syncope, excludes seizures and people with confusion. Selection Criteria Described? yes	Index test well described? yes: on website. Ref std well described? yes. Ref std OK? yes. Time between tests OK? yes. Ref std independent? yes	All get ref std? no: 14/477 had no follow up data; missing data for index test: 153 (32%) haematocrit testing; 7 shortness of breath data; 6 history of CHF data; 33 ECG. Same ref std? yes. Index test blinded? yes. Ref std blinded? yes	Same clinical data available? yes. Uninterpretable/Intermediate reported? yes: 27 (6%) had inpatient/outpatient data instead of phone follow up. Withdrawals explained? yes	Overall assessment: +

1.6 Decision rules for risk stratification review - QUADAS

1.6.1 Diagnostic Test: Boston Syncope Criteria

Grossman 2007	Representative? yes: seizures excluded. Selection Criteria Described? yes	Index test well described? yes. Ref std well described? yes. Ref std OK? yes: structured follow up. Time between tests OK? unclear: up to 30 days between. Ref std independent? yes: different assessors	All get ref std? yes: follow up available for 81%. Same ref std? yes. Index test blinded? yes. Ref std blinded? yes	Same clinical data available? yes. Uninterpretable/ Intermediate reported? no: follow up available for 81%. Withdrawals explained? yes: rates of adverse events in ED and hospital similar for missing data	Overall assessment: +
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1.6.2 Diagnostic Test: OESIL score

Hing 2005	Representative? no: patients only recruited if investigators present (22%); excludes seizures. Selection Criteria Described? yes	Index test well described? yes. Ref std well described? unclear. Ref std OK? no: follow up predominantly medical records and reliance on patient account; only limited input from HCPs. Time between tests OK? yes. Ref std independent? yes	All get ref std? no: but only 5% loss to follow up and 6% excluded because no troponin 4h results. Same ref std? yes. Index test blinded? yes. Ref std blinded? unclear: unclear who obtained reference standard results	Same clinical data available? yes. Uninterpretable/ Intermediate reported? N/A. Withdrawals explained? no	Overall assessment: - Reason: retrospective reference standard and 22% eligible recruited
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	Index test well described? yes. Ref std well described? yes. Ref std OK? yes. Time between tests OK? unclear: 3 months. Ref std independent? yes	All get ref std? yes. Same ref std? yes. Index test blinded? yes. Ref std blinded? unclear: unclear who recorded the reference standard outcomes	Same clinical data available? yes. Uninterpretable/ Intermediate reported? yes. Withdrawals explained? yes	Overall assessment: - Reason: Spectrum bias

1.6.3 Diagnostic Test: ROSE Rule

Reed 2010 (validation)	Representative? yes. Selection Criteria Described? yes	Index test well described? yes. Ref std well described? yes. Ref std OK? yes. Time between tests OK? yes. Ref std independent? yes: ECG used in both but different assessors	All get ref std? yes: 11/549 (2%) lost to follow up or withdrew consent. Same ref std? yes. Index test blinded? yes: different assessors. Ref std blinded? yes: independent assessor	Same clinical data available? yes. Uninterpretable/Intermediate reported? yes. Withdrawals explained? yes	Overall assessment: ++
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1.6.4 Diagnostic Test: San Francisco Syncope Rule

Birnbaum 2008	Representative? no: included large proportion of non-white people; syncope and near syncope; excluded seizures. Selection Criteria Described? yes	Index test well described? yes. Ref std well described? yes. Ref std OK? yes. Time between tests OK? yes. Ref std independent? yes	All get ref std? yes: but complete predictor data and complete follow up data missing for only 2 and 3% respectively. Same ref std? yes. Index test blinded? yes. Ref std blinded? yes	Same clinical data available? yes. Uninterpretable/Intermediate reported? yes. Withdrawals explained? yes	Overall assessment: +
Cosgriff 2007	Representative? no: TLoC, but seizures excluded; near syncope included; non-English excluded; nonconsecutive; 12% from records. Selection Criteria Described? yes	Index test well described? yes. Ref std well described? yes. Ref std OK? yes. Time between tests OK? yes. Ref std independent? yes	All get ref std? no: follow up for 79%; GDG considered this unacceptable. Same ref std? yes. Index test blinded? unclear: some from patient records apparently by same person. Ref std blinded? no: appeared to be same researcher	Same clinical data available? yes. Uninterpretable/Intermediate reported? yes. Withdrawals explained? yes	Overall assessment: - Reason: Follow up for 79% - GDG considered this unacceptable
Quinn 2005	Representative? yes: syncope and near syncope (latter not defined); seizures excluded; single hospital. Selection Criteria Described? yes	Index test well described? yes. Ref std well described? unclear: unclear if study nurse was independent of SFSR application. Ref std OK? yes. Time between tests OK? yes. Ref std independent? yes	All get ref std? yes. Same ref std? yes. Index test blinded? yes. Ref std blinded? unclear: unclear if study nurse was independent of SFSR application	Same clinical data available? yes. Uninterpretable/Intermediate reported? yes. Withdrawals explained? yes	Overall assessment: +
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	Index test well described? yes. Ref std well described? yes. Ref std OK? yes. Time between tests OK? yes: up to 30 days between. Ref std independent? yes	All get 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. Index test blinded? yes. Ref std blinded? yes: also had independent review by people blinded to predictor variables	Same clinical data available? yes. Uninterpretable/Intermediate reported? unclear: unclear how many patients in final analysis had >1 TLoC visit. Withdrawals explained? yes	Overall assessment: +

<p>Reed 2007 (ROSE pilot)</p>	<p>Representative? no: 62% patients missed (younger); study group skewed towards more serious risk; GDG considered this to be unacceptable. Selection Criteria Described? yes</p>	<p>Index test well described? yes. Ref std well described? yes. Ref std OK? yes. Time between tests OK? unclear: 3 months. Ref std independent? yes</p>	<p>All get ref std? yes. Same ref std? yes. Index test blinded? yes. Ref std blinded? unclear: unclear who recorded the reference standard outcomes</p>	<p>Same clinical data available? yes. Uninterpretable/Intermediate reported? yes. Withdrawals explained? yes</p>	<p>Overall assessment: - Reason: Spectrum bias</p>
<p>Schladenhaufen 2008</p>	<p>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</p>	<p>Index test well described? yes. Ref std well described? yes. Ref std OK? yes. Time between tests OK? yes. Ref std independent? yes</p>	<p>All get ref std? yes: apart from 12% missing data. Same ref std? yes. Index test blinded? yes. Ref std blinded? unclear: retrospective review</p>	<p>Same clinical data available? yes. Uninterpretable/Intermediate reported? no: 19% missing. Withdrawals explained? yes</p>	<p>Overall assessment: - Reason: retrospective study; missing data</p>
<p>Sun 2007</p>	<p>Representative? yes: only during day hours recruited (76%); syncope and near syncope, excludes seizures and people with confusion. Selection Criteria Described? yes</p>	<p>Index test well described? yes: on website. Ref std well described? yes. Ref std OK? yes. Time between tests OK? yes. Ref std independent? yes</p>	<p>All get 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. Index test blinded? yes. Ref std blinded? yes</p>	<p>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</p>	<p>Overall assessment: +</p>

2 12-lead ECG review

2.1 12-lead ECG for predicting serious events - QUADAS

Birnbaum 2008	Representative? no: included large proportion of non-white people; syncope and near syncope; excluded seizures. Selection Criteria Described? yes	Index test well described? no: no details re assessment. Ref std well described? yes. Ref std OK? yes. Time between tests OK? yes. Ref std independent? yes	All get ref std? yes: but complete predictor data and complete follow up data missing for only 2 and 3% respectively. Same ref std? yes. Index test blinded? yes. Ref std blinded? no: knowledge of admissions stated	Same clinical data available? yes. Uninterpretable/ Intermediate reported? unclear. Withdrawals explained? yes	Overall assessment: +
Colivicchi 2003	Representative? yes. Selection Criteria Described? no	Index test well described? yes. Ref std well described? yes. Ref std OK? yes: only all-cause deaths after 12 months; GDG considered this acceptable. Time between tests OK? yes: within 12 months; GDG considered this acceptable. Ref std independent? yes	All get ref std? yes. Same ref std? yes. Index test blinded? yes. Ref std blinded? unclear: not clear who did follow up	Same clinical data available? yes. Uninterpretable/ Intermediate reported? yes. Withdrawals explained? yes: none	Overall assessment: +
Hing 2005	Representative? no: patients only recruited if investigators present (22%); excludes seizures. Selection Criteria Described? yes	Index test well described? yes. Ref std well described? unclear. Ref std OK? no: follow up predominantly medical records and reliance on patient account; only limited input from HCPs. Time between tests OK? yes. Ref std independent? yes	All get ref std? no: but only 5% loss to follow up and 6% excluded because no troponin 4h results. Same ref std? yes. Index test blinded? yes. Ref std blinded? unclear: uncertain who obtained reference standard results	Same clinical data available? yes. Uninterpretable/ Intermediate reported? N/A. Withdrawals explained? no	Overall assessment: - Reason: retrospective reference standard and 22% eligible recruited
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	Index test well described? yes. Ref std well described? unclear: unclear if study nurse was independent of ECG. Ref std OK? yes. Time between tests OK? yes. Ref std independent? yes	All get ref std? yes. Same ref std? yes. Index test blinded? yes. Ref std blinded? unclear: unclear if study nurse was independent of ECG	Same clinical data available? yes. Uninterpretable/ Intermediate reported? yes. Withdrawals explained? yes	Overall assessment: +
Reed 2007 (ROSE pilot)	Representative? no: 62% patients missed (younger); study group skewed towards more serious risk; GDG considered this to be unacceptable. Selection Criteria Described? yes	Index test well described? unclear: unclear who did this. Ref std well described? yes. Ref std OK? yes. Time between tests OK? unclear: 3 months. Ref std independent? yes	All get ref std? yes. Same ref std? yes. Index test blinded? yes. Ref std blinded? unclear: unclear who recorded the reference standard outcomes	Same clinical data available? yes. Uninterpretable/ Intermediate reported? yes. Withdrawals explained? yes	Overall assessment: - Reason: Spectrum bias
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	Index test well described? unclear: not always clear which was outcome and which was index test. Ref std well described? yes. Ref std OK? yes. Time btw tests OK? yes: 2 wks Ref std independent? yes: index test ECGs used (but interpreted by different outcome assessors)	All get ref std? yes: 97% follow up; 33 (7%) did not have an ECG. Same ref std? yes. Index test blinded? yes. Ref std blinded? yes: blinded assessors	Same clinical data available? yes. Uninterpretable/ Intermediate reported? yes. Withdrawals explained? yes	Overall assessment: +

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 Assesse ment
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 Assesse ment
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 ($\leq 20\%$ 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 disease, 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 by 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% difference to confirm or exclude arrhythmia 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 ($\leq 20\%$ 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 ($\leq 20\%$ 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	

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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 2007; case series	Prospective? Yes All eligible included? Unclear	No	Yes	
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 ($\leq 20\%$ 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 Described? yes	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 Assesse ment
Boudoulas 1979	Representative? yes Selection Criteria Described? yes	Is index test well 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	All receive ref std? yes Same ref std? yes.	Same clinical data 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

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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

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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 Described? 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 Assessment
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	-
Carloz 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 Assesse ment
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	-
Hermosillo 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 Assesse ment
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 Assessment
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; 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-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	-

Study	Representative? Selection criteria described?	Tests well described? Reference standard OK? and independent?	Verification bias (partial and differential)	Other	Overall Assessment
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	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
Brignole 1991	Representative? 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	Representative? 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	Representative? 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	Representative? 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 ($\leq 20\%$ 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 ($\leq 20\%$ 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 Assesse ment
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4.2.2.1 tilt table for NMS

Gatzoulis 2003	Representative? 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	-
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4.2.2.2 Carotid sinus massage

Lagi 1991	Representative? 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	-
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4.2.2.3 Ambulatory ECG - implantable event recorder

Brignole 2006b	Representative? 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	-
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