Transient loss of consciousness (TLoC) management in adults

Full Guideline

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National Clinical Guidelines Centre

for Acute and Chronic Conditions

Please mark each comment with the correct page number and line number

Citation

To be added

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KEY PRIORITIES FOR IMPLEMENTATION

All of the recommendations, including these key priorities, are listed in the next section. Please make any comments on the content of these recommendations where they are listed in the next section.

Initial assessment and diagnosis

- Ask the person who has had the suspected TLoC, and any witnesses, to describe what happened before, during and after the event. Try to contact witnesses who are not present by telephone. Items to be recorded include the following.
  - Circumstances of the event.
  - Person's posture at outset.
  - Prodromal symptoms.
  - Appearance and colour of the person during the event.
  - Presence or absence of movement during the event.
  - Whether any tongue-biting or injury occurred during the event.
  - Duration of the event.
  - Length of time to recovery.
  - Presence or absence of confusion during the recovery period. **[1.1.1.1]**
- Record carefully the information obtained from all accounts of the suspected TLoC. Include paramedic records with this information. Give copies of all records to the receiving clinician when care is transferred, and to the person who had the suspected TLoC. **[1.1.1.2]**
- Record a 12-lead ECG. When available, use a 12-lead ECG with automated interpretation. If any abnormality is identified, seek expert advice. **[1.1.2.2]**
- Treat as an emergency (within 24 hours) anyone with TLoC who also has any of the following.
  - An ECG abnormality (see recommendation 1.1.2.3).
  - Heart failure.
  - TLoC on exertion.

  - Family history of sudden cardiac death in people aged younger than 40 years and/or an inherited cardiac condition.
  - Aged older than 65 years with no prodromal symptoms.
  - New or unexplained breathlessness.
  - A heart murmur.

  If assessed out of hospital send the person to the Emergency Department. If assessed in the Emergency Department, admit the person to hospital and arrange a specialist cardiology assessment within 24 hours. **[1.1.3.2]**

- Diagnose uncomplicated faint (vasovagal syncope) on the basis of the initial assessment when:
  - there are no features from the initial assessment that suggest an alternative diagnosis (note that brief seizure activity can occur during uncomplicated faints and is not necessarily diagnostic of epilepsy) **and**
  - there are features strongly suggestive of uncomplicated faint; that is, at least one of the following features is present ('the six Ps').
    - ◊ **P**osture (prolonged standing or sitting).
    - ◊ **P**rovoking factors (such as pain, fear, emotional distress or a medical procedure).
    - ◊ **P**rodromal symptoms (such as sweating or feeling warm/hot before TLoC).
    - ◊ **P**ost-TLoC nausea or vomiting.
    - ◊ **P**ost initial recovery, recurrence of TLoC provoked by sitting or standing up.
    - ◊ **P**revious similar episodes, in which TLoC has been prevented by lying down. **[1.1.4.1]**
- Refer people who present with one or more of the following features (that is, features that are strongly suggestive of epileptic seizures) for an assessment by a specialist in epilepsy; the person should be seen by the specialist within 4 weeks (see 'The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care [NICE clinical guideline 20]).
  - A bitten tongue.

- Abnormal behaviour (one or more of: witnessed amnesia for abnormal behaviour, witnessed unresponsiveness, unusual posturing, or prolonged limb jerking [note that brief seizure activity can occur during uncomplicated faints and is not necessarily diagnostic of epilepsy]).
- Post-ictal confusion.
- Head-turning to one side during TLoC.
- Prodromal déjà vu or jamais vu.

Consider that the episode may not be related to epilepsy if any of the following features are present.

- Pre-syncope, especially where syncope was avoided by postural change.
- Sweating.
- Prolonged standing that appeared to precipitate TLoC. **[1.1.5.1]**

Specialist cardiology assessment and diagnosis

- Carry out a specialist cardiology assessment as follows.
  - Reassess the person's:
    - detailed history of TLoC including any previous events
    - medical history and any family history of cardiac disease
    - drug therapy at the time of TLoC and any subsequent changes.
  - Conduct a clinical examination, including full cardiovascular examination and measurement of supine and standing blood pressure.
  - Repeat 12-lead ECG and examine previous ECG documentation.

  On the basis of this assessment, assign the person to one of the following types of syncope: suspected structural heart disease, suspected cardiac arrhythmic, suspected neurally mediated, or unexplained. Offer further testing as directed by recommendations 1.2.2.1 to 1.2.2.10. **[1.2.1.1]**

- For people with a suspected cardiac arrhythmic cause of syncope, offer an ambulatory ECG and do not offer a tilt test. The type of ambulatory ECG offered should be chosen on the basis of the person's history (and, in particular, frequency) of TLoC.

  - People with very frequent TLoC (daily or every few days): offer Holter monitoring (up to 48 hours if necessary). If no further TLoC occurs during the monitoring period, offer an external event recorder that provides continuous recording with the facility for the patient to indicate when a symptomatic event has occurred.
  - People who have less frequent TLoC (every 1–2 weeks): offer an external event recorder. If the person experiences further TLoC outside the period of external event recording, offer an implantable event recorder.
  - People who have TLoC infrequently (less than every 2 weeks): offer an implantable event recorder. A Holter monitor should not usually be offered unless there is evidence of a conduction abnormality on the 12-lead ECG. **[1.2.2.4]**
- For people who have a clear diagnosis of neurally mediated syncope on initial assessment, do not offer a tilt test to confirm the diagnosis. **[1.2.2.5]**
- Offer ambulatory ECG and do not offer a tilt test to people:
  - with unexplained syncope who are younger than 60 years of age
  - who are aged 60 years or older if carotid sinus massage is not diagnostic.

  The type of ambulatory ECG offered should be appropriate to the person's history of TLoC (see recommendation 1.2.2.4). **[1.2.2.9]**

RECOMMENDATIONS

This guidance refers to different types of syncope. The following definitions apply to this guideline. See also the glossary (in the last section of Chapter 2) for definitions of other terms used in this guideline.

- **Syncope** Transient loss of consciousness due to a reduction in blood supply to the brain.
- **Neurally mediated syncope** Sometimes called ‘reflex syncope’. Transient loss of consciousness due to a reflex bradycardia and/or hypotensive response to a number of causes; these include vasovagal syncope, carotid sinus syncope, and situational syncope.
- **Vasovagal syncope** A form of neurally mediated syncope due to excessive or inappropriate vagal activity. This is often, but not always, triggered by circumstances such as pain, prolonged standing (especially in a warm environment), or emotional stress. This commonly presents as an identifiable ‘uncomplicated faint’ but can present as sudden unprovoked syncope.
- **Carotid sinus syncope** A form of neurally mediated syncope in which pressure on one or other carotid artery causes syncope.
- **Situational syncope** A form of neurally mediated syncope occurring in certain situations, usually involving an increase in intra-abdominal pressure (for example, cough syncope and micturition syncope).
- **Cardiac arrhythmic syncope** Syncope caused by a sudden abnormality of heart rhythm, which may be a bradyarrhythmia (abnormal rhythm with a slow heart rate) or a tachyarrhythmia (abnormal rhythm with a fast heart rate).
- **Exercise-induced syncope** Syncope induced by exercise.

1.1 Initial assessment and diagnosis

1.1.1 Gathering information and recording of the suspected transient loss of consciousness (TLoC) event

Hyperlink to Chapter 3 - Initial Assessment and Diagnosis

1.1.1.1 Ask the person who has had the suspected TLoC, and any witnesses, to describe what happened before, during and after the event. Try to contact witnesses who are not present by telephone. Items to be recorded include the following.

- Circumstances of the event.
- Person's posture at outset.
- Prodromal symptoms.
- Appearance and colour of the person during the event.
- Presence or absence of movement during the event.
- Whether any tongue-biting or injury occurred during the event.
- Duration of the event.
- Length of time to recovery.
- Presence or absence of confusion during the recovery period.

1.1.1.2 Record carefully the information obtained from all accounts of the suspected TLoC. Include paramedic records with this information. Give copies of all records to the receiving clinician when care is transferred, and to the person who had the suspected TLoC.

1.1.1.3 When recording a description of the suspected TLoC from a witness, take care to ensure that their communication and other needs are taken into account. This is particularly important when communicating with a child or young person, or person with special communication needs.

1.1.1.4 Use information gathered from all accounts of the suspected TLoC (see recommendation 1.1.1.1) to confirm whether or not TLoC has occurred. If the person definitely did not have TLoC, instigate

suitable management accordingly (for example, if the person is determined to have had a fall, rather than TLoC, refer to 'Falls: the assessment and prevention of falls in older people' [NICE clinical guideline 21]).

1.1.2 History-taking, clinical examination, 12-lead electrocardiogram (ECG) and other tests for people who have experienced TLoC

Hyperlink to Chapter 3 - Initial Assessment and Diagnosis

Hyperlink to Chapter 4 - 12 Lead ECG

1.1.2.1 Assess and record:

- details of any previous TLoC, including number and frequency
- the person's medical history and any family history of cardiac disease (for example, personal history of heart disease and family history of sudden cardiac death)
- current medication
- supine and standing blood pressure
- vital signs (for example, pulse rate, respiratory rate and temperature) – repeat if clinically indicated
- cardiovascular and neurological examination
- resting 12-lead ECG (see recommendations 1.1.2.2 and 1.1.2.3)
- any further examination as directed by the person's history.

1.1.2.2 Record a 12-lead ECG. When available, use a 12-lead ECG with automated interpretation. If any abnormality is identified, seek expert advice.

1.1.2.3 If a 12-lead ECG with automated interpretation is not available, record a 12-lead ECG and have the reading interpreted by a healthcare professional who is trained and competent in identifying the following abnormalities.

- Conduction abnormality (any degree of heart block).

- Inappropriate persistent bradycardia.
- Any ventricular arrhythmia (including ventricular ectopic beats).
- Long QT (> 450 ms) and short QT (< 350 ms) intervals.
- Brugada syndrome.
- Ventricular pre-excitation (part of Wolff-Parkinson-White syndrome).
- Left or right ventricular hypertrophy.
- Abnormal T wave inversion.
- Pathological Q waves.
- Atrial arrhythmia (sustained).
- Paced rhythm.

1.1.3 Red flags

Hyperlink to Chapter 3 - Initial Assessment and Diagnosis

For this guideline, the term ‘red flags’ indicates that the person is considered to be at high risk of a serious adverse event and should be referred for urgent specialist assessment

1.1.3.1 If, during the initial assessment, it is found that TLoC is secondary to another condition that requires immediate treatment, instigate suitable management accordingly. Use clinical judgement to determine the urgency of treatment.

1.1.3.2 Treat as an emergency (within 24 hours) anyone with TLoC who also has any of the following.

- An ECG abnormality (see recommendation 1.1.2.3).
- Heart failure.
- TLoC on exertion.
- Family history of sudden cardiac death in people aged younger than 40 years and/or an inherited cardiac condition.
- Aged older than 65 years with no prodromal symptoms.
- New or unexplained breathlessness.
- A heart murmur.

If assessed out of hospital send the person to the Emergency Department. If assessed in the Emergency Department, admit the person to hospital and arrange a specialist cardiology assessment within 24 hours.

1.1.4 Making a diagnosis after the initial assessment of TLoC

Hyperlink to Chapter 3 - Initial Assessment and Diagnosis

Uncomplicated faint (vasovagal syncope)

1.1.4.1 Diagnose uncomplicated faint (vasovagal syncope) on the basis of the initial assessment when:

- there are no features from the initial assessment that suggest an alternative diagnosis (note that brief seizure activity can occur during uncomplicated faints and is not necessarily diagnostic of epilepsy) **and**
- there are features strongly suggestive of uncomplicated faint; that is, at least one of the following features is present ('the six Ps').
  - **P**osture (prolonged standing or sitting).
  - **P**rovoking factors (such as pain, fear, emotional distress or a medical procedure).
  - **P**rodromal symptoms (such as sweating or feeling warm/hot before TLoC).
  - **P**ost-TLoC nausea or vomiting.
  - **P**ost initial recovery, recurrence of TLoC provoked by sitting or standing up.
  - **P**revious similar episodes, in which TLoC has been prevented by lying down.

Situational syncope

1.1.4.2 Diagnose situational syncope on the basis of the initial assessment when:

- there are no features from the initial assessment that suggest an alternative diagnosis **and**
- syncope is clearly and consistently provoked by micturition (usually in men) or by coughing.

Orthostatic hypotension

1.1.4.3 Diagnose orthostatic hypotension on the basis of the initial assessment when:

- there are no features suggesting an alternative diagnosis **and**
- the history is typical of orthostatic hypotension **and**
- either the systolic blood pressure falls by at least 20 mm Hg in the first 5 minutes after standing up from a supine position or the systolic blood pressure falls below 90 mm Hg on standing.

1.1.4.4 After a diagnosis of orthostatic hypotension, manage according to the condition of the patient (for example, see 'Falls: the assessment and prevention of falls in older people' [NICE clinical guideline 21]).

1.1.5 Referral for further assessment

Hyperlink to Chapter 3 - Initial Assessment and Diagnosis

Predictive factors indicating need for referral to a specialist in epilepsy

1.1.5.1 Refer people who present with one or more of the following features (that is, features that are strongly suggestive of epileptic seizures) for an assessment by a specialist in epilepsy; the person should be seen by the specialist within 4 weeks (see 'The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care [NICE clinical guideline 20]).

- A bitten tongue.
- Abnormal behaviour (one or more of: witnessed amnesia for abnormal behaviour, witnessed unresponsiveness, unusual posturing, or prolonged limb jerking [note that brief seizure

activity can occur during uncomplicated faints and is not necessarily diagnostic of epilepsy]).

- Post-ictal confusion.
- Head-turning to one side during TLoC.
- Prodromal déjà vu or jamais vu.

Consider that the episode may not be related to epilepsy if any of the following features are present.

- Pre-syncope, especially where syncope was avoided by postural change.
- Sweating.
- Prolonged standing that appeared to precipitate TLoC.

Referral for specialist cardiology assessment – all other people with TLoC

1.1.5.2 Refer all people with TLoC for specialist cardiology assessment, except those in whom a firm diagnosis has been reached after the initial assessment or whose presentation is strongly suggestive of epileptic seizures.

1.2 Specialist cardiology assessment and diagnosis

1.2.1 Assessment and assignment to type of syncope

Hyperlink to Chapter 5 Specialist Assessment

1.2.1.1 Carry out a specialist cardiology assessment as follows.

- Reassess the person's:
  - detailed history of TLoC including any previous events
  - medical history and any family history of cardiac disease
  - drug therapy at the time of TLoC and any subsequent changes.
- Conduct a clinical examination, including full cardiovascular examination and measurement of supine and standing blood pressure.

- Repeat 12-lead ECG and examine previous ECG documentation.

On the basis of this assessment, assign the person to one of the following types of syncope: suspected structural heart disease, suspected cardiac arrhythmic, suspected neurally mediated, or unexplained. Offer further testing as directed by recommendations 1.2.2.1 to 1.2.2.10.

1.2.2 Diagnostic tests for different types of syncope

Hyperlink to Chapter 6 Diagnostic Tests

1.2.2.1 For people with suspected structural heart disease, investigate appropriately.

1.2.2.2 For people with exercise-induced syncope, if there is no clinical evidence of structural heart disease, such as aortic stenosis or hypertrophic cardiomyopathy, offer urgent[1] exercise testing. Advise the person to refrain from exercise until advised otherwise following further assessment.

1.2.2.3 When the mechanism for exercise-induced syncope is identified by exercise testing, carry out further investigation or treatment as appropriate in each individual clinical context. If exercise testing does not clarify the cause of TLoC, carry out further investigations assuming a suspected cardiac arrhythmic cause.

1.2.2.4 For people with a suspected cardiac arrhythmic cause of syncope, offer an ambulatory ECG and do not offer a tilt test. The type of ambulatory ECG offered should be chosen on the basis of the person's history (and, in particular, frequency) of TLoC.

- People with very frequent TLoC (daily or every few days): offer Holter monitoring (up to 48 hours if necessary). If no further

[1] 'Urgent' is defined as 'as soon as possible and no longer than 7 days from the TLoC'.

TLoC occurs during the monitoring period, offer an external event recorder that provides continuous recording with the facility for the patient to indicate when a symptomatic event has occurred.

- People who have less frequent TLoC (every 1–2 weeks): offer an external event recorder. If the person experiences further TLoC outside the period of external event recording, offer an implantable event recorder.
- People who have TLoC infrequently (less than every 2 weeks): offer an implantable event recorder. A Holter monitor should not usually be offered unless there is evidence of a conduction abnormality on the 12-lead ECG.

1.2.2.5 For people who have a clear diagnosis of neurally mediated syncope on initial assessment, do not offer a tilt test to confirm the diagnosis.

1.2.2.6 For people with suspected vasovagal syncope who have had recurrent episodes of TLoC that adversely affect their quality of life, or represent a high risk of injury, consider a tilt test to assess whether the syncope is accompanied by a severe cardioinhibitory response (usually asystole).

1.2.2.7 For people with unexplained syncope who are aged 60 years or older, and for people of any age with suspected carotid sinus syncope, offer carotid sinus massage. This test should be conducted in a controlled environment, with ECG recording, and with resuscitation equipment and a skilled team immediately available. When carotid sinus massage is being offered, it should be done before offering ambulatory ECG (see recommendation 1.2.2.9).

1.2.2.8 Diagnose carotid sinus syncope when carotid sinus massage reproduces syncope (usually due to a predominantly cardioinhibitory response).

1.2.2.9 Offer ambulatory ECG and do not offer a tilt test to people:

- with unexplained syncope who are younger than 60 years of age
- who are aged 60 years or older if carotid sinus massage is not diagnostic.

The type of ambulatory ECG offered should be appropriate to the person's history of TLoC (see recommendation 1.2.2.4).

1.2.2.10 When offering a person an implantable event recorder, provide one that has both patient-activated and automatic detection modes. Instruct the person and their family and/or carer how to operate the device. Advise the person that they should have prompt (usually the next day) follow-up (data interrogation of the device) after they have any further TLoC.

1.3 Providing information for people with a suspected or confirmed TLoC

1.3.1 Driving

1.3.1.1 When a person who has experienced TLoC first presents, give them advice on their eligibility to drive[2].

1.3.1.2 With the exception of people in whom TLoC is diagnosed as an uncomplicated faint (vasovagal syncope) and people with a clear history of micturition syncope, advise all people who have experienced TLoC that they must not drive.

1.3.1.3 After a firm diagnosis of orthostatic hypotension or when they have had a specialist assessment, advise the person that they must report their TLoC to the DVLA.

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[2] Please refer to 'Drivers Medical Group DVLA (2009): At a glance guide to the current medical standards of fitness to drive' available from: www.dft.gov.uk/dvla/~/media/pdf/medical/at_a_glance.ashx and www.dft.gov.uk/dvla/medical/medical_advisory_information/medicaladvisory_meetings/pmembers_nervous_system.aspx

1.3.2 Health and safety at work

1.3.2.1 Advise people who have experienced TLoC of the implications of their episode for health and safety at work and any action they must take to ensure the safety of themselves and those of other people.

1.3.3 Future events

1.3.3.1 Advise people who have experienced TLoC to try to record any future events (for example, a video recording [including using cameras in mobile telephones] or a detailed witness account of the event).

1.3.4 Explanation of causes of TLoC

1.3.4.1 Offer people a clear explanation of the possible causes of their TLoC.

1.3.5 People waiting for a specialist assessment

1.3.5.1 Provide the following advice to people waiting for a specialist assessment.

- What they should do if they have another similar event.
- What they should do if they have another event that is different.
- If appropriate, how they should modify their activity (for example, by avoiding physical exertion).

1.3.6 People who have a confirmed diagnosis

1.3.6.1 In people diagnosed with an uncomplicated faint (vasovagal syncope), reassure them that their prognosis is good. Advise them to consult their GP if they experience further TLoC, particularly if this occurs frequently or differs from their recent episode.

1.3.6.2 Offer lifestyle advice to people diagnosed with an uncomplicated faint (vasovagal syncope); for example, advise them:

- of the possible trigger events, and strategies for avoiding them

- to be vigilant for the onset of warning signs of fainting and to initiate counter measures immediately (such as lying down, if possible with their legs elevated)
- to avoid standing for long periods of time
- to initiate counter pressure manoeuvres (such as contracting calf or arm muscles or buttocks) if they are standing for long periods of time
- to get up cautiously when they feel well again after a faint, or to seek help if they don't get better
- to keep a record of their symptoms, when they occur and what they were doing at the time, in order to understand what causes them to faint.

1.3.6.3 Once a firm diagnosis of orthostatic hypotension has been made, provide the person with information about their condition. This should include:

- treatment options available
- prognostic implications of the diagnosis
- what they should do if they experience another TLoC.

1.3.6.4 Offer lifestyle advice to people diagnosed with orthostatic hypotension; for example, advise them to:

- avoid activities, such as:
  - eating heavy meals
  - sudden standing after meals/eating
  - taking hot baths or being subjected to excessive heat
  - becoming dehydrated; instead, they should increase fluid intake and have an adequate salt intake
  - straining to open their bowels
  - bending at the waist; instead, they should pick something up from the floor by bending at the knees (squatting)
- limit or avoid alcohol
- consider sleeping with the head of the bed slightly elevated

- take care when moving from a lying or sitting position to a standing position (for example, when getting out of bed, they should sit on the edge of the bed for a short time before standing)
- sit or lie down immediately after feeling lightheaded upon standing.

1.3.6.5 Offer lifestyle advice to people suspected of having an epileptic cause for their TLoC (see 'The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care [NICE clinical guideline 20]); for example, advise them:

- of safety issues, such as bathing and swimming, and working at heights and with machinery
- what to do if they experience another TLoC while waiting for a specialist appointment (for example, see their GP or attend the Emergency Department)
- to keep a record of any episodes of TLoC, including any witness accounts of the event; they should take these to the appointment with the specialist or Emergency Department clinician
- of first aid for tonic-clonic seizures (offer also to the person's family and/or carers).

1.3.6.6 Offer lifestyle advice to people suspected of having a cardiac cause for their TLoC; for example, advise them to:

- avoid situations that could trigger TLoC (for example, if their TLoC is caused by exercise) until advised further by a specialist
- not travel by air until advised further by a specialist, or advised by a specialist that it is safe to do so
- find out if there is any history of TLoC or sudden death in any members of the family (advise them to try to go back at least two generations)

CARE PATHWAYS

Box A

Ask the person who has had the suspected TLoC, and any witnesses, to describe what happened before, during and after the event. Try to contact witnesses who are not present by telephone

Items to be recorded include the following:

- Circumstances of the event.
- Person's posture at outset.
- Prodromal symptoms.
- Appearance and colour of the person during the event.
- Presence or absence of movement during the event.
- Whether any tongue-biting or injury occurred during the event.
- Duration of the event.
- Length of time to recovery.
- Presence or absence of confusion during the recovery period.

Box B

12-lead ECG – If an automated interpretation is not available, the unreported 12-lead ECG should be reviewed by someone who is able to identify the following abnormalities

- Conduction abnormality (any degree of heart block)
- Inappropriate persistent bradycardia
- Any ventricular arrhythmia (including Long QT (>450ms) and short QT (<350ms)
- Brugada syndrome
- Ventricular pre-excitation (Wolfe-Parkinson-White syndrome)
- Left or right ventricular hypertrophy
- Abnormal T wave inversion
- Pathological Q waves
- Atrial arrhythmia (sustained)
- Paced rhythm

Box C

Arrange for a specialist cardiology assessment within 24 hours if they have any of the following.

- ECG abnormality (as specified in Box B)
- Heart failure
- TLoC on exertion
- Family history of sudden cardiac death under 40 years and/or inherited cardiac condition
- Age is over above 65 years and there were no prodromal symptoms
- New or unexplained breathlessness
- Heart murmur

Suspected loss of transient consciousness (TLoC)

- Take patient's account of the suspected TLoC [box A]
- Take witness account (if available) of the suspected TLoC [box A]
- Record carefully information from all accounts, including paramedic

Accounts exclude TLoC?

Yes → **Manage according to non-TLoC presentation**

No

ASSESS AND RECORD THE FOLLOWING:

- **Details of any previous TLoC**
- **Current TLoC see box A**
- **Person's medical history & any family history of heart disease**
- **Current medication**
- **Supine and standing BP**
- **Vital signs (e.g. pulse rate, respiratory rate, temperature)**
- **Examine the heart and nervous system**
- **12-lead ECG (preferably automated) [box B]**
- **Any further examination as directed by the person's history.**

Is TLoC secondary to another condition requiring immediate treatment?

Yes → **Manage according to primary condition. Use clinical judgement to determine the urgency of treatment.**

No

Does the patient have signs and symptoms of possible life threatening condition? Ref Box C

YES → **If assessed out of hospital SEND THE PERSON TO ED. If assessed in the Emergency Department, admit the person to hospital and arrange specialist cardiology referral within 24 h.**

NO

Can a diagnosis of the cause of the TLoC be made? [box D]

YES → **Uncomplicated faint or situational syncope**

Whatever care setting, provide the person with information and lifestyle advice
Advise them to consult their GP if they experience further episodes that are frequent or which differ from their previous episodes.

YES → **Orthostatic hypotension**

- **Manage according to the condition of the patient.**
- **Provide the patient with information**
- **Refer to NICE Falls [CG 21] guideline if appropriate.**

NO → **Are there features strongly suggestive of Epilepsy? [box E]**

Yes

- **Refer for assessment by a specialist in epilepsy; the person should be seen within 4 weeks.**
- **Provide information and advice {see UNG}}.**
- **Manage according to NICE Epilepsy CG20 guideline.**

No → **Refer for specialist cardiology assessment within 24 hours if urgent**

Provide patient information and advice

Box D ' INITIAL ASSESSMENT'

Make a diagnosis of, **uncomplicated faint** when:

- There are no features that suggest an alternative diagnosis ……AND
- there are features strongly suggestive of uncomplicated faint; that is, at least one of following features is present ('the six Ps').
  - Posture (prolonged standing or sitting).
  - Provoking factors (such as pain, fear, emotional distress, a medical procedure).
  - Prodromal symptoms (such as sweating or feeling warm/hot before TLoC).
  - Post-TLoC nausea or vomiting.
  - Post initial recovery, recurrence of TLoC provoked by sitting or standing up.
  - Previous similar episodes, in which TLoC has been prevented by lying down.

Make a diagnosis of **situational syncope** when:

- there are no features from the initial assessment that suggest an alternative diagnosis……AND
- syncope is clearly and consistently provoked by micturition (usually in men) or by coughing

Make a diagnosis of **orthostatic hypotension** when:

- there are no features suggesting an alternative diagnosis ...AND
- the history is typical of orthostatic hypotension ...AND
- either the systolic BP falls by at least 20 mm Hg in the first 5 minutes after standing up from a supine position or the systolic BP falls below 90 mm Hg on standing.

Box E- Features strongly suggestive of seizures

- A bitten tongue.
- Abnormal behaviour (one or more of: witnessed amnesia for abnormal behaviour, witnessed unresponsiveness, unusual posturing, or prolonged limb jerking [note that brief seizure activity can occur during uncomplicated faints and is not necessarily diagnostic of epilepsy]).
- Post-ictal confusion.
- Head-turning to one side during TLoC.
- Prodromal déjà vu or jamais vu.

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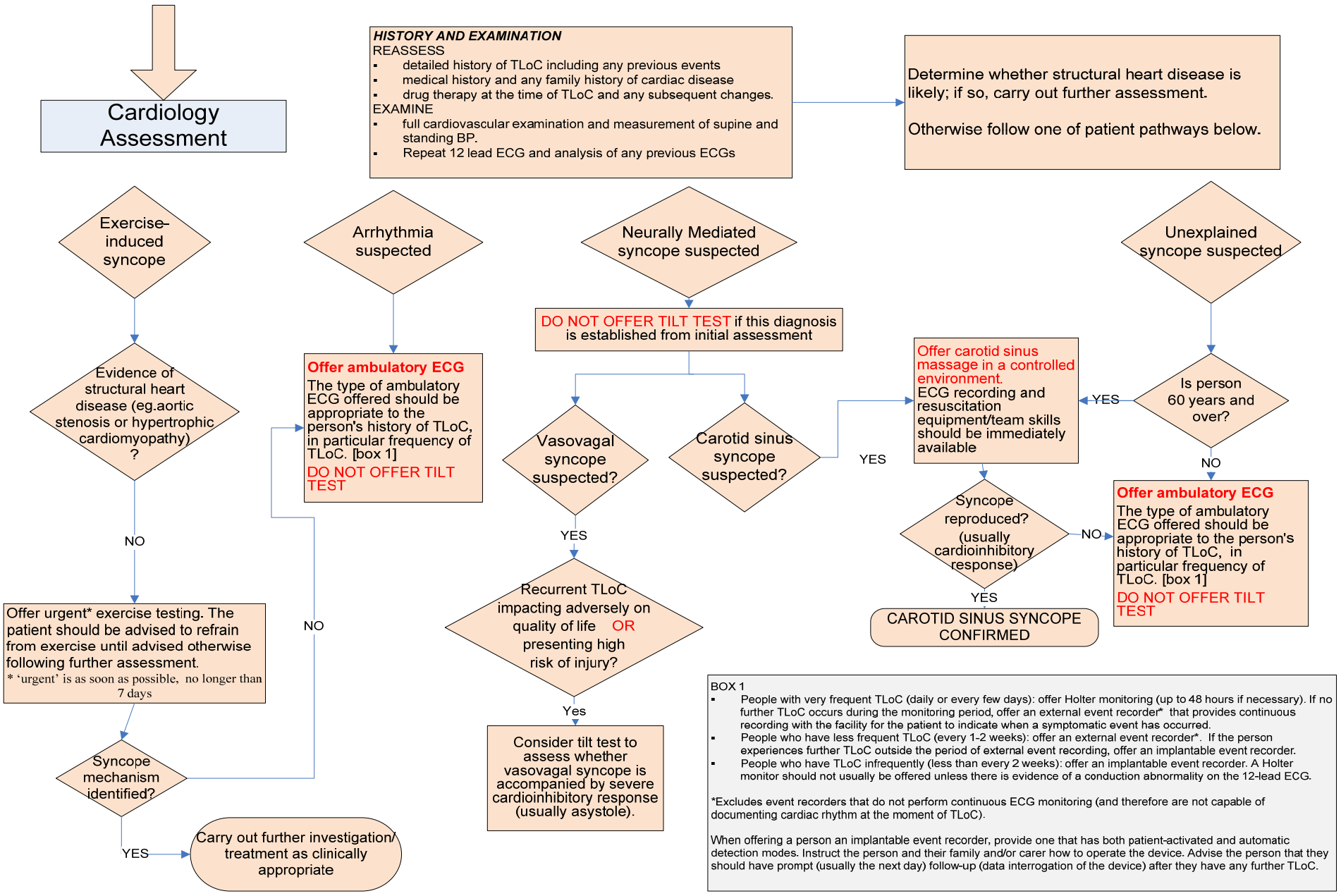


BOX 1

- People with very frequent TLoC (daily or every few days): offer Holter monitoring (up to 48 hours if necessary). If no further TLoC occurs during the monitoring period, offer an external event recorder* that provides continuous recording with the facility for the patient to indicate when a symptomatic event has occurred.
- People who have less frequent TLoC (every 1-2 weeks): offer an external event recorder*. If the person experiences further TLoC outside the period of external event recording, offer an implantable event recorder.
- People who have TLoC infrequently (less than every 2 weeks): offer an implantable event recorder. A Holter monitor should not usually be offered unless there is evidence of a conduction abnormality on the 12-lead ECG.

*Excludes event recorders that do not perform continuous ECG monitoring (and therefore are not capable of documenting cardiac rhythm at the moment of TLoC).

When offering a person an implantable event recorder, provide one that has both patient-activated and automatic detection modes. Instruct the person and their family and/or carer how to operate the device. Advise the person that they should have prompt (usually the next day) follow-up (data interrogation of the device) after they have any further TLoC.

1 Introduction Chapter

1.1 Clinical Needs Assessment for Transient Loss of Consciousness

1.1.1 Introduction:

Transient loss of consciousness (TLoC) is a loss of consciousness with complete recovery. It is usually spontaneous in onset and may be described by the person as a 'blackout'. The main causes of TLoC are: (a) syncope - due to dysfunction of the cardiovascular system, (b) epilepsy - due to dysfunction of the nervous system and (c) psychogenic seizures - due to dysfunction of the psyche. TLoC is a symptom, not a disease, the causes of which are varied.

The prevalence and mortality of the various causes of TLoC in England and Wales were determined. It was recognised that though the population of both England and Wales had access to the same healthcare system i.e., the National Health Service (NHS), there were differences in the way this healthcare was delivered to the population of the respective countries (Davies 2007). There were 50.1 million inhabitants in England in 2008, to whom health care was delivered through 152 Primary Care Trusts, controlled by 10 Strategic Health Authorities. On the other hand, in 2008, the population of Wales was 2.9 million. Health care to this population was delivered via 14 NHS trusts and 22 local health boards (Davies 2007).

1.1.2 Sources of Information

The sources of information used to assess the prevalence and mortality of various causes of TLoC were as follows:

- Hospital Episode Statistics Online from The NHS Information Centre in England (http://www.hesonline.nhs.uk).
- Patient Episode Database for Wales
- NHS Direct – England and Wales
- ICD -10 Code

- Office of National Statistics

(a) Hospital Episode Statistics (HES):

HES is a record-level data warehouse in the NHS Information Centre. It is the data source for a wide range of healthcare analysis for the NHS, government and many other organisations and individuals. Information available is extracted from routine data flows between healthcare providers and commissioners. The Information Centre administers the HES Service on behalf of the Secretary of State for Health.

Three main types of datasets are available:

(i) Admitted patients: these number about 15 million records/year and include inpatients and day cases. All NHS funded admitted patient care and private care within NHS hospitals in England, and NHS funded admitted patient care within the independent sector is included. Data are generated for each financial year.

(ii) Outpatient activity: collection of this information started in 2003 and is still experimental. It generates about 45 million records/year

(iii) Accident and Emergency activity: this is still under development and generates about 19 million records/year

Each HES record can contain more than 50 pieces of information.

Separate agencies for collection of data exist in Wales, Northern Ireland and Scotland.

Data available from HES can be analysed in 3 different ways:

(i) According to the diagnosis – based on the International Classification of Diseases

(ii) According to ‘procedures’ or ‘operations’ that patients undergo: based on the OPCS 4.4 classification system

(iii) According to Healthcare Resource Group (HRG): which is a group of clinically similar treatments and care that require similar levels of healthcare resource

Limitations of the HES record:

(i) Each record is a continuous period of care administered within a particular consultant speciality at a single hospital provider. If a patient is transferred to another consultant or to a different provider during an episode of treatment, a new record is generated. It is estimated that in about 8% of cases, the episode of treatment will generate more than one record and hence the true number of patients treated overestimated.

(ii) It is also common for a patient to undergo two or more separate episodes of inpatient treatment during a HES data year. Each episode will result in a separate record/records, thus overestimating the absolute number of patients being treated under any category.

(iii) Patients who have not completed an episode at the end of the financial year will not be counted and so the true number of patient episodes will be underestimated.

(b) Patient Episode Database for Wales:

The Patient Episode Database for Wales (PEDW) contains records of the inpatient/daycase care received by all patients in NHS Wales hospitals and for some Welsh residents treated in the other home countries. This database is administered by Health Solutions Wales, a division of the Velindre NHS Trust, Cardiff.

(c) International Classification of Diseases:

The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), in use since 1992, is a coding of diseases and signs, symptoms, abnormal findings, complaints, social circumstances and external causes of injury or diseases, as classified by the World Health

Organisation (WHO). The code set allows more than 155,000 different codes and permits tracking of many new diagnoses and procedures and is a significant expansion on the 17,000 codes available in ICD-9. It is used in many countries across the world for reporting mortality and morbidity statistics. Information about a patient's diagnosis, recorded in the medical notes by the treating physician is translated into ICD-10 codes by a clinical coder. This allows comparison of conditions consistently all over the world.

Under the ICD-10 coding, disorder of a system is usually coded by a single letter followed by 3 or more digits. A decimal point separates the third and fourth digits (e.g. I06.0 – rheumatic aortic stenosis). As there are many variations to the four character code, it is common practice to summarise at the 3 character level (e.g., I00-I99 – Diseases of the circulatory system). The R00-R99 ICD-10 codes are used for symptoms, signs and abnormal clinical and laboratory findings, not classified elsewhere.

(d) Office of National Statistics:

Mortality Statistics DR contains details of the deaths registered in England and Wales, classified by sex and age and by other selected information collected at the time of registration. Statistics for deaths in previous years are also included to show recent trends in mortality.

(e) NHS Direct England and NHS Direct Wales

After consensus from the Guideline Development Group, the ICD-10 classification was used for preparation of this report.

1.1.3 Results

The following ICD-10 codes were used for obtaining further statistics on the prevalence and mortality of the various causes of TLoC.

Broad Classification:

G00-G99: For diseases of the nervous system

I00-I99: For diseases of the circulatory system

R00-R99: For symptoms, signs and abnormal clinical and laboratory findings not classified elsewhere

F44: Dissociative disorders

Specific codes, within this broad classification, were used to obtain detailed information about specific causes of TLoC.

R55 Syncope and Collapse: for patients presenting with Vasovagal Syncope or Syncope where the cause was not known.

G40 Epilepsy : for patients presenting with epilepsy and included the following specific codes: *G40.2:* Localisation-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, *G40.3*: Generalised idiopathic epilepsy and epileptic syndromes, *G40.5*: Special epileptic syndromes, *G40.6*: Grand mal seizures, unspecified (with or without petit mal), *G40.7*: petit mal, unspecified, without grand mal seizures, *G40.8:* Other epilepsy, *G40.9*: Epilepsy, unspecified, *R56.8*: Other and unspecified convulsions, *G41*: Status Epilepticus

Carotid Sinus Hypersensitivity: G90.0 Disorders of the autonomic nervous system - Idiopathic peripheral autonomic neuropathy

Orthostatic Hypotension: included other specific codes i.e. G90.3: disorders of the autonomic nervous system, multisystem degeneration, I95.0: Idiopathic hypotension, I95.1: Hypotension, orthostatic hypotension, I95.2: Hypotension due to drugs

Aortic Stenosis: included the following specific codes: I06.0: Rheumatic aortic stenosis, I06.2: Rheumatic aortic stenosis with insufficiency, I08.0: Disorders of both mitral and aortic valves, I08.2: Disorders of both aortic and tricuspid valves, I08.3: Combined disorders of mitral, aortic and tricuspid valves, I08.8:

Other multiple valve diseases, I35.0: Aortic (valve) stenosis, I35.2: Aortic (valve) stenosis with insufficiency

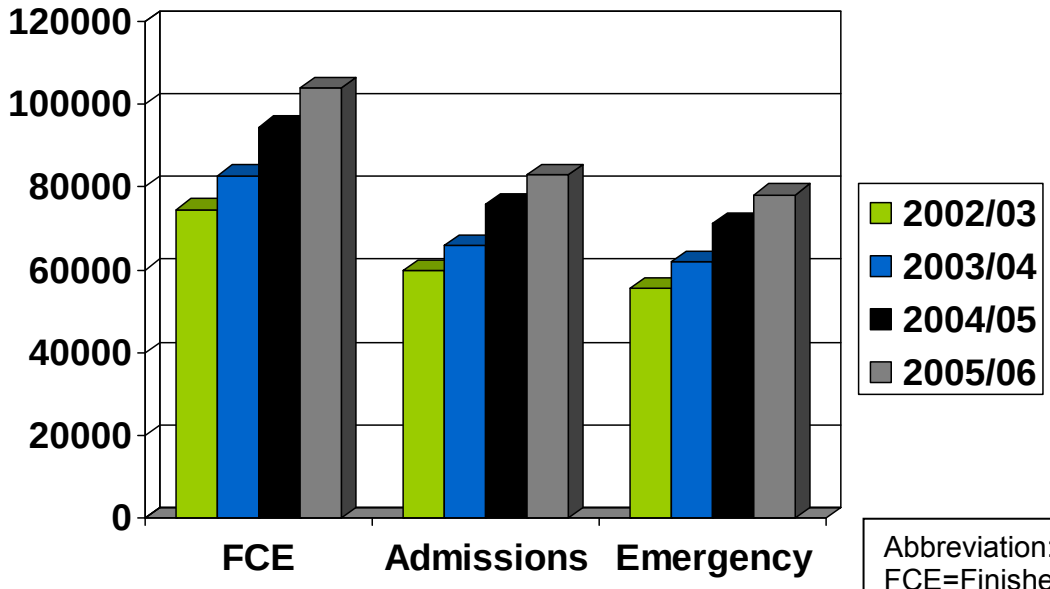
LV Dysfunction: included the following specific codes: I25.5 Ischemic cardiomyopathy, I42.0 Dilated cardiomyopathy, I50.0 Congestive heart failure

Arrhythmias: I44.1 Atrioventricular block, second degree, I44.2 Atrioventricular block, complete, I45.5 Other specified heart block, I45.8 Other specified conduction disorders, I45.9 Conduction disorder, unspecified, I45.6 Pre-excitation syndrome, I47.0 Re-entry ventricular arrhythmia, I47.2 Ventricular tachycardia, I47.1 Supraventricular tachycardia, I48.X Atrial fibrillation and flutter, I49.5 Sick sinus syndrome

Miscellaneous Group comprising other causes of TLoC: I26.0: Pulmonary embolism with mention of acute cor pulmonale, I31.9: Disease of pericardium, unspecified, I42.1: Obstructive hypertrophic cardiomyopathy, I42.2: Other hypertrophic cardiomyopathy, I71.0: Dissection of aorta [any part]

No ICD-10 codes existed for inherited cardiac conditions which could cause TLoC viz., Long QT syndrome or Brugada Syndrome.

(a) R55 Syncope and Collapse (ICD-10) – Data for England



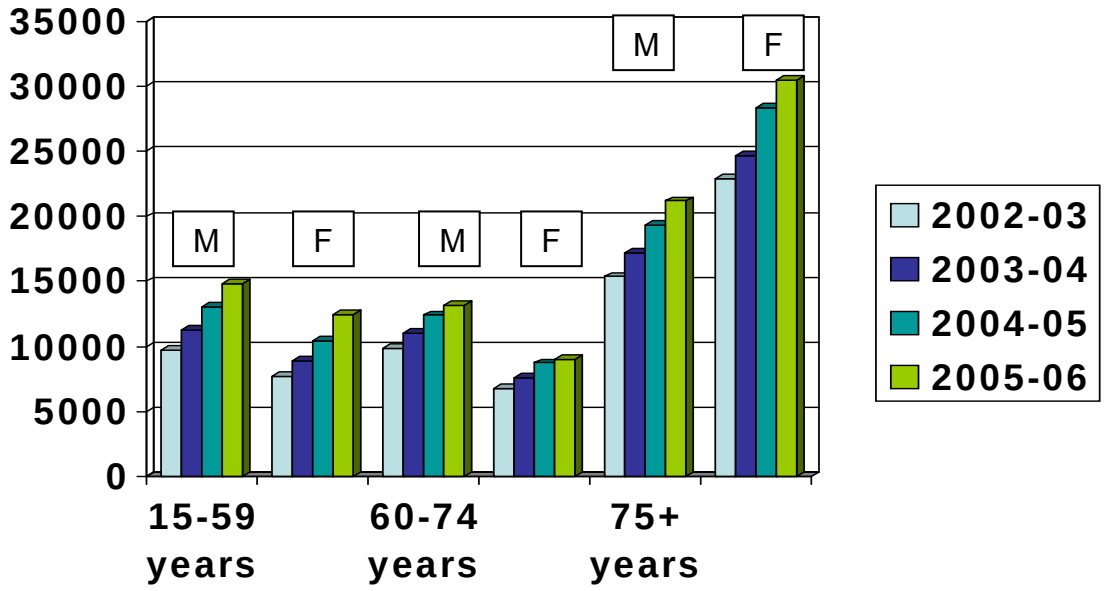
Abbreviation:
FCE=Finished Consultant Episode

Year	Finished Consultant Episodes	Admissions	Emergency	Mean length of stay (days)	Median Episode Duration (days)	Mean Age (years)
2005/06	103825 (↑ 39%*)	82999 (↑ 38.6%*)	78146 (↑ 40.4%*)	3.9 (↓ 36%*)	1	67
2004/05	94486	75850	71311	4.6	1	68
2003/04	82773	65986	61982	5.5	2	68
2002/03	74576	59851	55651	6.1	2	68

*relative to year 2002/03

In the year 2005-2006, there were a little over 100,000 finished consultant episodes for R55 Syncope and Collapse in England. A vast majority (82,999; 79.9%) of these patients presented as an emergency, out of which a majority (78,146; 75.3%) were admitted. Over the years 2002-2006, there has been a steady increase (about 40%) in the number of patients presenting with this condition, the number presenting as an emergency and the number of patients admitted. On the other hand, there has been a steady decrease in the mean length of stay (6.1 days in 2002-2003, 3.9 days in 2005-2006; a decrease of 36%) and in the median episode duration (2 days in 2002-2003 to

1 day in 2005-2006) over the same period. Little difference was noted in the mean age of patients.

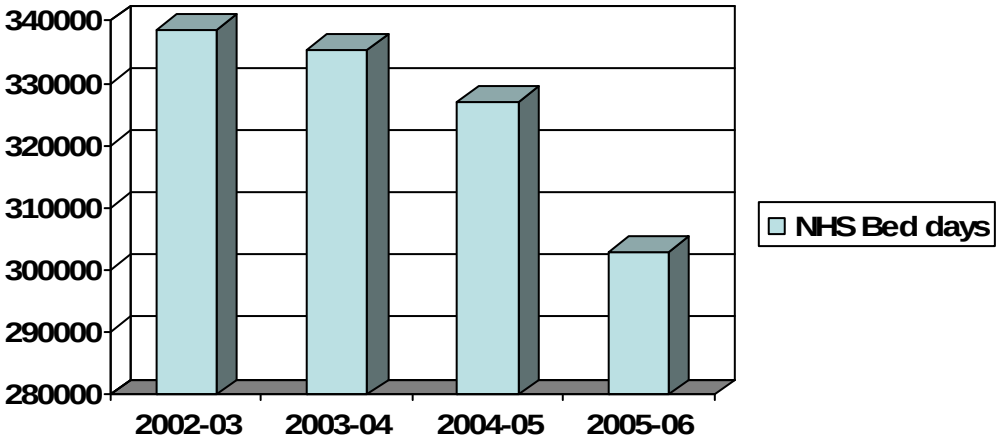


Abbreviations: M=Male, F=Female

Year	Finished Consultant Episodes					
	15-59 years		60-74 years		75 + years	
	Male	Female	Male	Female	Male	Female
2005/06	14839 (↑ 34.1%)	12413 (↑ 37.8%)	13207 (↑ 25.3%)	9049 (↑ 25.0%)	21175 (↑ 27.4%)	30483 (↑ 24.7%)
2004/05	13032	10461	12397	8716	19321	28376
2003/04	11239	8881	11003	7564	17187	24712
2002/03	9765	7711	9860	6787	15369	22944

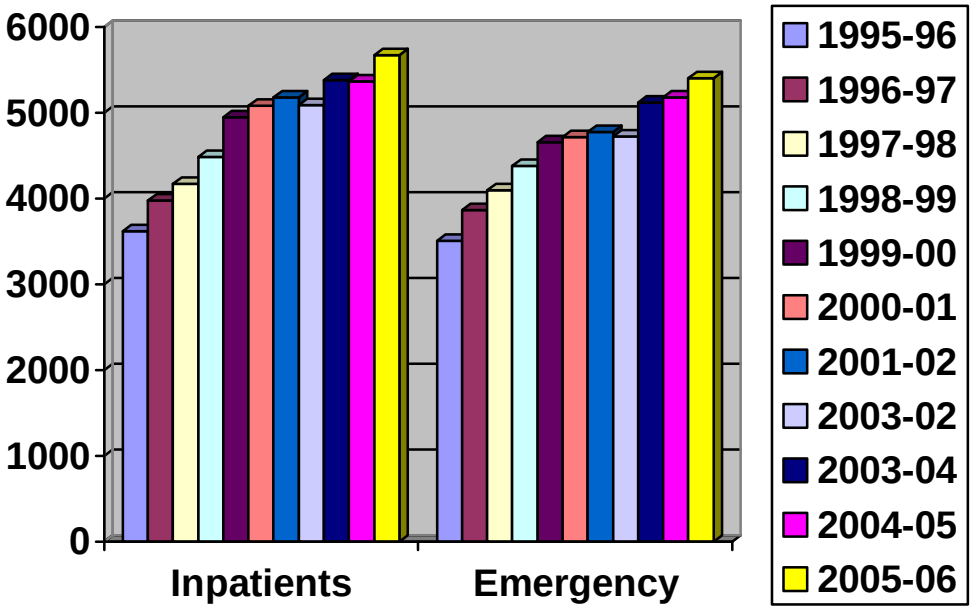
*relative to year 2002/03

A further analysis of the data between the years 2002 and 2006 shows that the increase in patient numbers has been across all age groups and in both sexes, with the maximum increase being in women in the 15-59 years age group (37.8%).



The number of bed days used for this condition has decreased over the period 2002-2006 as a result of the decrease in the mean length of stay and the median episode duration.

(b) R55 Syncope and Collapse (ICD 10) – Data for Wales.



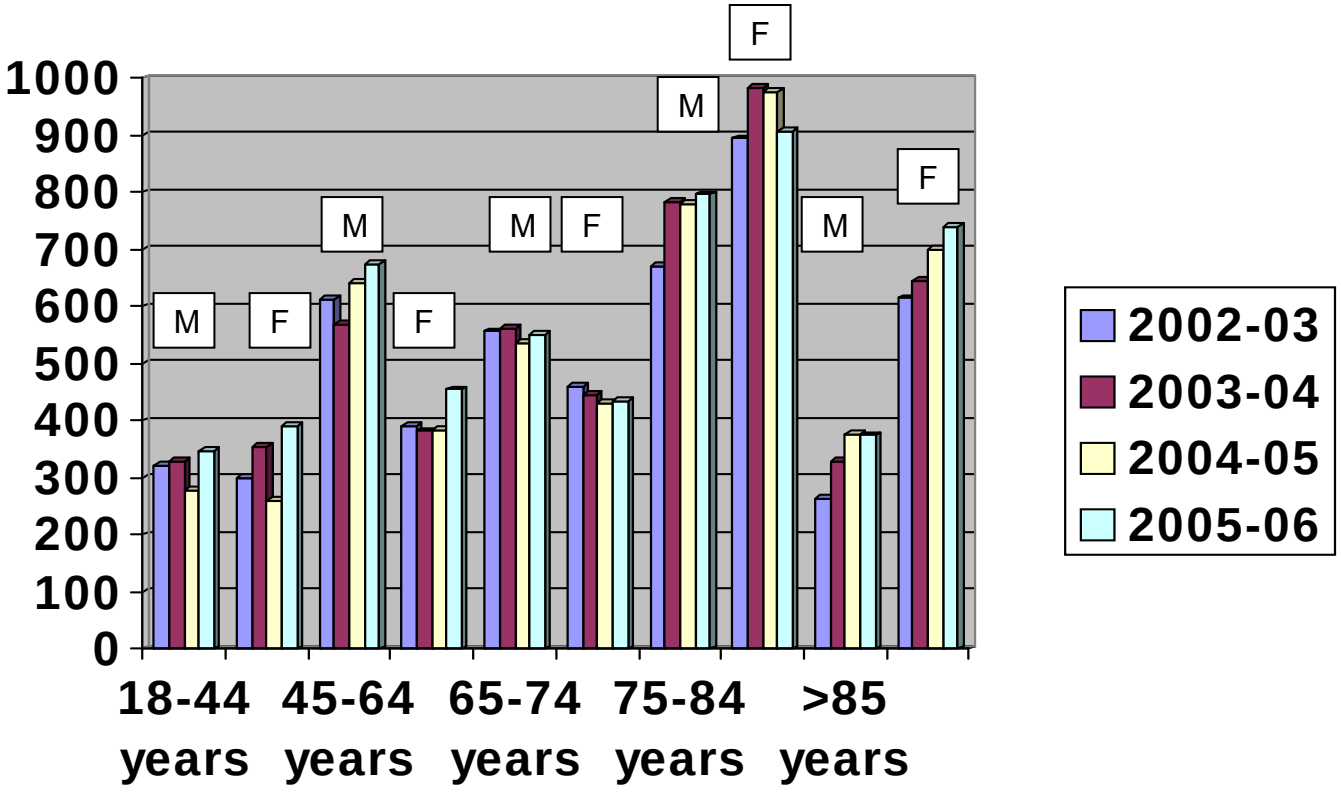
Year	Inpatient Episodes	Emergency	Mean length of stay (days)
2005/06	5671 (↑ 36.2%*)	5398 (95.2%)	7.3
2004/05	5361	5174 (96.5%)	7.8
2003/04	5380	5120 (95.2%)	7.3
2002/03	5088	4720 (92.8%)	6.8
2001/02	5177	4777 (92.3%)	6.8
2000/01	5080	4716 (92.8%)	7.2
1999/00	4948	4653 (94.0%)	8.0
1998/99	4481	4381(97.8%)	7.2
1997/98	4170	4093 (98.2%)	8.1
1996-97	3977	3862 (97.1%)	10.5
1995/96	3617	3509 (97.0%)	7.1

* relative to year 1995/96

Data on the number of inpatient episodes for R55 Syncope and Collapse (ICD 10) in Wales were available for the years 1995-2006. Similar to the trend observed in England, there has been a steady increase in the number of patients presenting with this condition, with an increase of 36.2% when data for 1995-96 is compared to that of 2005-2006. The proportion of patients with this condition presenting as an emergency are much higher than in England and has remained much the same, ranging from 94.0 - 98.2%, between the years 1995 and 2006. Also, there has been little change in the mean length of stay in the same time period and is more than twice than that for patients in England with the same condition. Unlike in England, no data were available on the number of Finished Consultant Episodes, the median stay duration and the mean age of patients.

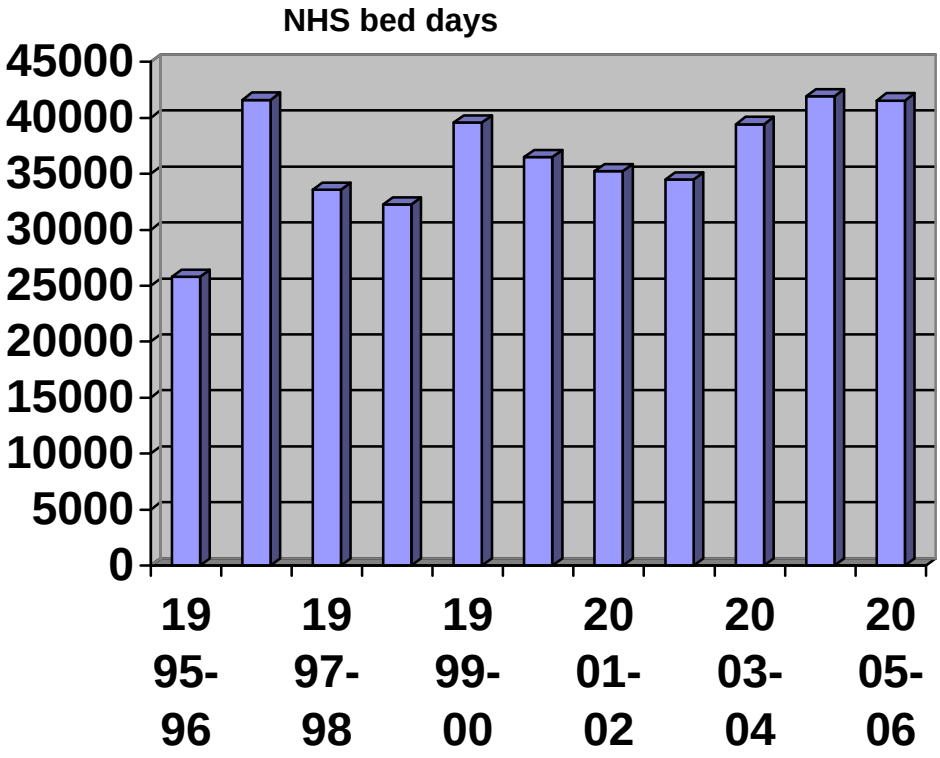
Year	Finished Consultant Episodes	18-44 years	45-64 years	65-74 years	75-84 years	>85 years
2005/06	5671 (↑ 36.2%*)	738 (↑ 30.8%*)	1130 (↑ 5.7%*)	985 (↑18.6%*)	1704 (↑40.5%*)	1114 (↑49.5%*)
2004/05	5361	538	1028	966	1754	1075
2003/04	5380	682	951	1008	1766	973
2002/03	5088	622	1004	1018	1566	878
2001/02	5177	674	1039	1004	1618	842
2000/01	5080	716	1052	1001	1515	796
1999/00	4948	626	937	978	1585	822
1998/99	4481	518	804	962	1418	779
1997/98	4170	514	830	881	1256	689
1996-97	3977	520	817	821	1215	604
1995/96	3617	511	727	802	1014	563

1 * relative to year 1995/96



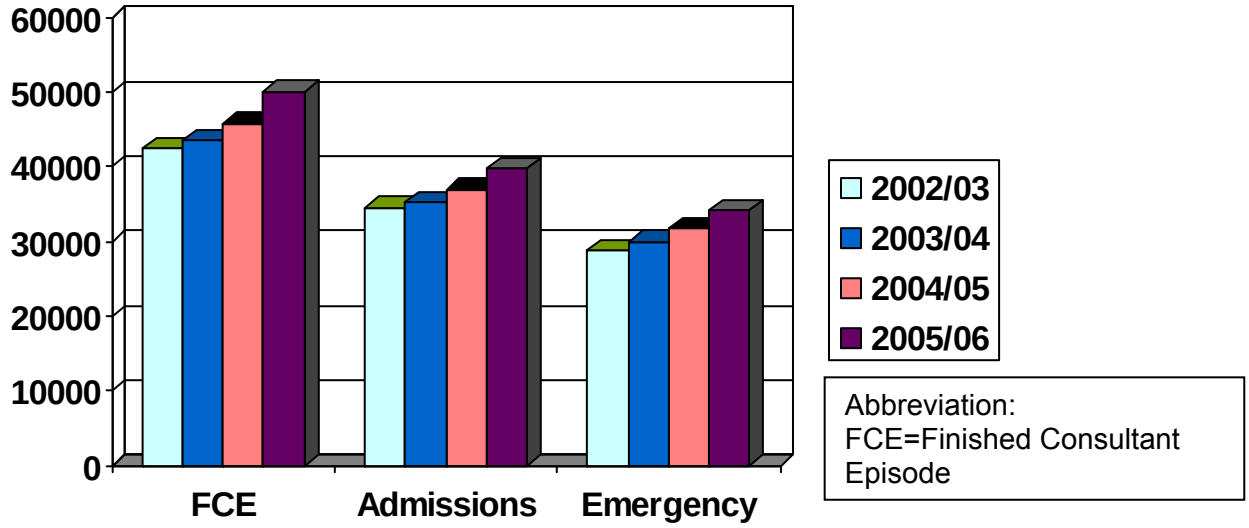
2 Unlike the data available for England, more detailed age-specific data were
3 available for Wales. These data show that the number of patients presenting
4 with R55 Syncope and Collapse (ICD 10) has increased across all age groups

between years 1995 and 2006, with the largest increase being among females over 85 years of age.



In contrast to the situation in England, the number of NHS bed days used in Wales for this condition has not shown any significant decrease between the years 1995 and 2006. This is because the number of patients with this condition has increased over the same time period without a significant decrease in the mean length of stay.

(c) G40 – Epilepsy (ICD-10) Data for England

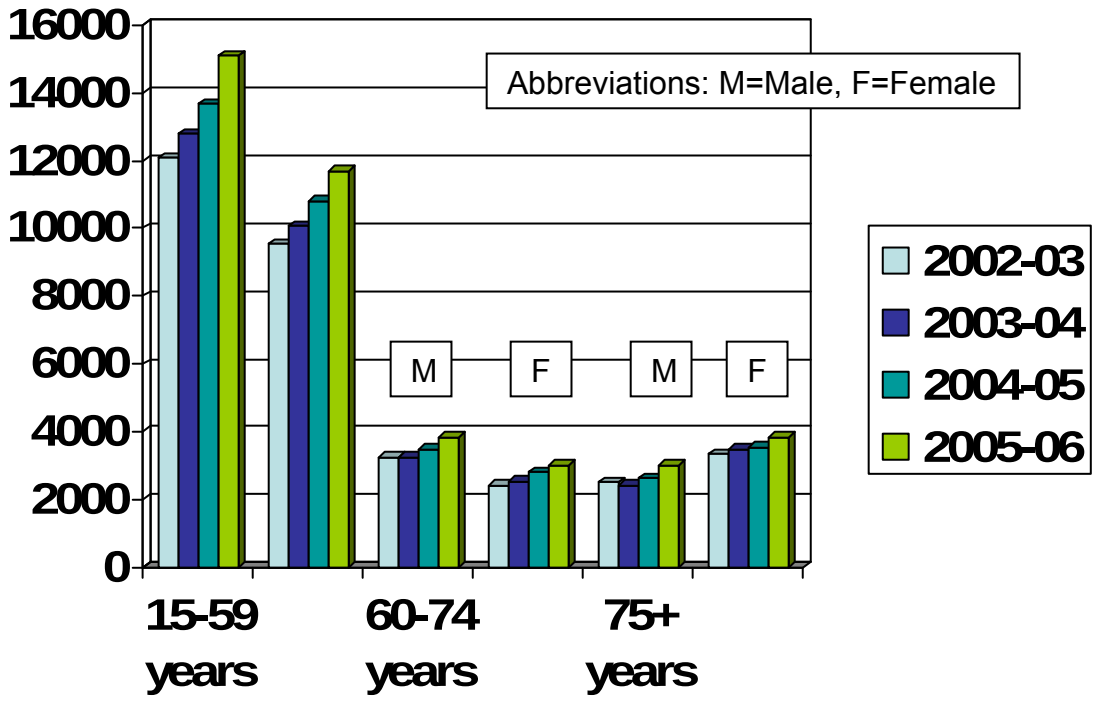


Year	Finished Consultant Episodes	Admissions	Emergency	Mean length of stay (days)	Median Episode Duration (days)	Mean Age (years)
2005/06	50112 (↑15.2%*)	39871 (↑13.3%*)	34226 (↑15.8%*)	5.0 (↓12.3%*)	1	42
2004/05	45811	36984	31722	5.5	1	41
2003/04	43453	35327	29989	5.5	2	41
2002/03	42473	34580	28818	5.7	2	40

* relative to 2002/03

The absolute number of patients presenting with all forms of epilepsy is roughly half that of R-55 Syncope and collapse, but shows a similar trend, in that there has been a steady increase in patient numbers, patients presenting as an emergency and the number of patients admitted between the years 2002 and 2006. The percentage increase is smaller than for R-55 Syncope and collapse.

Similar to R55 syncope and collapse, the mean length of stay has decreased by 12.3% (from 5.7 days to 5.0 days) and so has the median episode duration (from 2 days to 1 day). The mean age of patients with epilepsy is much lower



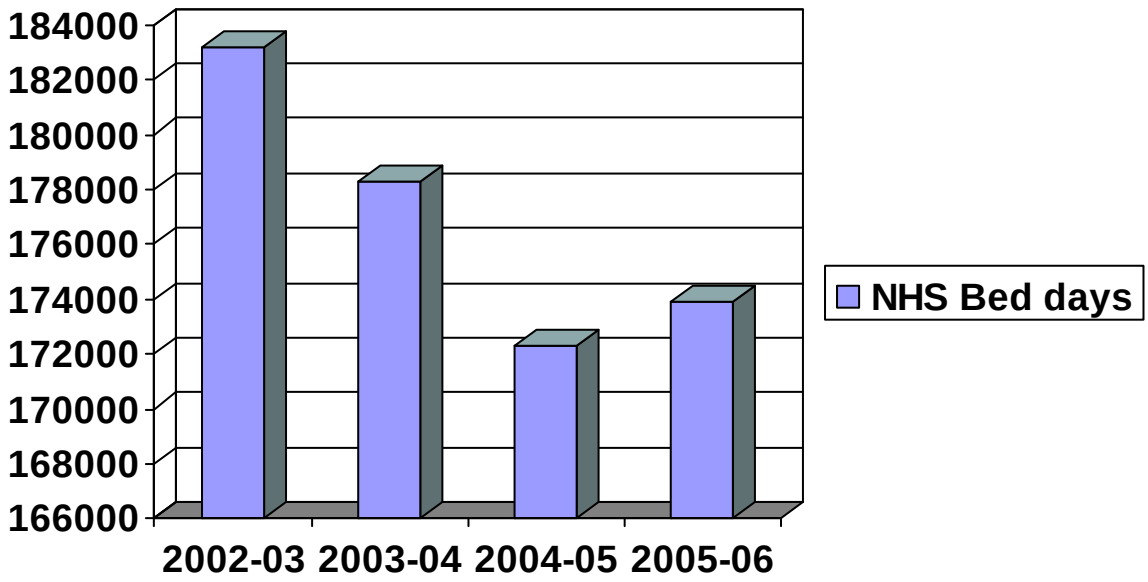
(42 years versus 67 years) than patients with R55 Syncope and Collapse. There has been a slight increase in the mean age of the patients with epilepsy over the corresponding period from 40 years to 42 years.

Finished Consultant Episodes

Year	Finished Consultant Episodes					
	15-59 years		60-74 years		75 + years	
	Male	Female	Male	Female	Male	Female
2005/06	15090 (↑15.3%*)	11689 (↑18.5%*)	3829 (↑15.6%*)	3006 (↑20.1%*)	2984 (↑16.2%*)	3836 (↑13.5%*)
2004/05	13682	10809	3478	2790	2617	3541
2003/04	12785	10076	3251	2510	2419	3462
2002/03	12088	9531	3230	2403	2502	3320

*relative to 2002/03

Similar to R55 Syncope and Collapse, there has been an increase in patients presenting with epilepsy across all age groups and for both sexes. However, the magnitude of this increase is less so for patients presenting with epilepsy.

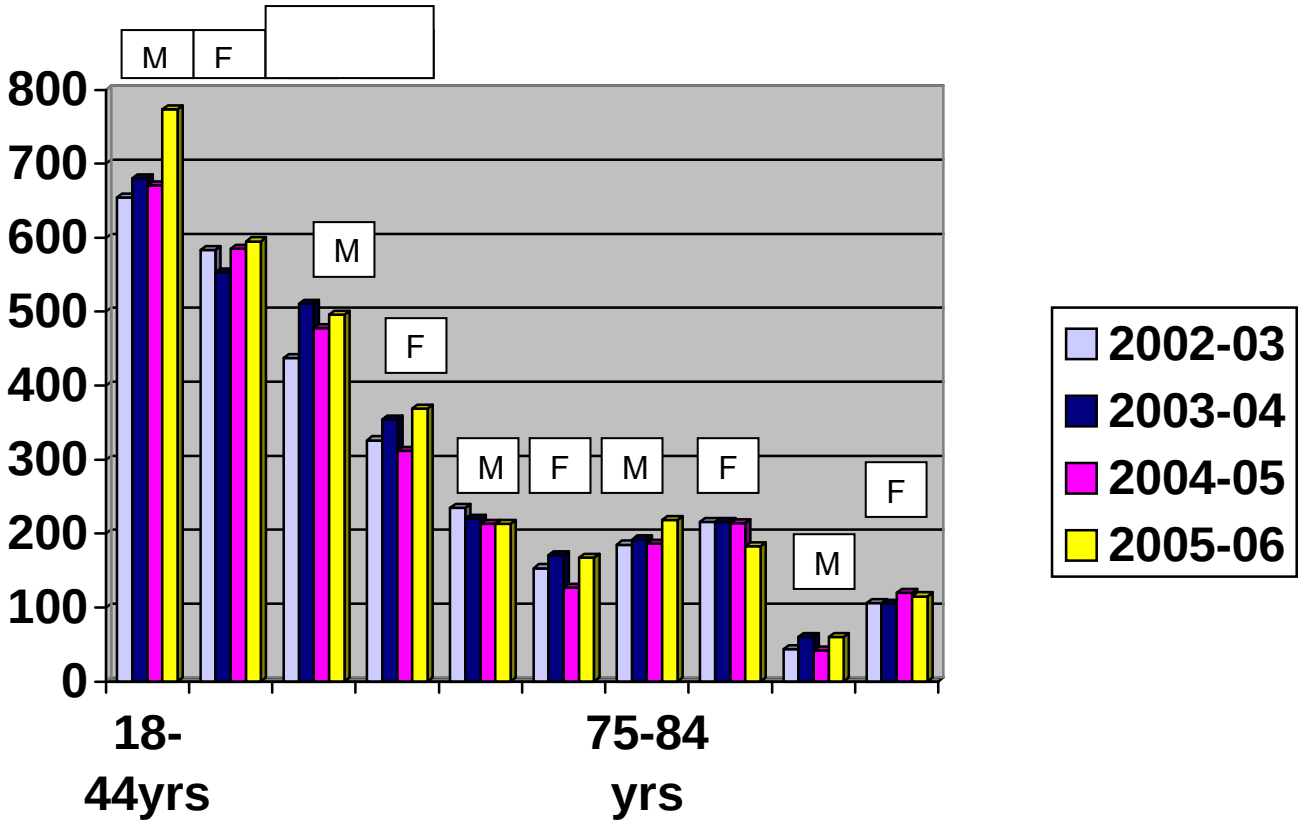


Similar to the trend observed with R55 Syncope and Collapse, overall, between the years 2002 and 2006, there has been a downward trend in the number of NHS bed days, driven by the decrease in the mean length of stay and the median episode duration.

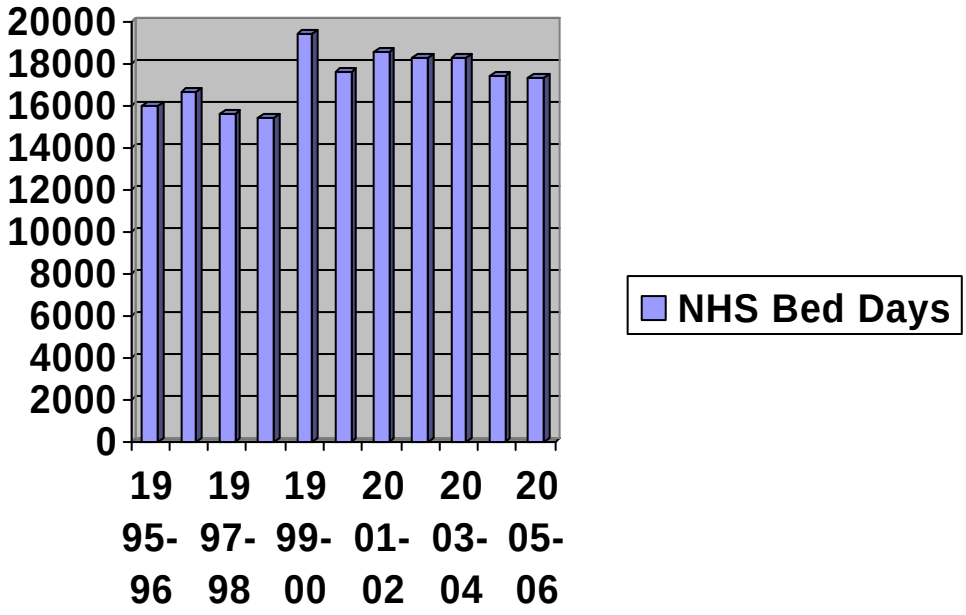
(d) G40 Epilepsy and R56.8 Other and unspecified convulsions (ICD-10) – data for Wales

Year	Number admitted	Emergency	Mean length of stay (days)
2005/06	3190 (↑ 15.5%)	2984 (↑ 13.6%)	5.4 (↓9.2%)
2004/05	2949	2793	5.9
2003/04	3062	2891	6.0
2002/03	2940	2820	6.2
2001/02	3231	3056	5.8
2000/01	3026	2882	5.8
1999/00	2993	2882	6.5
1998/99	3020	2912	5.1
1997/98	2909	2800	5.4
1996-97	2693	2568	6.2
1995-96	2696	2578	5.9

Year	Finished Consultant Episodes	18-44 years	45-64 years	65-74 years	75-84 years	>85 years
2005/06	3190	1369 (↑ 11.5%)	865 (↑ 33.8%)	380 (↑ 7.1%)	401 (↑ 12.0%)	175 (↑ 32%)
2004/05	2949	1257	790	340	400	162
2003/04	3062	1233	865	391	408	165
2002/03	2940	1238	763	388	401	150
2001/02	3231	1448	816	395	425	147
2000/01	3026	1323	771	387	423	122
1999/00	2993	1334	720	446	372	121
1998/99	3020	1351	770	390	385	124
1997/98	2909	1292	753	393	344	127
1996-97	2693	1195	683	372	351	92
1995/96	2696	1212	659	353	353	119



Inpatient data for Wales was available for the last 10 years i.e. between 1995 and 2006. Similar to the situation in England, there has been an increase in the number of patients admitted with epilepsy during this period. A vast majority attended as an Emergency. The increases have been maximum in the 45-64 and >85 years age group.



Overall, there has been an increase in the number of NHS bed days used by this condition over the period 1995-2006. This is because of a small decrease in the mean length of stay offset by the increase in the number diagnosed with epilepsy.

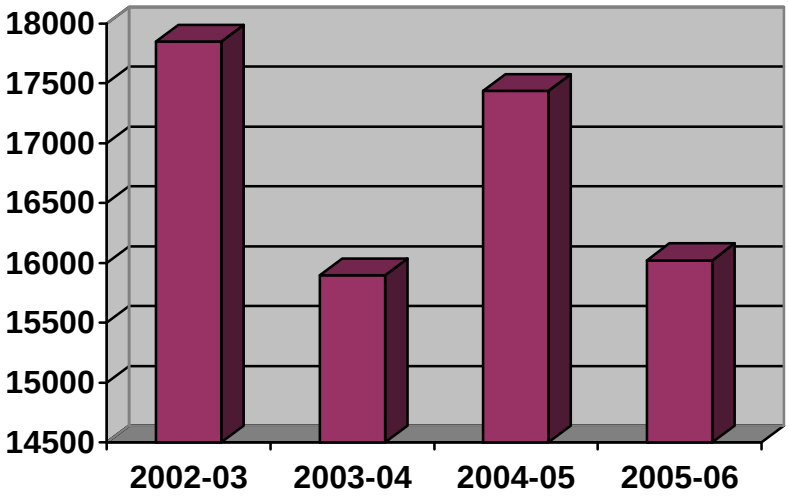
(e) F44 Dissociative disorders (ICD 10) – Data for England

Data on dissociative disorders, which includes patients diagnosed with psychogenic blackouts, was available only for England.

Year	Finished Consultant Episodes	Admissions	Emergency	Mean length of stay (days)	Median Episode Duration (days)	Mean Age (years)
2005/06	1013	827	514	18.1	8	47
2004/05	1010	824	579	22.4	9	47
2003/04	958	797	516	21.6	8	48
2002/03	1046	882	532	23.2	9	47

Year	Finished Consultant Episodes					
	15-59 years		60-74 years		75 + years	
	Male	Female	Male	Female	Male	Female
2005/06	179	439	50	50	74	139
2004/05	191	475	58	60	57	126
2003/04	184	389	42	48	87	129
2002/03	192	452	39	63	91	120

The number of Finished Consultant Episodes, the number admitted and the number presenting as an emergency has shown a marginal decrease between the years 2002 and 2006. Though the mean length of stay has decreased from 23.2 days to 18.1 days, it still remains high and higher than those for either R55 Syncope and Collapse or G40 Epilepsy. Neither the median episode duration nor the mean age has shown a significant change during this period. A disproportionately large percentage of patients with this condition in the 15-59 year age group are females.



The number of NHS bed days used by this condition has decreased when data for 2005-06 are compared with those from 2002-03.

(f) Mortality data for England and Wales (from the Office of National Statistics):

Comparative mortality data for England and Wales for the three conditions were obtained from the Office of National Statistics. Deaths in patients under 19 years of age were excluded. Consistent data for ICD-10 R55 Syncope and Collapse were not available. Hence, data for ICD-10 R50-69 (General symptoms and signs) are given.

Year	Total number of deaths (all causes)	ICD R50-69	R55	G40	F44
2006	496696	9462 (1.9%)	No data	873 (0.18%)	2 (0.0004%)
2005	507106	10131 (2.0%)	1 (0.0002%)	913 (0.18%)	5 (0.001%)
2004	506934	10180 (2.0%)	1 (0.0002%)	448 (0.09%)	8 (0.002%)
2003	532422	11613 (2.2%)	1 (0.0002%)	942 (0.18%)	6 (0.001%)
2002	527807	11855 (2.3%)	No data	802 (0.15%)	2 (0.0004%)

The above table shows that the total number of deaths in patients over 19 years, due to any cause, has remained roughly the same at around 500,000 per year between the years 2002 and 2006. The absolute number of deaths due to R55 Syncope and Collapse and F44 Dissociative Disorders is low and in single digits. Deaths due to G40 Epilepsy are higher than in the other two categories and have roughly remained the same during 2002 and 2006, barring 2004.

NHS Direct

NHS Direct provides 24-hour health care advice to people in the UK. The organisation, which started in 1997, has grown and changed since its launch, most noticeably since 2004. Its mission statement is ‘to provide information and advice about health, illness and health services, to enable patients to

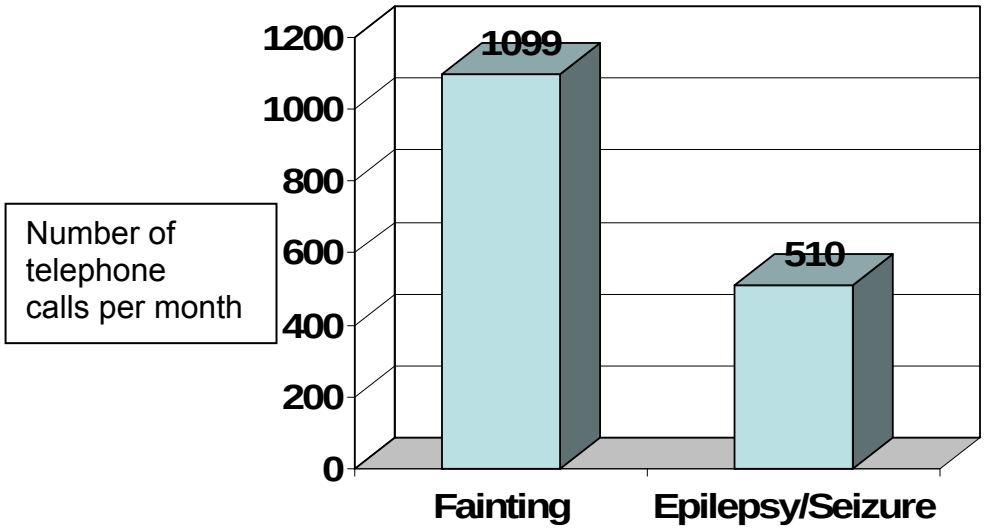
make decisions about their healthcare and that of their families'. It is estimated that over 2 million people use NHS Direct every month. Services are delivered via telephone, through their website and also through the NHS Direct digital television services.

Data were sought in April 2008, under the Freedom of Information Act 2000, from NHS Direct England and NHS Direct Wales about the number of people accessing their service, in the last 5 years, for symptoms of 'faints', 'syncope' and 'epilepsy'.

Information obtained from these two organisations differed and is detailed below.

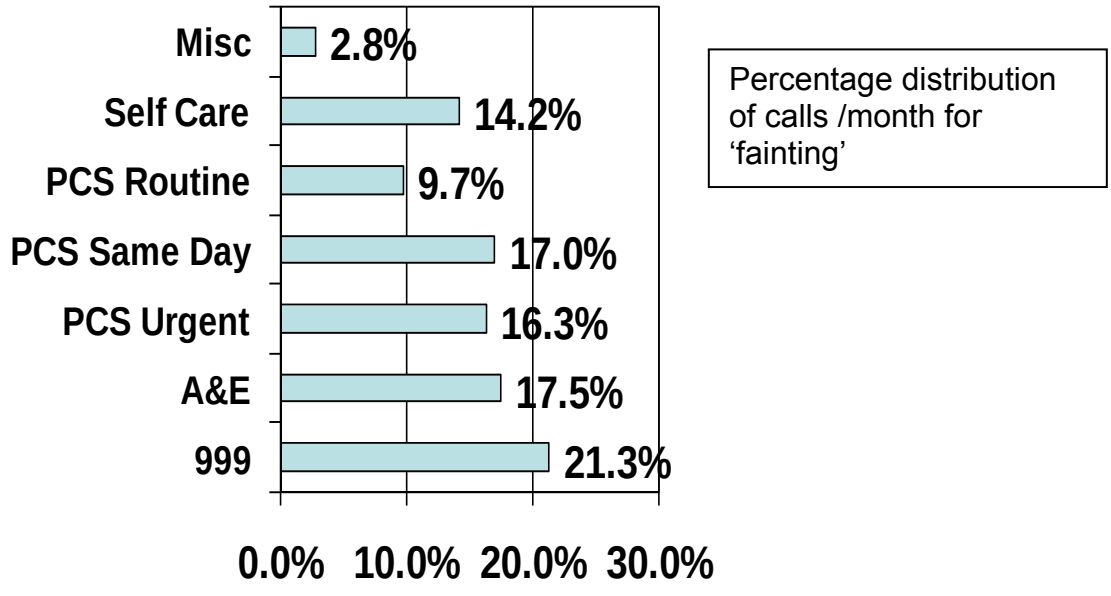
NHS Direct England:
Information on only 'fainting' and 'epilepsy' was available as the term 'syncope' did not fit into their algorithm. Though information for the last 5 years was sought, prior to January 2006, different regions making up NHS Direct England were using different versions of the database and so the results could not be collated and made available. Also, information only about the number of telephone calls received every month between January 2006 and May 2008 was available. Information on the number of people accessing their website or using the digital television services was unavailable. We were also informed that neither 'fainting' nor 'epilepsy' were among the top 35 search subjects.

The mean number of telephone calls per month received for 'fainting' between January 2006 and May 2008 was 1099 ± 121.5 (range: 903-1450) and was nearly twice that received for 'epilepsy' (510 ± 49.4, range: 423-629).



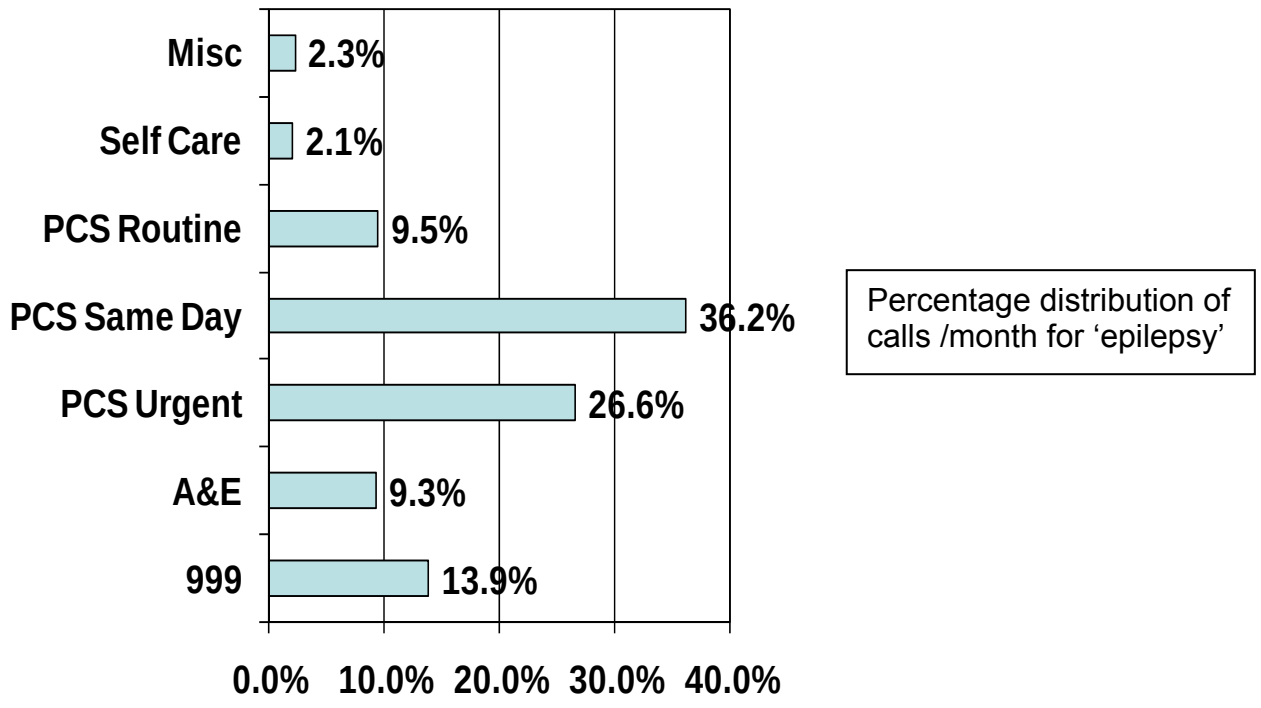
The outcome of these telephone calls for both 'fainting' and 'epilepsy' was as follows:

'Fainting'



1 in 5 patients calling the service for 'fainting' were sent an ambulance by NHS Direct and taken to the nearest Accident and Emergency Department. In these cases, NHS Direct made the '999' call. A further 17.5% of patients were asked to attend their nearest Accident and Emergency Department. Roughly 1 in 6 patients (16.3% and 17.0%) were asked to see their General Practitioner either urgently or on the same day (Primary Care Service Urgent, Primary Care Service Same Day). One in 10 patients were advised to seek a routine appointment from their General Practitioner. Self care advice involved getting lots of rest, elevating a bruised ankle, applying ice packs etc. with the caveat that if there was no improvement; patients could call NHS Direct back or see their General Practitioner. 'Miscellaneous' covered a multitude of options e.g. seek pharmacy advice, attend the nearest walk-in centre etc.

'Epilepsy':



When compared to patients calling for symptoms suggestive of 'fainting', a smaller percentage of patients were despatched an ambulance by NHS Direct, by calling '999', for symptoms of 'epilepsy'. Conversely, a higher proportion of patients were asked to attend their Primary Care Service provider i.e. General Practitioner, either urgently or on the same day.

NHS Direct Wales:

Two types of data were available from NHS Direct Wales in response to the same query.

(a) Telephone Calls:

Information on telephone calls made to the service between the years 2002 and 2007, for symptoms of 'fainting', 'fainting spells' and 'epilepsy' were available. The former two terms were combined for analysis as they dealt with people presenting with similar symptoms. As expected, the absolute number of calls for these symptoms were lower in Wales because of the smaller population base.

'Fainting':

Year	999	A&E	PCS Urgent	PCS Same Day	PCS Routine	Self care	Misc
2002-03 (n=373)	78 (20.9%)	36 (9.7%)	30 (8.0%)	155 (41.6%)	29 (7.8%)	24 (6.4%)	26 (7.0%)
2003-04 (n=405)	100 (24.7%)	58 (14.3%)	15 (3.7%)	177 (43.7%)	20 (4.9%)	17 (4.1%)	16 (3.9%)
2004-05 (n=365)	100 (27.3%)	55 (15%)	58 (15.8%)	95 (26%)	24 (6.5%)	16 (4.3%)	17 (4.6%)
2005-06 (n=436)	72 (16.5%)	74 (16.9%)	140 (32.1%)	69 (15.8%)	33 (7.5%)	42 (9.6%)	6 (1.3%)
2006-07 (n=510)	94 (18.4%)	82 (16%)	139 (27.2%)	89 (17.4%)	44 (8.6%)	40 (7.8%)	22 (4.3%)

There has been a 27% increase in the number of patients accessing the service for symptoms of 'fainting' between the years 2002 and 2007. In roughly 20% of cases, NHS Direct called '999' and sent an ambulance to the patient's location to transport the patient to the nearest Accident and

Emergency Department. This figure is similar to that seen in England. The number of patients advised to attend the accident and Emergency Department has remained much the same since 2002-03. There has been an increase in the number of patients asked to see their General Practitioner urgently from 8.0% in 2002 to 27.2% in 2006-07 and a corresponding decrease in the number of patients asked to see their General Practitioner on the same day (41.6% to 17.4%). The reason for this change is not known.

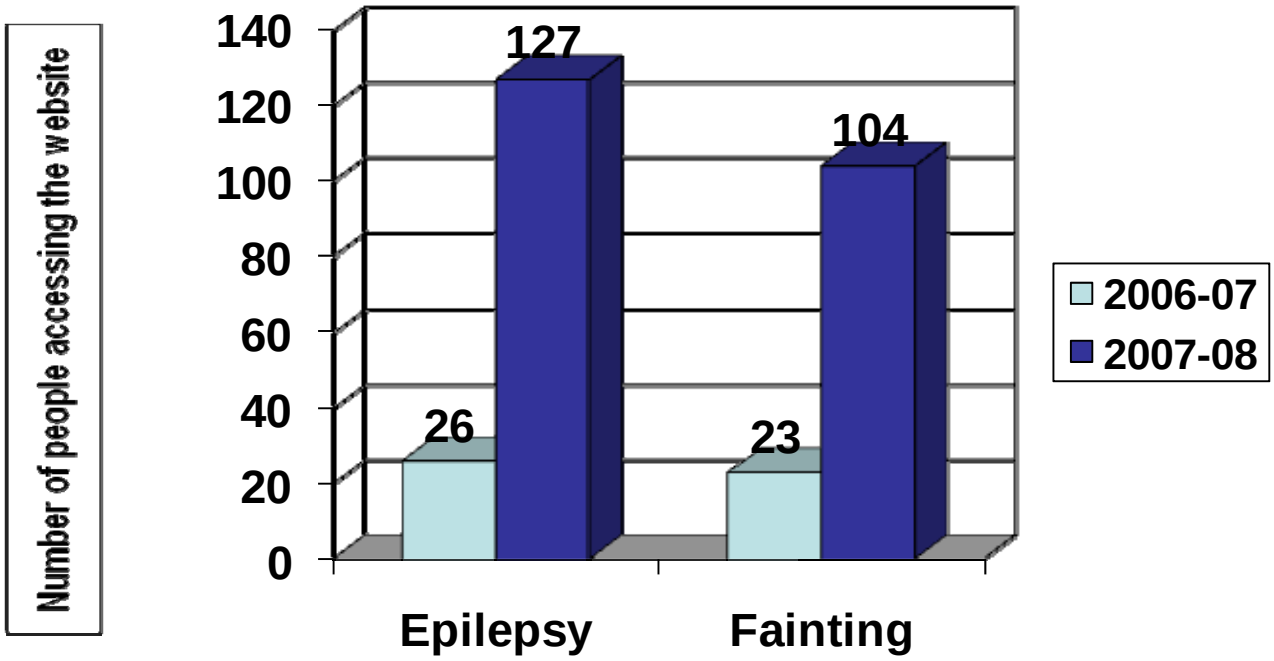
'Epilepsy':

Year	999	A&E	PCS Urgent	PCS Same Day	PCS Routine	Self care	Misc
2002-03 (n=27)	6 (22.2%)	2 (7.4%)	4 (18.2%)	12 (54.5%)	1 (4.6%)	0	2 (7.4%)
2003-04 (n=28)	7 (25%)	1 (3.6%)	2 (7.1%)	17 (60.7%)	0	0	1 (3.6%)
2004-05 (n=35)	9 (25.7%)	0	7 (20.0%)	15 (42.8%)	1 (2.9%)	0	3 (8.6%)
2005-06 (n=37)	9 (24.3%)	4 (10.8%)	12 (32.4%)	10 (17.2%)	0	1 (2.7%)	1 (2.7%)
2006-07 (n=26)	1 (3.9%)	3 (11.5%)	7 (26.9%)	11 (42.3%)	2 (7.7%)	0	2 (7.7%)

Once again, the absolute and relative numbers of patients accessing the service was lower than in England. In contrast to the practice in England, a larger proportion of patients with symptoms of 'epilepsy' were despatched an ambulance by NHS Wales by calling '999'. Also, in contrast to the practice in England, a larger proportion of patients were asked to see their General Practitioner the same day.

(b) Access to the website:

Limited information was available on this topic as the website was relaunched in February 2007. Only statistics for the financial years 2006-2007 and 2007-2008 were available and as are follows.



The Digital TV access was not available in Wales as it was a NHS Direct England only initiative.

1.2 Context Definitions and Approach of the guideline

Context:

Transient loss of Consciousness (TLoC) is very common, it affects up to half of us at some point in our lives. TLoC may be defined as a spontaneous, transient, complete loss of consciousness with complete recovery. It is often described by patients as a ”blackout”. There are a number of potential causes: including cardiovascular disorders, which are probably the most common, neurological conditions such as epilepsy, and psychological symptoms.

The diagnosis of the underlying cause is often inaccurate, inefficient, and delayed. Misdiagnosis is common, for instance 20-30% of people with epilepsy have an underlying cardiac cause,(ref NICE Guideline CG20) and this is despite inappropriate and excessive tests being performed on many patients; nevertheless patients are often discharged without any clear diagnosis.

Approach:

Our approach was to produce a guideline in the form of an algorithm, pointing clinicians, and patients, towards those areas where guidance already exists such as epilepsy, and filling gaps where guidance is lacking.

1.3 Aim of the guideline

There are a number of existing guidelines, for epilepsy, falls and cardiac arrhythmias; which all relate to TLoC, but there is no guideline which addresses the initial assessment and management of patients who blackout. As such patients may come under the care of a range of clinicians, the lack of a clear pathway contributes to their misdiagnosis, and inappropriate treatment, as described above.

This guideline aims to define the appropriate pathways for the initial assessment of these patients, and so to derive the correct underlying diagnosis quickly, efficiently, and cost-effectively, and tailor the management plan to suit their true diagnosis

1.4 How the guideline is set out

Unlike most NICE guidelines, this guideline does not address a condition, but a symptom. It suggests a pathway to follow to determine the cause of the person's TLoC, advice on appropriate management until a diagnosis is made and to ensure that the correct referral is made. An algorithm based on this pathway can be found in Chapter 2.

The clinical content of this guideline is in two sections. The first section in Chapters 3 and 4 addresses the initial assessment following TLoC. This provides guidance on determining the cause of TLoC, use of ECG and therefore the appropriate pathway. Generally, the cause of TLoC will be one of the following:

1. Uncomplicated faint or situational syncope
2. Orthostatic hypertension
3. Dysfunction of the nervous system (epilepsy)
4. Dysfunction of the cardiovascular system (syncope),
5. Dysfunction of the psyche (psychogenic seizures)

When the person's TLoC is judged to be an uncomplicated faint or caused by orthostatic hypertension and no further therapy is required, advice on management is given in these chapters. As there is an existing NICE guideline on epilepsy (CG20 currently being updated), no further guidance is provided in this document if the person's TLoC is judged to have a neurological cause. This guideline also does not address the assessment and management of psychogenic seizures and there is currently no NICE guidance on this topic. Therefore, the second section of the guideline, Chapters 5 and 6, addresses in detail only assessment and further testing in people for whom the event is judged to have a cardiovascular cause.

The guideline also provides advice on the information needs of people who have TLoC. The recommendations were written by GDG consensus and

therefore there is not an evidence chapter. Further information regarding the development of these recommendations is in Chapter 2 section 5.

1.5 Scope

Transient loss of consciousness (TLoC) is a loss of consciousness with complete recovery. It is usually spontaneous in onset and may be described by the person as a 'blackout'.

The guideline addresses TLoC in adults aged 16 years and over. It does not address the management of patients who have experienced TLoC after sustaining a physical injury, people who have experienced a collapse without loss of consciousness or patients who have experienced a prolonged loss of consciousness without spontaneous recovery.

The guideline covers the initial management of people who have experienced a TLoC within any setting in which NHS care is received and further diagnostic investigations within secondary care, including specialist blackout clinics, but does not address treatment in secondary care following diagnosis.

The full scope can be found in Appendix A

1.6 Responsibility and support for guideline development

1.6.1 National Clinical Guideline Centre - Acute and Chronic Conditions

Until April 2009, this guideline was developed by the National Collaborating Centre for Nursing and Supportive Care (NCC-NSC). The Royal College of Nursing acted as the host organisation. In April 2009, the NCC-NSC merged with three other collaborating centres. From this point, this guideline was developed in the National Clinical Guideline Centre for Acute and Chronic Conditions (NCGC-ACC) and based in the Royal College of Physicians. This guideline will therefore be published by the NCGC-ACC. All funding for the guideline was from the National Institute for Health and Clinical Excellence. A review is scheduled for [add when published].

1.6.2 Technical Team

The technical team had the responsibility for this guideline throughout its development. They were responsible for preparing information for the Guideline Development Group (GDG), for drafting the guideline and for responding to consultation comments. The technical team working on this guideline consisted of the:

- **Guideline lead**
  who is a senior member of the Centre who has overall responsibility for the guideline
- **Information scientist**
  who searched the bibliographic databases for evidence to answer the questions posed by the GDG
- **Reviewer**
  who appraised the literature and abstracted and distilled the relevant evidence for the GDG
- **Health economist**
  who reviewed the economic evidence, constructed economic models in selected areas and assisted the GDG in considering cost-effectiveness
- **Project manager**
  who was responsible for organising and planning the development, for meetings and minutes and for liaising with NICE and external bodies
- **Chair**
  who was responsible for chairing and facilitating the working of the GDG meetings

The members of the technical team attended the GDG meetings and participated in them. The team also met during the development of the guideline to review progress and plan work.

1.6.3 GDG Membership

Both the Chairman and the GDG were recruited following open advertising and application as detailed in the NICE Guidelines Manual http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/clinical_guideline_development_methods.jsp

A Chairman was chosen for the group and his primary role was to facilitate and chair the GDG meetings.

Guideline Development Groups (GDGs) are working groups consisting of a range of members with the experience and expertise needed to address the scope of the guideline. Applications for GDG members were invited from the public and relevant stakeholder organisations which were sent the draft scope of the guideline with some guidance on the expertise needed. Two patient representatives and nine healthcare professionals were invited to join the GDG.

Each member of the GDG served as an individual expert in their own right and not as a representative of their organisation.

In accordance with this guidance from NICE, all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships, and support from the healthcare industry. Details of these can be seen in Appendix B

The names of GDG members are listed below.

Dr. Paul Cooper (Chairman)
Consultant Neurologist, Salford Royal Hospital (Hope Hospital)

Dr. Robin Beal
Consultant in Emergency Medicine, St Marys Hospital, Newport, Isle of Wight

Ms. Mary Braine
Lecturer, School of Nursing & Midwifery , University of Salford

Ms. Julie Fear
Patient/Carer Representative

Ms. Melesina Goodwin
Epilepsy Specialist Nurse, Northampton General Hospital

Dr. Richard Grünewald
Consultant Neurologist, Royal Hallamshire Hospital

Ms. Paddy Jelen (from December 2008)
Patient/Carer Representative

Dr Fiona Jewkes (Resigned June 2008)
General Practitioner, Wiltshire

Mr. John Pawelec
Paramedic Clinical Tutor, Yorkshire Ambulance Service NHS Trust

Dr. Sanjiv Petkar
Cardiologist, Hull and East Riding of Yorkshire NHS Trust

Dr. David Pitcher
Consultant Cardiologist, Worcestershire Royal Hospital

Ms. Alison Pottle
Cardiology Nurse Consultant, Harefield Hospital

Dr. Greg Rogers
General Practitioner and GP with a Special Interest in Epilepsy [GPwSI] for Eastern and Coastal Kent Primary Care Trust.

Mr. Garry Swann
Emergency Care Nurse Consultant, Heart of England Foundation Trust in Birmingham

Social and Clinical Lead (Urgent Care), West Midlands Strategic Heath Authority

Technical Team

Dr. Ian Bullock (Guideline Lead)

Chief Operating Officer, NCGC

Ms. Sarah Davis

Health Economic Lead, NCGC

Mr. Paul Miller

Senior Information Scientist

Ms. Emma Nawrocki

Project Co-ordinator

Ms. Nancy Turnbull

Project Manager, NCGC

Dr. Maggie Westby (Reviewer)

Clinical Effectiveness Lead, NCGC

2 Methods

2.1 Introduction

This chapter sets out in detail the methods used to generate the recommendations for clinical practice that are presented in the subsequent chapters of this guideline. The methods are in accordance with those set out by the Institute in 'The guidelines manual'. January 2009. London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk/guidelinesmanual. *How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS* describes how organisations can become involved in the development of a guideline.

2.2 Developing key clinical questions (KCQs)

The first step in the development of the guideline was to refine the guideline scope into a series of key clinical questions (KCQs). These KCQs formed the starting point for the subsequent reviews and as a guide to facilitate the development of recommendations by the Guideline Development Group (GDG).

The KCQs were developed by the GDG with assistance from the technical team. The KCQs were refined into specific evidence-based questions (EBQs), which were in turn developed into review protocols. These specified the study design, population, interventions, comparisons and outcomes ('PICO') for intervention reviews, and population, index tests, reference standard and target condition for reviews of diagnostic test accuracy. The protocols also indicated *a-priori* how studies would be combined, and which sensitivity and subgroup analyses should be carried out. The protocols formed the basis of the literature searching, appraisal and synthesis; general features of the protocols are given in section 1.4, with more detail given in the clinical effectiveness chapters of the guideline.

The full list of KCQs identified is listed in Appendix C1. The technical team, in liaison with the GDG, identified those KCQs where a full literature search and critical appraisal were essential.

2.3 Literature search strategy

All searches were conducted on the following databases: Medline (OVID), Embase (OVID), Cinahl (EBSCO) and the Cochrane Library unless otherwise noted below. Selected searches were also conducted on Psycinfo (Silverplatter/OVID). No date restrictions were applied to searches; dates searched were as follows:

Database	Date searched from
Medline	1950
Embase	1980
Cinahl	1982
Psycinfo	1970

Search filters were applied where appropriate, including filters for randomised controlled trials (RCT) and systematic reviews (SR). The RCT filter used was based on that recommended by Cochrane (Higgins, 2005). An exclusions filter was designed to remove irrelevant results such as letters and editorials.

The complete search strategies are reproduced in Appendix C2. Note that the searches make use of controlled vocabulary which varies between databases and between search interfaces. Amendments were made where necessary in order to take these variations into account.

Where possible, searches were restricted to articles written in English. All searches were updated on November 2nd 2009.

Hand searching was not undertaken by the NCC-NSC following NICE advice that exhaustive searching on every guideline review topic is not practical

(Mason 2002). Reference lists of articles were checked for further articles of potential relevance.

2.4 How the evidence was reviewed and synthesized

2.4.1 Identifying the evidence

2.4.1.1 Selection criteria: general

The following general selection criteria were applied to studies to determine their suitability for inclusion in the reviews:

For reviews of diagnostic test accuracy, the cross sectional study was to be the primary study design. Studies were to be included if diagnoses obtained using a new (index) test were compared with 'true' diagnoses obtained using a reference standard, with both tests being carried out in the same patients. Case control studies were to be considered only in the absence of cross sectional studies. For intervention studies, the randomised trial (RCT) and quasi randomised trial (e.g. allocation by alternation, date of birth, etc) were to be the primary trial designs.

Studies were to be excluded if there were fewer than 20 patients in each arm for comparative studies and if there were fewer than 20 patients overall for non-comparative studies. Initially, we did not restrict the size of the studies of diagnostic test accuracy.

For all reviews, participants were to be adults (16 years and older), who had had a TLoC, defined as a loss of consciousness with complete recovery.

Reviews of diagnostic test accuracy are sensitive to the population and these were carefully defined in the review protocols, taking into account prior tests the patients had received and the suspected cause of TLoC.

In some diagnostic reviews, the reference standard was the same as the index test and the reviews reported the diagnostic yield, i.e. the proportion with a diagnosis using the test. Otherwise the outcomes to be recorded were sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio, diagnostic odds ratio, pre- and post-test probabilities. These

were to be calculated from raw data, and occasionally raw data were back-calculated from the test accuracy statistics.

2.4.1.2 Sifting process and data extraction

Once the search had been completed, the following sifting process took place:

- 1st sift: One reviewer sifted the title/abstract for articles that potentially met the selection criteria.
- 2nd sift: Full papers were ordered that appeared relevant and eligible or where relevance/eligibility was not clear from the abstract.
- 3rd sift: Full papers were appraised that meet eligibility criteria. Generally, one reviewer appraised the papers using an inclusion criteria form, and this was checked where necessary by a second reviewer.

Once individual papers were retrieved, the articles were checked for methodological rigour (see below), applicability to the UK and clinical significance.

Data from included studies were extracted by one reviewer for each review, and were usually checked by a second reviewer, and entered into a Microsoft Access database that had been especially designed for the guideline.

2.4.2 Critical appraisal of the evidence

The methodological quality of studies was examined for all reviews.

2.4.2.1 Randomised trials of interventions

For RCTs of interventions, the following factors were considered in assessing the potential for bias:

- Method of generation of the randomisation sequence:
- Allocation concealment at randomisation
- Baseline comparability of treatment groups for relevant risk factors
- Patients stated to be blinded, especially for comparisons with placebo

- Outcome assessor stated to be blinded
- Loss to follow up for each outcome
  - Studies with at least 20% of data missing from any group were to be considered to be potentially biased, more so if there is a differential drop out from any one group or if the missing data is known to be significantly different from the remaining data
  - Those with moderate loss to follow up (20 to 50%) were to be considered in sensitivity analyses
  - Those with 50% or more patients missing from any one group were to be regarded as flawed and not analysed further (but would be included in the review)
- Early stopping of a trial on the basis of positive interim results

2.4.2.2 Non-randomised studies

For non-randomised studies, the following factors were considered in assessing the potential for bias; further details are given in The Cochrane Handbook for Systematic Reviews of Interventions (http://www.cochrane-handbook.org/ : Box 13.1.a: Some types of non-randomised study design used for evaluating the effects of interventions).

- Selection bias:
  - Account is taken of the confounding factors, either by design (e.g. matching or restriction to particular subgroups) or by methods of analysis
- Prospectiveness
- No loss to follow up (see RCTs)

2.4.2.3 Studies of diagnostic test accuracy

For studies of diagnostic test accuracy, the study quality was assessed using a modified version of the 'QUADAS' list, with each item scored as 'yes', 'no' or 'unclear' (Whiting 2003). The following factors were considered in assessing the potential for bias:

- Representative spectrum: whether or not the patients had delirium and were representative of the population of the review.
  - Studies that recruited a group of healthy controls and a group known to have the target disorder were coded as 'no' on this item
- Clear description of selection criteria
- Reference standard likely to classify the target condition correctly
- Acceptable delay between tests: period between the reference standard and the index test was short enough to be reasonably sure that the target condition did not change between the 2 tests.

An overall assessment for each study was given of ++ (good), + (acceptable, with some reservations) and – (unacceptable)

2.4.3 Data synthesis

2.4.3.1 Reviews of interventions

Meta-analysis of similar intervention trials was carried out, where appropriate, using *The Cochrane Collaboration's* analysis software, Review Manager (Version 5). Studies were combined if they had similar PICO characteristics.

Trials were pooled using a fixed effects model and plotted on forest plots. Where there was significant heterogeneity, a random effects model was used as a sensitivity analysis.

For dichotomous studies, intention to treat analyses (including all participants according to their assigned groups) were used, when reported by the study authors, and failing that, available case analyses (all those reporting an outcome) as reported by the authors. When there were incomplete data reported (more than 20% missing in any one group), we carried out sensitivity analyses, excluding these studies. Outcomes were summarised for dichotomous data using relative risks.

Heterogeneity between trials was assessed by visual inspection of forest plots, noting where there was poor overlap of horizontal lines, and by using statistical measures: the X^2 test for heterogeneity and the level of

inconsistency, I^2 ($I^2 = [(\chi^2 - df)/ \chi^2] \times 100\%$, where df is the degrees of freedom). We considered that there was heterogeneity if the p-value (heterogeneity) was less than 0.1 and/or I^2 is greater than 50%. Any heterogeneity was explored further, either in sensitivity analyses for items of methodological quality (see below) or using subgroup analyses (see the review protocols), and unexplained heterogeneous results were not used as the basis for recommendations.

Sensitivity analyses were carried out to investigate assumptions within the analyses. These included the following:

- Methodological quality
- Fixed effects model
- Other features specific to each review.

In terms of methodological quality, we paid particular attention to allocation concealment and loss to follow-up (missing data). We did not include studies with more than 50% loss to follow-up in the analyses. Otherwise we carried out sensitivity analyses on studies that had between 20 and 50% withdrawals or protocol deviations in any group (that were eliminated from the study's analyses).

2.4.3.2 Studies of diagnostic test accuracy

For diagnostic test accuracy studies, 2 by 2 tables (positive and negative results for the index test versus positive and negative results for the reference standard) were constructed from raw data, which allowed calculation of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio, diagnostic odds ratio, pre- and post-test probabilities. Calculations were done within the Access database, and Review Manager (version 5) was also used for the calculation of sensitivity and specificity and the representation of these in both forest plots and the receiver operating characteristic (ROC) space.

In some of the initial assessment reviews, we reported the likelihood ratio in forest plots. A good test was considered to be one for which the positive likelihood ratio was more than 5 or the negative likelihood ratio was less than 0.2. A strong test was considered to be one in which the likelihood ratios were more than 10 or less than 0.1. Heterogeneity was examined visually.

In other reviews, sensitivity and specificity pairs were reported in both forest plots and receiver operator characteristic (ROC) space, which plots sensitivity versus (1-specificity). The latter plot is normally used when diagnostic test accuracy studies explore the effect of different cut-off thresholds on sensitivity and specificity. A summary ROC curve is obtained by fitting a regression curve to pairs of sensitivity and specificity. The summary ROC curve and the area under it present a global summary of test performance and show the trade off between sensitivity and specificity. A symmetric, shoulder like ROC curve suggests that variability in the thresholds used could, in part, explain variability in study results. Weighted analyses are provided (by sample size). A good test is considered to be one in which the summary ROC curve is close to the 100% sensitivity, 100% specificity point. Heterogeneity is represented on a ROC curve by vertical displacements around the ROC curve, and this is examined in subgroup analyses.

It might be expected that for a single threshold, such as tilt positive / tilt negative, that the sensitivity-specificity pairs would be similar. However, in some reviews, the index tests have different thresholds because of different definitions, and a more meaningful approach is to summarise the joint distribution of sensitivity and specificity using the summary ROC curve. Unlike a traditional ROC plot that explores the effect of varying thresholds on sensitivity and specificity in a single study, each data point in the summary ROC space represents a separate study.

Heterogeneity was not calculated, but was assessed visually for the spread around the summary ROC curve.

In the ambulatory ECG reviews, the diagnostic yield was reported as a proportion with its standard error (calculated from the formula: sqrt (p (1-p)/n),

where p is the proportion and n is the number of patients). Meta-analysis was carried out purely to quantify any heterogeneity, and the pooled summary statistics were not used. The proportion and its standard error data were entered into Review Manager using the generic inverse variance method.

2.4.4 Grading evidence: intervention studies

The GRADE[‡] scheme for intervention studies (GRADE working group 2004) was used to assess the quality of the evidence for each outcome using the approach described below, and evidence summaries across all outcomes were produced.

According to the GRADE scheme, evidence is classified as high, moderate, low or very low:

- High: further research is very unlikely to change our confidence in the estimate of effect
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- Very low: any estimate of effect is very uncertain.

The following procedure was adopted when using GRADE: an initial quality rating was assigned, based on the study design, for example, RCTs started as high and observational studies as low.

This rating was up- or down-graded according to specified criteria: study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below. Criteria were given a downgrade mark of −1 or –2 depending on the severity of the limitations.

The downgrade/upgrade marks were then summed and the quality rating revised. For example, a decrease of –2 points for an RCT would result in a

[‡] GRADE – Grading of Recommendations Assessment, Development and Evaluation

rating of 'low'. Wherever possible, reasoning was explained for the downgrade marks.

2.4.4.1 Risk of bias

Risk of bias is assessed against standard criteria, depending on the study design. For randomised trials, we took into account: the adequacy of allocation concealment; blinding of participants and outcome assessors for comparisons and outcomes susceptible to bias; attrition (missing data); baseline comparability and early stopping. A downgrade mark of –1 was given for inadequate or unclear allocation concealment and for a loss to follow-up of more than 20% in any one group or overall. Studies with more than 50% missing data were excluded from the analysis unless they were the only study, in which case they were given a downgrade mark of –2. If the evidence was a meta-analysis, we took into consideration the proportion and weighting of higher risk studies, and in some instances carried out sensitivity analyses disregarding these studies and giving a separate rating for the new meta-analysis.

2.4.4.2 Inconsistency

When several studies have widely differing estimates of treatment effect (heterogeneity or variability in results), the results are regarded as inconsistent. We defined this as a p-value for heterogeneity less than 0.1 and/or an I^2 value greater than 50%. Where this was the case, we gave a downgrade mark of –1. If the p-value was less than 0.1 and the I^2 value was greater than 80%, we gave a downgrade mark of –2. Where possible, we carried out pre-defined subgroup analyses to investigate heterogeneity and reported these results separately.

2.4.4.3 Indirectness

Directness refers to the extent to which the population, interventions, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is only relevant if there is a compelling reason to expect important differences in the size of the effect. For example, many interventions have more or less the same relative effects

across patient groups, so extrapolation is possible and reasonable. In this guideline the type of TLoC (population) was important for determining directness.

2.4.4.4 Imprecision

Evidence is considered to be imprecise if:

- The confidence interval for the effect estimate is consistent with different conclusions, for example, both a clinically important effect (benefit or harm) and no clinically important effect; or the confidence interval is consistent with important harms, no clinically important effect and important benefits. Interpretation of precision requires the GDG to decide what are clinically important harms and benefits for that outcome measure. For dichotomous outcomes we used a relative risk reduction of 50% (RR of 1.5 or 0.5) to indicate the clinically important threshold for recurrence of TLoC in the pacemaker reviews; this value was given in one of the studies.
- If the confidence interval did not cross either of the clinically important thresholds (i.e. precise rating), the sample size was taken into consideration. If there was a power calculation for that outcome and comparison, it was used to decide if a study was 'small', otherwise 300 events total was assumed as the minimum size.

2.4.4.5 Reporting bias

Reporting bias occurs in two main ways: publication bias, in which papers are more likely to be published if their results are statistically significant; and the potential for bias associated with industry sponsorship.

2.4.5 Economic analysis

Health economic evidence is useful in guideline development as it assesses the costs and benefits of alternative courses of action which could be recommended within the guideline. Cost-effectiveness evidence can be used to determine whether a particular recommendation would result in the efficient use of NHS resources by considering whether it achieves additional health gain at an acceptable level of cost. Two approaches were employed to

provide cost-effectiveness evidence for the GDG to consider when making recommendations. Firstly, a review of the health economic literature was carried out, and relevant health economic evidence was presented to the GDG. Secondly, further economic analysis was carried out for selected clinical questions. Whilst cost-effectiveness is an important consideration for all recommendations made within the guideline, it is not usually feasible for the health economist to conduct an original economic evaluation for all aspects of the guideline. It was therefore necessary to establish which areas of the guideline were considered to be priorities for further economic evaluation. The economic priorities for this guideline were identified by the health economist, in conjunction with the GDG, after considering the importance of each clinical question in terms of the number of patients likely to be affected, and the impact on costs and health outcomes for those patients.

The use of diagnostic tests to identify the cause of TLoC was considered to be a high priority area for economic evaluation as it has potentially important implications for both patients and the NHS. A failure to diagnose the true cause can lead to recurrent episodes of TLoC, sometimes with serious consequences if the underlying cause is life-threatening. Further more, inappropriate investigations can lead to misdiagnosis and inappropriate treatment. The economic modelling for this guideline focused on the diagnostic tests for which the GDG felt there was significant uncertainty regarding the balance of costs and benefits after considering the published literature on clinical and cost-effectiveness.

For those clinical questions not prioritised for economic analysis, the GDG considered the likely cost-effectiveness of associated recommendations by making a qualitative judgement on the likely balance of costs, health benefits and any potential harms.

2.4.5.1 Health economic evidence review

The aim of the economic review was to present existing published economic evaluations which were relevant to any of the guideline's clinical questions.

Types of studies

Economic evaluations compare the costs and benefits of alternative courses of action. To be included in the economic literature review a paper had to present a full or partial economic evaluation. A full economic evaluation is one which compares all relevant cost and patient outcomes and uses these to estimate a single measure of incremental costs and benefits. A partial economic evaluation is one which only reports some of the relevant outcomes. Types of economic evaluations included in the review were trial or model based economic evaluations including cost-effectiveness analyses, cost-utility analyses or cost-benefit analysis. Cost-minimisation studies were excluded except when there was evidence to demonstrate that the intervention and comparator had equivalent benefits. Non-comparative studies or studies comparing groups according to outcomes (e.g costs in patients with and without TLoC) were excluded. Studies reporting analyses in non OECD member countries or prior to 1990 were also excluded as these were felt to be less relevant to current practice in the UK.

2.4.5.2 Search strategy for identification of studies

An economic filter was applied to the broad search used to identify efficacy evidence. In addition to this, the patient filter was applied to the NHS EED and HTA databases. Further details on the search strategy can be found in Appendix C2. The search identified 615 titles which were sifted by the health economist. Of the papers sifted 34 were considered to be possible economic evaluations based on the title and abstract alone. Twenty six of these did not meet the inclusion criteria once the full articles were considered, leaving eight papers included in the review. The most common reasons for exclusion were that the studies were not comparative or they were not economic evaluations in that they did not report both costs and benefits. Three of the excluded studies (Farwell 2004a, Del Greco 2003 and Brignole 2006) considered the economic impact of introducing a management protocol or standardised care pathway. These were excluded as the care prior to the introduction of the protocol was not well defined making it difficult to determine whether the

comparison was generalisable to other settings. All of the included studies evaluated the cost-effectiveness of diagnostic testing strategies. Included economic papers have been summarised after the relevant clinical evidencein each chapter.

2.4.5.3 Cost effectiveness modelling

The economic literature review identified some evidence on the cost-effectiveness of diagnostic testing but most of the papers did not consider the impact of diagnosis on patient outcomes, and the only cost per QALY estimate identified was for a non-UK setting. Further analysis was therefore required to estimate the cost-effectiveness of diagnostic tests in people who have experienced a TLoC through estimating the impact of diagnosis and subsequent treatment on patient outcomes. After considering the clinical effectiveness evidence, the GDG further prioritised the diagnostics tests requiring economic evaluation to focus on those areas where they felt there was significant uncertainty regarding the balance of costs and benefits. Two priority areas were identified as follows;

1) Ambulatory ECG in patients who have been referred for specialist cardiology assessment based on their initial assessment. This population was split into those with a suspected arrhythmic cause and those with unexplained syncope.

2) Testing strategies using tilt-testing, ambulatory ECG or sequences of these tests in patients with suspected vasovagal syncope in whom pacemaker therapy is being considered

In these economic models, benefits were measured in terms of the quality-adjusted life-years (QALYs) gained, and cost was assessed from an NHS and personal social services perspective. The net present value of future costs and benefits were discounted at 3.5% (NICE 2008).

Where one diagnostic strategy was less costly than the comparator strategy but resulted in greater QALY gains, it was said to ‘dominate’ the comparator strategy in terms of cost-effectiveness. Where one diagnostic testing strategy was more costly but resulted in greater QALY gains than the comparator

strategy, the incremental cost per QALY was estimated and this was compared to a cost-effectiveness threshold of £20,000 to £30,000 per QALY in line with the principles laid out in the NICE Guidelines Manual (NICE 2009). Where there were several strategies being compared the GDG considered which strategy would result in the most cost-effective use of NHS resources. For this we estimated the incremental net benefit (INB) of each strategy compared to a common comparator strategy. The INB is the monetary value of a strategy compared to an alternative when the decision maker values a gain of 1 QALY at a given monetary value which is know as the “willingness to pay threshold”. So for example, if a gain of 1 QALY is valued at £20,000 the incremental net monetary benefit is calculated as follows:

INB = (incremental QALY gain compared to comparator strategy)*£20,000

- (incremental cost compared to comparator strategy)

The strategy with the highest INB is the optimal strategy for the given “willingness to pay threshold”. The cost-effectiveness model was used to estimate the optimal strategy for various “willingness to pay thresholds” and this information was used by the GDG to inform their recommendations.

Further details on the two economic models developed are given in Chapters 5and 6, but the following general principles were applied:

- modelling was carried out using the best available evidence and according to the NICE reference case for economic evaluations (NICE 2008)
- assumptions made in the model have been described explicitly; the validity of these assumptions was discussed with the GDG during the development of the model and the interpretation of the cost-effectiveness results
- the importance of model assumptions was examined through scenario sensitivity analysis
- parameter uncertainty was explored by carrying out a probabilistic sensitivity analysis (PSA)
- limitations of the analysis have been explicitly discussed alongside the cost-effectiveness results

2.5 Development of Patient Information Recommendations

People experience TLoC for a variety of reasons, and TLoC can have many underlying causes. These can range from an uncomplicated faint to life threatening causes. People can receive a firm diagnosis quickly or it may take a few years to have a clear cause established. In addition, some people have the cause of their TLoC misdiagnosed or undiagnosed despite numerous tests, and people who have had one TLoC do not know whether or when they may have another event. Furthermore, people who have experienced TLoC for any reason may be at risk of injuring themselves or others if they blackout again and therefore require guidance on safety at work and when driving. Overall, TLoC often leads to uncertainty and fear in the daily living of people who have had an event, and this may be exacerbated by a lack of information concerning what happened to them and why. It was the view of the GDG that appropriate information is crucial on all these matters.

The GDG took into consideration the experience of a similar diagnostic NICE guideline *'Investigation, Assessment and Management of Acute Chest Pain of Suspected Cardiac Origin',* which found that, while the evidence about the provision of information once a diagnosis was made was extensive, none was found relating to the diagnostic pathway. Therefore, this TLoC guideline did not carry out a search of the evidence.

The information recommendations were developed from three sources:

1. As the GDG was developing clinical recommendations, where appropriate, complementary information recommendations were drafted.

2. The chairman of the GDG contacted the DVLA for information to help with drafting recommendations on driving restrictions.

3. A sub-group comprising the two GDG patient representatives and the Cardiology and Epilepsy specialist nurses then met to develop further recommendations based on their own experience and those of patient organisations.

The guideline does not cover treatments for the causes of TLoC, but the sub-group wished to provide the person with information on what may have caused their TLoC; what they should do whilst waiting for a specialist referral, lifestyle advice addressing how the person can best self-manage the cause of their TLoC, including helping to prevent future events; and safety advice.

Initially, the sub-group planned to base their draft recommendations on those of the NICE Chest Pain guideline, but later decided that this did not capture what they wished to communicate, so they restarted their consensus process based on their own experience with TLoC. The sub-group members were keen that the information recommendations should complement the clinical recommendations, and focused particularly on additional content to help the person (and their family or carers) who had had TLoC, rather than considering how information should be imparted. The sub-group considered that the best way the health care professional could help the person with TLoC was to provide information to answer their questions, reassurance to allay their fears, where possible, and advice to help improve the person's quality of life. The sub-group agreed a set of draft recommendations, and these were presented to the full GDG, discussed thoroughly and modified at a GDG meeting. The full GDG agreed the final recommendations through consensus at the meeting.

2.6 Interpretation of the evidence and development of the recommendations

In preparation for each meeting, the narrative and extractions for the questions being discussed were made available to the GDG one week before the scheduled GDG meeting. These documents were available on a closed intranet site and sent by post to those members who requested it.

GDG members were expected to have read the narratives and extractions before attending each meeting. The GDG discussed the evidence at the meeting and agreed evidence statements and recommendations. Any changes were recorded.

Recommendations were also documented in a care pathway which was reviewed regularly by the GDG.

All work from the meetings was posted on the closed intranet site following the meeting as a matter of record and for referral by the GDG members.

2.7 Consensus methodology

The table of clinical questions in Appendix C1 indicates which questions were searched.

In cases where evidence was sparse, the GDG derived the recommendations via informal consensus methods, using extrapolated evidence where appropriate. All details of how the recommendations were derived can be seen in the 'Evidence to recommendations' section of each of the chapters.

2.8 Choice of Key Priorities for Implementation (KPI's)

As a group, the GDG nominated recommendations as KPI's during the final GDG meeting, which were subsequently put to a vote by email. They considered the criteria in the NICE Technical Manual in their choice of KPI's. From the NICE manual, the reasons for the choice were as follows:

Recommendations 1.1.1.1, 1.1.1.2, 1.1.2.2, 1.1.3.2, 1.1.5.1 and 1.2.1.1 were chosen because they are expected to improve care, decrease variation in practice and promote safer practice

Recommendations 1.1.4.1, 1.2.2.4 and 1.2.2.9 were chosen because they are expected to decrease variation in practice, promote safer practice and use resources more effectively

Recommendation 1.2.2.5 was chosen because it is resource saving and recommends against using a test that is not expected to improve patient outcomes

2.9 Consultation

The guideline has been developed in accordance with the Institute's guideline development process (Guidelines Manual 2009) http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/clinical_guideline_development_methods.jsp). This has included allowing registered stakeholders the opportunity to comment on the scope of the guideline and the draft of the full and short form guideline. In addition, the draft was reviewed by an independent Guideline Review Panel (GRP) established by the Institute.

The comments made by the stakeholders, peer reviewers and the GRP were collated and presented for consideration by the GDG. All comments were considered systematically by the GDG and the development team responded to comments.

2.10 Relationships between the guideline and other national guidance

2.10.1 Related NICE Guidance

It was identified that this guideline intersected with the following NICE guidelines published or in development. Cross reference was made to the following guidance as appropriate.

Published

- Stroke: diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). NICE clinical guideline 68 (2008). Available from www.nice.org.uk/CG68
- Head injury: Triage, assessment, investigation and early management of head injury in infants, children and adults. NICE clinical guideline 56 (2007). Available from www.nice.org.uk/CG56
- Atrial fibrillation: the management of atrial fibrillation. NICE clinical guideline 36 (2006). Available from www.nice.org.uk/CG36
- Anxiety (amended): management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary,

secondary and community care. NICE clinical guideline 22 (2007). Available from www.nice.org.uk/CG22

- Falls: the assessment and prevention of falls in older people. NICE clinical guideline 21 (2004). Available from www.nice.org.uk/CG21
- The epilepsies: The diagnosis and management of the epilepsies in adults and children in primary and secondary care. NICE clinical guideline 20 (2004). Available from www.nice.org.uk/CG20

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Acute coronary syndromes: the management of unstable angina and non-ST segment elevation myocardial infarction. NICE clinical guideline. Publication expected March 2010.
- The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (update). NICE clinical guideline. Publication expected March 2010.

2.10.2 Other National Guidance

National service framework for coronary heart disease

National service framework for Long term conditions

2.11 Research Recommendations

2.11.1 Development of a robust system for promoting good-quality information from a witnessed TLoC

Research question

Does providing people who have experienced TLoC and their family/carers with information on the importance of witnessed accounts reduce the time to correct diagnosis and prevent inappropriate referrals?

Research recommendation

Development of a robust system for providing good-quality information from a witnessed TLoC by patients/carers/family to improve diagnostic outcomes.

Why this is important

Patient and witness accounts of TLoC are essential to a correct diagnosis. Information is an important part of the patient journey and central to the overall quality of each patient's experience of the NHS. Improving information for patients was a commitment in the NHS Plan (DH 2000) and more recently in Lord Darzi's review of the NHS, 'High quality care for all' (DH 2008). There is a need to improve and monitor the effectiveness of information provided across the NHS. There is a need for good-quality trials in people with TLoC to establish whether providing specific information to patients/carers helps healthcare professionals to reach a correct diagnosis more quickly and improves outcomes for the patient. The information should address which details of a TLoC are required to aid diagnosis. This would also identify those patients who have been incorrectly sent down the wrong TLoC pathway.

Such studies should consider a number of delivery mechanisms including advice-specific information leaflets or visual data (information given in pictorial form).

2.11.2 Investigation of the accuracy of automated ECG interpretation

Research question

Does using automated ECG interpretation improve the accuracy of diagnosis in the TLoC population compared with expert interpretation, and what is the overall effect on patient outcomes, including patients with inherited long QT syndromes?

Research recommendation

Investigation of the accuracy of automated ECG interpretation compared with expert interpretation in the diagnosis and outcomes in the TLoC population, including people with inherited long QT syndromes.

Why this is important

The prevalence of syncope in the UK population is estimated to be approximately 25%. The Framingham study identified people with cardiac syncope to have a poorer prognosis than those with neurally mediated syncope or those in whom the cause of TLoC was uncertain. Risk-stratification studies undertaken in Emergency Departments in patients with TLoC have identified that an abnormal resting 12-lead ECG at presentation is a marker of high risk of death. A 12-lead ECG is cheap, widely available and can be performed quickly at the patient's bedside. In the past, all recorded ECGs were manually read and interpreted, the latter depending on the skill of the interpreter. Most of the ECGs recorded today are digitally acquired and automatically read. Scientific studies have been undertaken to compare the accuracy of this automatic interpretation with expert interpretation in the general population. However, no such scientific studies are available in the population with TLoC. It is therefore recommended that studies be undertaken in adults to assess the accuracy of automatically interpreted ECGs versus those interpreted by an expert in diagnosing the cause of TLoC, including in people with long QT syndrome.

2.11.3 Diagnostic yield of repeated ECG and physiological parameter recording

Research question

Does a serial assessment approach (taking repeated ECGs or repeated observations of vital signs) improve diagnosis of high-risk cardiac arrhythmias when compared with a single assessment approach in people with TLoC in any setting?

Research recommendation

Investigation to determine whether the diagnostic yield and accuracy of high-risk cardiac arrhythmias improves with serial assessments when compared with a single assessment approach in people with TLoC in any setting.

Why this is important

Current consensus opinion suggests that a single assessment approach has the same diagnostic yield as serial assessments for high-risk cardiac arrhythmias in patients presenting with TLoC, despite there being little evidence to support this approach during the critical phase of a presentation. Variable length QTc and changes in T-wave morphology can occur with heart rates as low as 90 beats per minute and may be paroxysmal in nature. Undertaking a serial assessment approach may therefore be more sensitive for detecting QTc length variability for high-risk patients with potential long QT syndrome during initial presentations than a single recording of an ECG.

2.11.4 Investigation of the benefit and cost-effectiveness of 12-lead ECG

Research question

In people who are considered on the basis of clinical history and examination to have had an uncomplicated faint, what is the additional clinical effectiveness and cost effectiveness of a 12-lead ECG?

Research recommendation

Investigation of the benefit and cost effectiveness of 12-lead ECG in all people who are considered on the basis of clinical history and examination to have had an uncomplicated faint.

Why this is important?

Uncomplicated fainting is a very common cause of TLoC. It has a good prognosis and in most cases can be diagnosed accurately from the person's history and from observations made by witnesses or healthcare professionals, without the need for any tests. Most healthy people who faint have a normal ECG; in a few, ECG features of no importance may generate unnecessary concern and further tests.

Much less commonly, relatively rare heart conditions cause TLoC in otherwise healthy young people, who are at risk of dying suddenly unless the condition is recognised and treated. In many of these people, an abnormal ECG will provide evidence of the heart condition. Although TLoC in these conditions is not usually typical of an uncomplicated faint, the diagnosis has been missed in some people, with disastrous consequences.

It is important that research is conducted to establish whether:

- making a diagnosis of uncomplicated faint from typical clinical features and without an ECG will miss dangerous heart conditions that would have been identified if an ECG had been recorded

- it is cost effective to record ECGs in large numbers of people who have had an uncomplicated faint to try to avoid missing a more dangerous condition in a small number of people.

2.11.5 Cost effectiveness of implantable event recorders in patients with TloC.

Research question

Under what circumstances is the implantable cardiac event recorder the investigation of choice for TLoC in people in whom a cardiac cause is suspected?

Research recommendation

Investigation of the cost effectiveness of implantable cardiac event recording compared with alternative investigation strategies (for example, prior external event recording) in people with suspected cardiac cause of TLoC.

Why this is important

This guideline recommends that people with a suspected cardiac cause of TLoC, who have infrequent episodes (every 1–2 weeks or less), should be offered an implantable cardiac event recorder. It is unclear when it would be more cost effective to use a strategy of alternative investigation (for example, external event recording).

2.12 Acknowledgements

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2.13 Glossary and Abbreviations

12-lead ECG	Recording of the heart's electrical signals obtained by attaching electrodes in 10 standard positions on the limbs and the surface of the chest. This provides a display of the electrical activity of the heart viewed from 12 different directions.
Annual risk reduction	The difference between the percentage annual incidence of an adverse outcome in a treatment group compared with that in a control group
Arrhythmia	An abnormal heart rhythm
Asystole	Sustained absence of the heart's electrical activity
Atrioventricular block	General term used to describe abnormally slow or absent conduction of electrical signals from the heart's atria to its ventricles. More severe degrees of AV block may cause syncope and may predispose to sudden death
Aura	Brief experience immediately prior to an episode. (*From the Greek, meaning: "A breath of wind")* Aura a brief, lasting from several seconds to several minutes, perceptual disturbance experienced by a person
Blackout	Sudden and spontaneous transient loss of consciousness. . Temporary lack of awareness followed by a return to full wakefulness. .
Bradycardia	Slow heart rate (irrespective of rhythm), conventionally defined as below 60/minute
Brugada syndrome	An inherited ion channel disorder characterised by abnormal ST segment elevation in leads V1 to V3 on ECG. This predisposes to ventricular arrhythmia and sudden cardiac death and may present with syncope.
Cardiac arrhythmic syncope	Syncope caused by a sudden abnormality of heart rhythm, which may be be a bradyarrhythmia (abnormal rhythm with a slow heart rate) or a tachyarrhythmia (abnormal rhythm with a fast heart rate)
Carotid sinus syncope	A form of neurally mediated syncope in which pressure on one or other carotid artery causes syncope. Syncope is caused by a sudden abnormality of heart rhythm, which may be be a bradyarrhythmia (abnormal rhythm with a slow heart rate) or a tachyarrhythmia (abnormal rhythm with a fast heart rate)
Carotid sinus syndrome	A spontaneous, or possibly neck movement precipitated, syncope occurs in the presence of carotid sinus hypersensitivity, documented on CSM testing
Collapse	A sudden fall, or prostration, due to many possible causes.
Cost-benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment as a net gain results.
Cost-consequences analysis	A type of economic evaluation where various health outcomes are reported in addition to the costs for each intervention under consideration. There is however no formal synthesis of the costs and health effects.
Cost-effectiveness acceptability curve (CEAC)	A CEAC plots the probability of an intervention being cost-effective compared with alternative intervention(s), for a range of maximum monetary values, that decision-makers might be willing to pay, for a particular unit change in outcome.
Cost-effectiveness analysis	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of incremental costs per unit of effectiveness.

Cost-minimisation analysis	An economic evaluation that finds the least costly alternative therapy. This type of analysis implicitly assumes that the health benefits of the competing interventions are equivalent.
Cost-utility analysis	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Cough syncope	A form of neurally mediated syncope in which coughing provokes syncope
Déjà-vu	An intense sensation that what is happening for the first time has already occurred previously. This is common particularly in adolescence, but may occur immediately prior to an epileptic seizure.
Diaphoresis	Technical term for excessive and profuse perspiration/sweating commonly associated with shock and other medical emergency conditions
Discounting	Discounting is the process by which economist make allowances for society's time preference for costs and benefits. All else being equal, society places a higher value on the same unit of cost and benefit today than it does for the same unit in the future. For example, society prefers to receive £100 today as opposed to £100 in n years' time. The differential is expressed in terms of the discount factor DF, where $DF = 1/ (1+ r)^n$ and where *r* is the discount rate, and *n* is the number of years forward from the current year.
Dominance	A health intervention is said to be dominant if it is both more effective and less costly than an alternative intervention.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Epilepsy	A neurological disorder characterized by recurrent episodes due to spontaneous abnormal neuronal activity in the brain (seizures).
Evidence statements	A summary of the evidence distilled from a review of the available clinical literature
Evidence-based questions (EBQs)	Questions which are based on a conscientious, explicit and judicious use of current best evidence
Exercise-induced syncope	Syncope induced by exercise
Extended dominance	Where a combination of two alternative strategies dominates a third.
External event recorder	A small portable recorder that is capable of monitoring and storing ECG recordings from electrodes on the skin in order to record the heart's rhythm during symptoms (including syncope) that occur intermittently,
Faint	Episode of Transient Loss of Consciousness due to vasovagal syncope. Fainting is a temporary loss of consciousness due to a drop in blood flow to the brain. The episode is brief and is followed by rapid and complete recovery
Health Economic Model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporates evidence from a variety of sources in order to estimate costs and health outcomes.
Health economics	The branch of economics concerned with the allocation of society's scarce health resources, between alternative healthcare treatments/programmes, in an attempt to improve the health of the population.
Health-related quality of life	An attempt to summarise an individual's or the population's quality of life resulting from the combined effect of their physical, mental, and social well-being.
Heart block	A disorder of heart rhythm, usually with a slow pulse, due to failure of electric conduction within the heart, specifically between the atria and ventricles.
Holter monitor/recorder	A small portable recorder that is capable of continuous ECG recording from electrodes on the skin, usually used over 24-72 hours.

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Implantable event recorder	Small implantable device capable of monitoring and storing ECG recordings of the heart's rhythm.
Incremental cost-effectiveness ratio (ICER)	The difference in the costs of two alternative treatment strategies/programmes, divided by the difference in the effectiveness outcomes of the treatment strategies/programmes for a defined population of interest. That is: $\frac{\text{Cost treatment B} - \text{Cost treatment A}}{\text{Effectiveness treatment B} - \text{Effectiveness treatment B}}$
Inherited cardiac condition	In this context this refers to a cardiac condition that is genetically determined. Many such conditions predispose to syncope, ventricular arrhythmia and sudden death, including long and short QT syndromes, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, catecholaminergic polymorphic ventricular tachycardia, hypertrophic cardiomyopathy, familial dilated cardiomyopathy. Many of these are due to abnormalities in ion channels, which are microscopic pores in cell membranes, important for the normal functioning of the cells.
Jamais-vu	A feeling of lack of familiarity, that what should be familiar is happening for the first time; it is usually abnormal, it doesn't commonly occur in healthy people.
Life years	The number of years lived by an individual or a population. For example, if a population of 50 patients live for an average addition 2 years each as the result of receiving a healthcare intervention, then the intervention has provided 100 life years gained.
Long QT syndromes	Inherited conditions □haracterized by prolongation of a specific portion of the on ECG. They predispose to ventricular arrhythmia and sudden cardiac death and may present with syncope.
Meta regression Analysis	An approach for aggregating data from different clinical trials which examine the same question and report the same outcomes, and relating sources of variation in treatment effects to specific study characteristics
Micturition syncope	A form of neurally mediated syncope provoked by passing urine. Mostly occurs in men.
Multiple logistic regression analysis	In a clinical study, an approach to examine which variables independently explain an outcome
Neurally mediated syncope (NMS)	Sometimes called "reflex syncope": Transient Loss of Consciousness due to a reflex bradycardia and/or hypotensive response to a number of causes; these include vasovagal syncope, carotid sinus syncope, and situational syncope.
Opportunity cost	The cost in terms of health benefits foregone by allocating resources to one intervention over an alternative intervention. The definition implicitly acknowledges the concept of scarcity of healthcare resources.
Orthostatic hypotension	Condition in which a marked fall in blood pressure is provoked by a change in posture from lying to sitting or from lying or sitting to standing. This may cause lightheadedness ("dizziness"), a fall, or TloC.
Pacemaker	Implantable device used (most commonly) to prevent the heart from beating too slowly
Post-ictal	An abnormal state that follows an attack, usually referring to a disturbed condition after an epileptic seizure.
Pre-syncope	A sensation of impending fainting/loss of consciousness
Probabilistic sensitivity analysis (PSA)	The process of measuring the degree of uncertainty around outcomes in an economic evaluation by assigning probability distributions to all of the key parameters in the evaluation, and then simultaneously generating values from each of these distributions using techniques of random number generation such as Monte Carlo methods.
Prodrome	Symptoms which precede the episode, usually considered to be more prominent than an aura, which is usually very brief.

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Psychogenic Non Epileptic Seizure (PNES)	Episode resembling an epileptic seizure, but where there are no abnormal electrical discharges in the brain, They are due to a subconscious psychological condition.
Quality adjusted life year (QALY)	An index of survival weighted to account for quality of life. The year of life is weighted by a utility value U (where $0 \leq U \leq 1$). U reflects the health related quality of life, such that a U of zero represents the worst possible quality of life (equivalent to being dead), and a U of 1 represents perfect health. For example, 1 QALY is achieved if one patient lives in perfect health for one year, or alternatively if 2 people live in perfect health for 6 months each. Alternatively, a person living with a quality of life represented by a u value of 0.5 for 2 years is also representative of 1 QALY value. QALYs have the advantage of incorporating changes in both quantity (longevity/survival) and quality of life (morbidity as represented by psychological, physical and social functioning for example). QALYs are core to cost-utility analysis where the QALY is used as the measure of effectiveness in the economic evaluation.
Relative risk reduction	The ratio of the probability of an event occurring in the treatment group compared to the control group.
Seizure	Derived originally from the idea of demonic possession, it now refers to any episode due to epileptic activity in the brain. Does not require the presence of abnormal movements. The distinction between epileptic seizures and psychogenic non-epileptic seizures requires specialised assessment by a neurologist.
Sensitivity	Sensitivity is the proportion of people with the disease who have a positive test. Sensitivity reflects how good the test is at identifying people with the disease. A measure of the diagnostic accuracy in including individuals with the condition. Number of True Positives divided by (Number of True Positives + Number of False Negatives) True positive: People correctly diagnosed with the condition False positive: Healthy people wrongly diagnosed with the condition True negative: Healthy people correctly identified as healthy False negative: People wrongly identified as healthy
Short QT syndrome	Inherited condition characterised by a specific portion of the ECG being of abnormally short duration. This predisposes to ventricular arrhythmia and sudden cardiac death and may present with syncope.
Situational Syncope	A form of neurally mediated syncope occurring in certain situations, usually involving an increase in intra-abdominal pressure (for example, cough syncope and micturition syncope).
Specialist	A healthcare professional who has expert knowledge of and skills in a particular clinical area, especially one who is certified by a higher medical educational organization.
Specificity	Specificity is the proportion of people free of disease who have a negative test. Specificity reflects how good the test is at identifying people without the disease. A measure of the diagnostic accuracy in excluding individuals without the condition. Number of True Negatives divided by (Number of True Negatives + Number of False Positives) True positive: People correctly diagnosed with the condition False positive: Healthy people wrongly diagnosed with the condition True negative: Healthy people correctly identified as healthy False negative: People wrongly identified as healthy
Spell	American term for episode of a disturbed physical and/or mental state, often referring to a transient loss of consciousness
Syncope	Transient loss of consciousness due to a reduction in blood supply to the brain.
Tachycardia	Fast heart rate (irrespective of rhythm), conventionally defined as above 100/minute
Tilt test	Test in which a patient is exposed to passive head-up tilt, during which

	they have beat-to-beat measurement of heart rate and blood pressure, to try to demonstrate whether or not they have a provocable tendency to vasovagal syncope
Transient Loss of Consciousness (TLoC)	Preferred term for a blackout
Vasovagal Syncope	A form of neurally mediated syncope due to excessive or inappropriate vagal activity. This is often, but not always, triggered by circumstances such as pain, prolonged standing (especially in a warm environment), or emotional stress. This commonly presents as an identifiable 'uncomplicated faint' but can present as sudden unprovoked syncope.
Ventricular fibrillation	Chaotic electrical activity in the heart's ventricles, causing loss of pumping action and resulting cardiac arrest. If not corrected immediately this will lead to death.
Ventricular tachycardia	Tachycardia arising from the heart's ventricular muscle. This can in some people cause syncope or cardiac arrest and sudden death.
Willingness to pay (WTP)	The amount of money that an individual or society is willing to pay in order to achieve a specified level of health benefit. For example, it is generally recognised that the current willingness to pay for an incremental QALY gain in the NHS is somewhere between £20,000 and £30,000.

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Abbreviations	
AF	Atrial fibrillation
AV	Atrioventricular
CAD	Coronary artery disease
CHD	Coronary heart disease
CI	Confidence intervals
CSH	Carotid sinus hypersensitivity
CSM	Cardiac sinus massage
CSS	Carotid sinus syncope
CT	Computed Tomography
CV	Cardiovascular
CVA	Cerebro vascular accident
DDD (pacemaker)	dual mode, dual chamber, dual sensing (pacemaker mode)
Echo	Echocardiography
ED	Emergency Department also known as Accident and Emergency
EP	Electrophysiology
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GTN	Glyceryl trinitrate
EEG	Electro-encephalogram
ECG	Electro-cardiogram
EER (ELR)	External event recorder (external event recorder)
EP	Electrophysiology
HCM,	Hypertrophic cardiomyopathy
HOCM	Hypertrophic cardiomyopathy
HUT	Head-up tilt
ICD	Implantable cardioverter-defibrillator
ICD	International classification of disease
IER (ILR)	Implantable event recorder (external loop recorder)
IPN	Isoproterenol / isoprenaline
IQR	Interquartile range
ISDN	Isosorbide dinitrate
LR	Likelihood ratio
MA	Meta-analysis
MI	Myocardial infarction

MRI	Magnetic resonance imaging
NM	Neurally mediated
NMS	Neurally mediated syncope
NSR	Normal Sinus Rhythm
OH	Orthostatic hypotension
OHT	Orthostatic hypotension
OR	Odd ratio
PICO	Population-Intervention-Comparator-Outcome
PM	Pacemaker
PNES	Psychogenic Non Epileptic Seizure
PPV	Positive predictive value
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
QoL	Quality of life
QUADAS	Quality assessment tool of diagnostic accuracy studies
RCT	Randomised clinical trial
RDR	rate drop response (of pacemakers)
ROC	Receiver operating characteristic
RR	Relative risk
SD	Standard Deviation
SHD	Structural heart disease
SR	Sinus Rhythm
SVT	Supra ventricular tachycardia
TLoC	Transient Loss of Consciousness
VT	Ventricular tachycardia
VVS	Vasovagal Syncope

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2

3 Initial assessment and diagnosis of people who have had TLoC

3.1 Clinical questions

The clinical questions appropriate to this section are:

- Q2) In people who have experienced a TLoC, what aspects of patient history (including eye-witness accounts) are useful in discriminating between patients with syncope (cardiac or vascular), epilepsy, psychogenic non-epileptic seizures and other causes of TLoC?
- Q3) In people who have experienced a TLoC, what aspects of physical examination are useful in discriminating between patients with syncope (cardiac or vascular), epilepsy, psychogenic non-epileptic seizures and other causes of TLoC?
- Q4) In people who have experienced a TLoC, what routine laboratory tests are useful in discriminating between patients with syncope (cardiac or vascular), epilepsy, psychogenic non-epileptic seizures and other causes of TLoC
- Q5) Which signs, symptoms and other features of presentation (e.g patient history) are associated with an increased risk of a serious adverse event
- Q6) Which signs, symptoms and other features of presentation (e.g patient history) are associated with an increased likelihood of spontaneous remission
- Q7) Can clinical decision tools or risk stratification tools be used to discriminate between patients who would benefit from admission and patients who can be safely discharged?
- Q9) When providing immediate care in the pre-hospital setting to a person who has experienced a TLoC, what aspects of the initial assessment should be performed in the pre-hospital setting?
- Q10) When is transfer to hospital by ambulance appropriate in the immediate care of a person who has experienced a TLoC and what discharge advice should be provided when transfer is not appropriate?

3.2 Interactive diagnostic simulation

In order to understand the context of initial stage assessment and to elicit GDG views in the early stages of guideline development, the GDG took part in an interactive diagnostic simulation exercise.

General practitioner (GP) training has focussed on the importance of what happens within a typical patient consultation. This is usually recorded and analysed to enable new GPs to reflect on the detail within the consultation, in particular, the quality of verbal and non-verbal behaviour, the sequencing of questions and information gathered to enable diagnosis. This is based around simulation and objective structured clinical examination methodology and has effectively enabled GP trainees to experience and develop understanding related to the importance of clinical history prior to physical examination.

In order to test the usefulness of different aspects of patient history including eye witness account, the technical team ran an interactive diagnostic simulation with members of the GDG. A patient profile, based on detailed notes kept by a real patient with recurrent TLoC, was shared by an actor. The patient profile used is given in Appendix D5.

Four GDG members (a GP, an ED physician, and two cardiologists, one of whom worked in a specialist blackout clinic) then role-played a consultation, with an actor playing the part of the patient, timed at about 10 minutes consultation. All the clinicians observed each others' consultations, three of whom carried out full consultations and the consultant in the Blackout clinic asked additional questions to which he required answers, to avoid repetition. In the consultation in ED, another GDG member played the part of the patient's husband, and gave an eye witness account. During each of the role-plays, GDG members were asked to observe the consultation.

The technical team then discussed with the GDG what aspects of patient history had been considered and how these could be used to inform

management of the patient, moving towards a possible diagnosis/view of the cause of the TLoC.

The content was analysed and grouped in patient history themes, including eye witness accounts. The number of clinicians addressing each issue is also reported.

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1. Pre-TLoC	**No. of clini-cians**	**comments**
How did the attack start?	1	
Any precipitating factors, e.g stress	3	
Pre-TLoC symptoms, e.g. light headed, feeling weak, cold and clammy, breathless and sick	4	
Of eye witness, did patient look pale?	2	
Did patient know it was about to happen? ("like a bird knows it's going to rain")	0	Additional suggestion by GDG
How did eye witness describe it? "I thought she was dying"	1	Indicates seriousness
How long was pre-TLoC warning?	2	Including how long was the chest pain before blackout. Relates to driving, & usefulness of external recorder
Were there auras preceding the event	1	
Were there palpitations preceding the event?	1	
2. The TLoC event itself	**No. of clini-cians**	**comments**
First determine if it was TLoC	1	
How long was attack?	2	30 minutes is unlikely to be syncope
How long unconscious? (of eye witness)	2	
Pain	1	
What is the tone of the body during blackout?	1	Stiffer tone with epilepsy; floppy and pale => syncope
Was there incontinence, tongue biting, abnormal movements, injuries on black out?	1	Syncope can be associated with abnormal movements and incontinence too
Was blackout related to posture or environment?	1	
Could patient abort an attack?	1	
Details about chest pain and pressure in chest	1	
Epilepsy can probably be diagnosed	0	GDG: Clear epileptic seizure can probably be diagnosed from initial information
3. Eye witness account	**No. of clini-cians**	**comments**
Did patient look pale?	2	
How did eye witness describe it? "I thought she was dying"	1	Indicates seriousness
How long was patient unconscious?	1	
Record with mobile phone	0	GDG: recommended that the eye witness should record event with mobile phone video if possible

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4. Post-TLoC	**No. of clini-cians**	**comments**
How quickly came round/how long till felt normal	2	
Were there prolonged symptoms?	1	Epilepsy more likely to have post symptoms
How did patient feel?	1	
What did patient remember on coming round	1	Lack of memory of the event is more likely to be epilepsy
Any palpitations or fast heart beat	1	
Was oxygen given in the ambulance?	1	
Was ECG done in the ambulance?	1	
Ambulance investigation notes need to stay with the patient	1	Lot of the assessment is done by ambulance staff
Ambulance staff can give information on home environment e.g. presence of intoxicating substances	0	GDG suggestion
5. Patient history of TLoC	**No. of clini-cians**	**comments**
How many previous occasions?	3	
How frequent?	3	
How long had it been going on?	2	Long duration (11y) suggested less likely to be structural heart disease or ischaemia
Has it changed with time?	1	Same each time is more likely to be cardiac cause
What is difference between attacks (chest pain) with and without TLoC?	1	
How many times admitted because of blackout?	1	
How did it all start?	1	
6. Other aspects of patient history	**No. of clini-cians**	comments
How patient was when giving information, e.g. calm?	1	Was there a need for acute care/resuscitation?
Did the patient have any symptoms during consultation?	1	
Need to take into consideration the patient themself	0	GDG: could be psychogenic after 11 years
What happens when patient at rest? (re chest pain and any irregular heart flutters)	1	
What happens when walking up hill, any chest pain?	1	
Any other comorbidities?	2	Looking for serious medical conditions, e.g. diabetes, hypertension, rheumatic fever, smoking; also exploring other causes of loss of consciousness
Family history e.g. of early death	1	
Questions re previous investigations what were they and findings	3	Were the following done: treadmill, ECG, ambulatory ECG; external recorder
Any allergies?	1	Routine question
Any head injuries		GDG question
Previous history of myocardial infarction	1	
Age	1	Take into consideration

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7. Drugs	**No. of clini-cians**	comments
Investigate different prescribed drugs – what are they for?	3	e.g. amitriptylene is antidepressant GDG: is the TLoC drug induced?
Prescribed drugs	0	Looking for history not reported by patient (e.g. psychiatric); confirmation of other indications
Alcohol intake?	1	
8. Clinical examination the clinicians would carry out	**No. of clini-cians**	**comments**
Blood pressure	1	
Bp sitting down and standing up	1	Cardiac, postural hypotension
Neurology questions (basic)	1	
Listen to heart	1	
Unspecified	1	
9. Routine tests the clinicians would order	**No. of clini-cians**	**comments**
12-lead ECG	2	GDG agreed that should be done for all patients
Finger prick test	1	diabetes

Both the GP and the ED consultant stated that their approach to the consultation was to determine if there were any areas requiring urgent action, so they focussed immediately on the chest pain symptoms.

The GP used the consultation to determine if the patient should be referred to secondary care for further investigation, and this was based on the perceived seriousness of symptoms, in this case, the chest pain. In some ways it was more difficult for the GP **not** to refer the patient.

The ED consultant, however, commented it was more difficult to admit the patient for further investigation; e.g. there was no direct route from ED into cardiology.

The GDG was concerned about referral patterns.

The clinicians concluded that the patient should not be considered to be in urgent need for referral because the events had been going on for 11 years, but she should be followed up fairly soon (a few weeks). The GDG noted that there was a need to ensure follow up if the patient was discharged, and there was a need to give lifestyle and safety advice.

The GDG concluded that there was a low chance of structural heart disease or ischaemia because the events had been going on for 11 years, the 12-lead ECG was normal, and problems did not occur on exertion. They suspected an infrequent arrhythmia (tachycardia) which they would investigate either with an external ECG recorder (used when the patient had another attack) or an implantable event recorder.

3.3 Reviews of diagnostic test accuracy: initial assessment

3.3.1 Introduction

There are two main reasons for evaluating patients who have had a TLoC: to make a diagnosis of the cause of TLoC and to determine the prognosis for the person with TLoC, i.e. to determine the risk of future adverse events.

Questions 2, 3, 4 and 8 (Section 3.1) illustrate the GDG's first objective in this initial assessment stage: to use symptoms and tests either to predict or diagnose a cause for the TLoC or to state that there is no clear causal diagnosis at this stage (unexplained TLoC).

Knowing the likely cause also enables the clinician to determine the patient's risk of death or adverse events or recurrence of the TLoC. It also determines the referral route for the patient: whether the patient should be admitted to a speciality department in which further tests can be carried out urgently (and if so, which speciality); whether it is referral to outpatient departments for further tests, or whether it safe to send the patient home with follow up in the community.

Questions 2 to 4 were intended to discriminate between:

- cardiac syncope (arrhythmia based or structural heart disease based)
- vascular syncope (including neurally mediated, situational, orthostatic hypotension)
- epileptic seizures
- psychogenic non-epileptic seizures

- other causes of TLoC
- unexplained TLoC

TLoC itself is a symptom rather than a disease or condition, and because of its transitory nature, studies of diagnostic test accuracy can only investigate the causes of TLoC, rather than the event itself. This is further complicated by the fact that symptoms of the cause may not be present except during a TLoC.

There are numerous possible conditions that can give rise to syncope and the GDG divided this into two main categories, cardiac and vascular syncope, after the ESC guideline (Brignole 2004, Moya 2009):

- Cardiac syncope
  - Caused by structural heart disease
    - e.g. myocardial infarction, aortic stenosis, hypertrophic cardiomyopathy, atrial myxoma, congenital heart disease
  - Caused by arrhythmias
    - e.g. bradycardia or tachycardia
- Vascular syncope
  - Neurally mediated syncope: a temporary disturbance of autonomic control of heart rate and vascular tone resulting in bradycardia and hypotension, plus cerebral ischaemia
  - Carotid sinus syncope
  - Orthostatic hypotension: an important manifestation of autonomic dysfunction, especially in older people:
    - pure autonomic failure, which may be caused by: ageing; metabolic conditions (e.g. diabetes); connective tissue disorders (e.g. rheumatoid arthritis); trauma; multiple system atrophy (or Shy Drager syndrome)
    - autonomic failure associated with Parkinson's disease.

Clinical questions 2 to 4 can be answered either in terms of predictors for a particular cause of TLoC relative to all other causes, or the predictors for two different causes of TLoC can be compared directly.

The GDG's second objective is illustrated by questions 5, 6 and 7, and is to determine directly predictors or combinations of predictors / risk stratification tools for adverse events, with a view to identifying patients at 'high', 'moderate' and 'low' risk. This, in turn, should determine the necessity of admission to speciality departments (with the appropriate degree of urgency) and should also indicate which patients can be safely discharged.

Questions 9 and 10 are addressed by all of the work in this chapter.

There are two ways in which we can consider predictors:

- Whether or not a particular sign/symptom predicts one target condition (either diagnosis or adverse events) compared to another. For example, whether coronary artery disease is a predictor for a cardiac cause of syncope rather than for non-cardiac syncope. In these analyses, the outcome is the likelihood ratio, which is the number of patients with the sign/symptom (e.g. coronary artery disease) in those who have the disease (e.g. cardiac cause of syncope), divided by the proportion with the sign/symptom in those without the disease (e.g. the non-cardiac syncope group).
- Whether having a particular sign/symptom puts a patient more at risk of the target condition (event or diagnosis) compared to not having that sign/symptom. For example, whether the patient is more at risk of a cardiac cause of syncope if they have coronary artery disease compared to not having CAD. In these analyses the outcome is the **risk ratio** (or odds ratio), which, for the RR, is the proportion of patients with the disease in those who have the sign/symptom divided by the proportion who have the disease in those who do not have the sign/symptom.

We are more likely to use the first method when we want to see if a particular sign or symptom enables us to distinguish between different causes of TLoC

(the first three clinical questions listed at the start of this chapter). We are more likely to use the second method when we want to see if a high or a low score on a risk stratification tool or if the presence/absence of a particular sign/symptom predicts an adverse event (the fourth and fifth clinical questions listed).

There are four main ways in which these problems have been tackled in studies:

- Univariate analyses which examine the effect of a predictor without taking into account any other factors
- Multivariate analyses, in which all likely predictors are entered into an iterative regression analysis program in order to determine the effect, on the outcome concerned, of each predictor, taking into account the effects of all the others.
- The multivariate equation for predictors of a cause of TLoC or an event can be combined to form a model, or decision rule, that predicts the likelihood of that cause of syncope or event. Often authors determine the multivariate predictors in the decision rule in one population (derivation cohort) and validate the tool in a second population (validation cohort). We have decided to exclude from this section, where possible, the test accuracy results for the derivation cohort (they are covered in the previous section).
- Finally, studies may examine a complex algorithm for diagnosis or prediction of risk categories.

Where the outcome considered is diagnosis of the cause of TLoC, the predictor is considered in the context of a reference standard, and the outcome measure is usually diagnostic test accuracy statistics (e.g. sensitivity and specificity). Where the outcome is an event, diagnostic test accuracy statistics may be provided, or the effect of predictors on the incidence of the event may be determined, giving outcomes as summary statistics such as odds ratios or relative risks.

3.3.2 Methods of the review

3.3.2.1 Selection criteria

The selection criteria given in the methods section were used, in combination with the following review specific criteria:

3.3.2.2 Types of participants

Adult patients who have had a TLoC presenting to emergency departments or general practice surgeries. Participants are not expected to have had any prior tests.

3.3.2.3 Reference standard

Diagnosis by expert clinician (following second stage tests); and follow up.

3.3.2.4 Comparator tests

Clinician decision making, or other tests.

3.3.2.5 Target condition

The target condition for these reviews was to be:

- the various causes of TLoC
- adverse events, which could be death only, death plus cardiac events, or any serious adverse event. The GDG defined a ‘serious adverse event’ to be death, any cardiac event, any cerebral event and serious injury. This combination of adverse events is equated to admission to hospital

3.3.2.6 Outcomes

Diagnostic test accuracy statistics

- Sensitivity
- Specificity
- Positive and negative predictive values
- Likelihood ratio (for this, the GDG considered the test to be good if it had a positive LR of more than 5 or a negative LR less than 0.2; the test was considered to be strong if the LR was greater than 10 or less than 0.1)

- Pre- and post test probabilities
- Diagnostic odds ratio

3.3.3 Description of studies (Appendix D1)

Twenty-three reports of 22 studies were included (Alboni 2001; Ammirati 2000; Birnbaum 2008; Colivicchi 2003; Cosgriff 2007; Crane 2002; del Rosso 2008; Elseber 2005; Graf 2008; Grossman 2007; Quinn 2004; Quinn 2005; Quinn 2006; Quinn 2008; Reed 2007; Romme 2008; Sarasin 2003; Schladenhaufen 2008; Sheldon 2002; Sheldon 2006; Sun 2007; Sun 2008; van Dijk 2008); the Romme (2008) study was an additional report of van Dijk (2008). The Ammirati (2000) study reported a diagnostic algorithm, but did not give details of the initial stage evaluation and so this study was not considered further in this review.

3.3.3.1 Study Design

Two studies had a cross sectional design (del Rosso 2008; Sarasin - 2003); three studies were retrospective cohort studies, comparing index tests with follow up (Crane 2002; Elseber 2005; Schladenhaufen 2008), with the index test results obtained from patient records; and the rest were prospective cohort studies. Twelve studies compared two or more index tests in the same patients for the same target condition (Birnbaum 2008; Crane 2002; Colivicchi 2003; Cosgriff 2007; Elseber 2005; Grossman 2007; Quinn 2004; Quinn 2005; Reed 2007; Sheldon 2002; Sheldon 2006; Sun 2007) and one studied two tests with different target conditions (del Rosso 2008).

Two studies (Crane 2002; Reed 2007) were conducted in the UK. Eleven studies were carried out in the USA (Birnbaum 2008; Elseber 2005; Grossman 2007; Quinn 2004; Quinn 2005; Quinn 2006; Quinn 2008; Sarasin 2003 (part); Schladenhaufen 2008; Sun 2007; Sun 2008); three were in Italy (Alboni 2001; Colivicchi 2003; del Rosso 2008); two were in Canada (Sheldon 2002; Sheldon 2006), two in Switzerland (Graf 2008; Sarasin 2003 (part)) and one each in Australia (Cosgriff 2007), Switzerland and The Netherlands (van Dijk 2008).

Six studies received some funding from Medronic (del Rosso 2008; Elseber 2005; Reed 2007; Sheldon 2002; Sheldon 2006; van Dijk 2008), but this was considered unlikely to be an important influence. Four studies had their decision rule validated by the same groups (same principal author) as were involved in the derivation study (Quinn 2005, 2006 (different reports); Graf 2008; Sheldon 2002; Sarasin 2003; Sheldon 2006. One study reported results for the decision rule in the derivation cohort (Colivicchi 2003).

Two included studies had fewer than 100 patients (Graf 2008 validation cohort, n=65; Reed 2007, n=99). Seven studies had more than 500 patients (Birnbaum 2008; Quinn 2004; Quinn 2005; Quinn 2006; Quinn 2008; Schladenhaufen 2008; Sun 2007) and the rest had between 250 and 500 patients.

3.3.3.2 Population

Setting

The majority of studies were conducted in an emergency department setting. The exceptions were three studies that took place in various hospital departments: Sheldon 2002 and Sheldon 2006 were set in tertiary referral and acute care facilities only; and van Dijk 2008 included patients from neurology, cardiology, internal medicine, cardiac emergency room and the emergency department (ED). Two other studies were set in a syncope unit, to which patients were referred (Alboni 2001; Graf 2008). Patients in the Graf (2008) study had unexplained syncope, but it was not clear why the patients were referred in the Alboni (2001) study.

Prior tests

Four studies stated that all the patients had received prior tests (Graf 2008; Sarasin 2003; Sheldon 2002; Sheldon 2006); one study reported some patients had prior tests (van Dijk 2008). Two stated that none of the patients had prior tests (Grossman 2007; Reed 2007) and the remaining studies did not say.

Patient characteristics

The studies varied in the ages of patients included: two studies also included children (Quinn 2004; Quinn 2006) and the Schladenhaufen (2008) study was in people over 65 years.

- Two studies had adults with a mean age of over 65 years (Cosgriff 2007; Reed 2007 (median); Schladenhaufen 2008)
- Three studies had a mean age around 65 years (del Rosso 2008; Elseber 2005; Quinn 2008; Sarasin 2003)
- 14 studies had a mean age below 65 years (Alboni 2001; Birnbaum 2008; Crane 2002; Colivicchi 2003; Graf 2008; Grossman 2007; Quinn 2004; Quinn 2005; Quinn 2006; Sarasin 2003b; Sheldon 2002; Sheldon 2006; Sun 2007 (median); Sun 2008; van Dijk 2008).

No studies were carried out solely in female patients or solely in male patients. The proportion of male patients ranged from 38% to 60%. Ethnicity was reported in three studies (Birnbaum 2008; Sun 2007; Sun 2008), in which 17% (Birnbaum 2008) to 77 or 78% (Sun 2007 and Sun 2008) of patients were white. The Birnbaum (2008) study included 39% Hispanic patients and 38% black patients, and so would not necessarily be representative for the guideline's UK population.

In addition, patients in the studies varied in their history of heart disease. Four studies did not state if there was heart disease (Alboni 2001; Quinn 2006; Quinn 2008; Schladenhaufen 2008); and the rest had some patients with heart disease. The proportions in the latter ranged from 8% to 35%.

Definition of TLoC

The studies described TLoC in various ways:

- Ten studies reported that the patients had had a TLoC, defined as 'sudden transient loss of consciousness with inability to maintain postural tone and spontaneous recovery' (Alboni 2001; Colivicchi 2003; Colivicchi 2003; Crane 2002; Elseber 2005; Graf 2008; Grossman 2007; Quinn 2006; Reed 2007; Sarasin 2003)

- Two studies stated that the patients had a loss of consciousness and loss of control of posture (Sheldon 2002; Sheldon 2006).
- One study stated that the patients had a self limited TLoC not due to head trauma (van Dijk 2008)
- One study stated that the patients had 'syncope' which excluded other causes of TLoC (del Rosso 2008)
- Seven studies included patients with syncope or near syncope (Birnbaum 2008; Quinn 2004; Quinn 2005; Quinn 2008; Schladenhaufen 2008; Sun 2007; Sun 2008)

Type of TLoC

The two Sheldon studies included patients with an established cause of TLoC or unexplained cause, but excluded patients with more than one plausible cause. The analyses of both these studies excluded some patient groups:

- Sheldon (2002) excluded patients with epileptic seizures that were not supported by EEG
- Sheldon (2006 restricted the included patients to those with an apparent absence of structural heart disease and did not include in the analysis, patients with no apparent cause of syncope who did not have a positive tilt test.
- Both stated that they excluded people with 'pseudoseizures' (psychogenic non-epileptic attacks)

Therefore, these studies had a case control design, which is likely to give increased risk of bias.

The majority of studies included unselected patients presenting to the emergency department. However, the Reed (2007) study reported that the distribution of risk groups was skewed towards the more serious end, which may have meant possible exclusion of younger patients with vasovagal syncope. The Crane (2002) study reported 33% of the patients were on cardioactive or psychotropic drugs. The Sarasin (2003) study included patients who had no clear suspicion of the cause of syncope from initial tests

(history, physical examination, blood pressure measurements, 12-lead ECG). Further details are given in Appendix D1.

Many of the studies reported that patients with epileptic seizures were excluded:

- One excluded patients with epileptic seizures not diagnosed by EEG (Sheldon 2002)
- Three excluded patients with a known seizure disorder (Colivicchi 2003; Crane 2002 (also those with focal neurological signs); Sheldon 2006)
- One excluded patients with a history of seizure with a prolonged post-ictal phase (Reed 2007)
- Seven excluded patients with a definite seizure (Birnbaum 2008; Cosgriff 2007; Quinn 2004; Quinn 2005; Quinn 2006; Quinn 2008; Sarasin 2003)
- Five excluded patients with seizures or 'typical seizure presentations' (del Rosso 2008; Elseber 2005; Graf 2008; Grossman 2007; Schladenhaufen 2008)
- Two excluded patients who had a witnessed seizure (Sun 2007; Sun 2008)
- One excluded patients from the analysis if they had a neurological or psychiatric cause (Alboni 2001)
- Two included patients with epileptic seizures
  - about 2% were diagnosed with epilepsy in van Dijk (2008) and 4% in Crane (2002)
  - the Sarasin (2003) study reported 9% and 13% patients had seizures or psychiatric diagnoses in the validation and derivation cohorts respectively

The studies also varied in whether they excluded patients with psychogenic non-epileptic seizures:

- Two studies excluded patients with PNES (Sheldon 2002; Sheldon 2006); and del Rosso (2008) reported that patients with non-syncopal causes of TLoC were excluded
- One study reported that 2% patients had a 'psychiatric diagnosis' (Crane 2002)

- One study had 17% patients with PNES (Graf 2008) and one had 3% (van Dijk 2008)

Previous episodes of TLoC

One study (Grossman 2007) reported that all patients had had at least one previous episode of TLoC; six studies reported that some patients had recurrent TLoC (Alboni 2001; Colivicchi 2003; del Rosso 2008; Elseber 2005; Sarasin 2003; van Dijk 2008), with the Elseber (2005) study stating that 19% had at least two episodes in the previous month; and the rest did not say if the TLoC was recurrent.

3.3.3.3 Index tests and reference standards

A range of index tests was investigated, ranging from aspects of patient history (predictors) to diagnostic algorithms.

For the patient history items, some of the studies take the form of case control studies, in which 'cases' are one type of TLoC and 'controls' are another (as defined by the reference standard), and the study determined if a particular sign or symptom is predictive of one type of TLoC rather than the other.

For each index test or set of tests, we have described the reference standard used with that test.

A) Patient history, physical examination, tests and decision rules, for diagnosis

A1. Patient history for diagnosis: epileptic seizures versus syncope (Sheldon 2002)

Population – selected (patients were excluded if they had epileptic seizures not diagnosed by EEG, and if they had PNES)

Index test

Patient characteristics (e.g. age)

- Medical history (e.g. coronary heart disease)

  - TLoC history
  - Predisposing / precipitating factors (e.g. hot/warm place; stress)
  - Prodromal symptoms before TLoC (e.g. hallucinations, nausea)
  - Signs and symptoms during TLoC (e.g. tongue biting)
  - Prodromal symptoms after TLoC
- Univariate and multivariate analyses carried out
- Case control design (patients included if they had a diagnosis according to preset criteria and if there was no reasonable diagnostic confusion; they were excluded if they had more than one plausible cause of syncope)
- Reference standard
  - Diagnosis following secondary tests
    - ◊ Seizures were diagnosed on the basis of a suggestive EEG and causes of syncope were determined using a positive tilt test for vasovagal and orthostatic hypotension; ECG/electrophysiology for arrhythmias/heart block (and the diagnosis also included palpitations pre-syncope)

A2. Patient history initial evaluation decision rules for diagnosis of epilepsy (Sheldon 2002)

- Population – selected
- Index test
  - Initial evaluation decision rule based on symptoms alone, with positive and negative scoring items
  - Rule consists of items that are significant predictors in a multivariate analysis (which included all items of patient history significant at the $p<0.05$ level)
  - Scores are assigned according to the relative magnitude of the regression coefficients
  - **Rule 1:** in the absence of knowledge of the numbers and historic duration of TLoC and lightheaded spells
    - ◊ Score +2 for: waking with a cut tongue

    - ◊ +1 for: abnormal behaviour noted (one or more of: witnessed amnesia for abnormal behaviour, witnessed unresponsiveness, unusual posturing or limb jerking)
    - ◊ +1 for: TLoC with emotional stress
    - ◊ +1 for: postictal confusion
    - ◊ +1 for: head turning to one side during TLoC
    - ◊ +1 for: prodromal déjà vu or jamais vu
    - ◊ score -2 for : any presyncope
    - ◊ -2 for: TLoC with prolonged standing or sitting
    - ◊ -2 for: diaphoresis (sweating) before TLoC
    - ◊ Patients are classified as having a seizure if the total points score is 1 or more
  - **Rule 2**: with knowledge of the number of TLoC episodes and length of the history of TLoC and lightheaded spells
    - ◊ Score +2 for: head turning to one side during TLoC
    - ◊ +1 for: more than 30 episodes of TLoC
    - ◊ +1 for: unresponsiveness during TLoC
    - ◊ -1 for: diaphoresis (sweating) before TLoC
    - ◊ -2 for: any presyncope
    - ◊ -3 for: loss of consciousness with prolonged standing or sitting
    - ◊ Patients are classified as having a seizure if the total points score is 0 or more.
- Case control design (patients included if they had a diagnosis according to preset criteria and if there was no reasonable diagnostic confusion; they were excluded if they had more than one plausible cause of syncope)
- Reference standard
  - Diagnosis following secondary tests (see (1) above)

A3. Patient history for diagnosis of neurally mediated versus other types of syncope (Alboni 2001; Graf 2008; Sheldon 2006)

Some studies reported the different types of syncope separately, but we decided it was more pragmatic to report the patient history predictors for a

particular type of syncope, versus not having that type of syncope, rather than having a head-to-head comparison of selected groups, although we note that this selection was done in the Sheldon (2006) study.

- Population varied: all the studies had selected patients (see above)
  - The Graf (2008) study combined the results for people diagnosed with vasovagal syncope (23%) and psychogenic non-epileptic seizures (17%)
  - The Sheldon (2006) study excluded patients with structural heart disease and did not analyse patients with syncope of unknown cause with a negative tilt test result.
- Index test
  - Patient characteristics (e.g. age)
  - Medical history (e.g. coronary heart disease)
  - TLoC history
  - Predisposing / precipitating factors (e.g. hot/warm place; stress)
  - Prodromal symptoms before TLoC (e.g. hallucinations, nausea)
  - Signs and symptoms during TLoC (e.g. tongue biting)
  - Duration of TLoC
  - Recovery after TLoC
  - Prodromal symptoms after TLoC
- Univariate and multivariate analyses carried out
- Study design varied:
  - Case control design
    - ◊ Vasovagal syncope (tilt positive) versus 'Secondary causes' (84% cardiac). Patients were included if they had an apparent absence of structural heart disease, and they had a positive tilt test (vasovagal syncope) or they had another known diagnosis of syncope; patients with more than one plausible cause of TLoC were excluded from the study and patients with test negative unknown syncope were excluded from the main analysis (Sheldon 2006)
  - Cross-sectional studies
    - ◊ Neurally mediated (NM) syncope versus non-NM syncope in patients referred to a syncope unit (Alboni 2001)

- ◊ Vasovagal syncope plus psychogenic non-epileptic seizures (PNES) versus other syncope in patients referred to a syncope clinic for unexplained syncope (Graf 2008)

- Reference standard
  - Diagnosis following secondary tests
    - ◊ Initial ECG plus ECG monitoring or 24h Holter or during electrophysiological study (del Rosso 2008)
    - ◊ Initial evaluation plus other tests (unspecified) (Alboni 2001)
    - ◊ Positive tilt test for vasovagal and orthostatic hypotension; ECG/electrophysiology for arrhythmias/heart block (diagnosis also included palpitations pre-syncope); EEG (Sheldon 2006)
    - ◊ 12-lead ECG, positive tilt test, supine and upright CSM, continuous blood pressure measurement, adenosine triphosphate and dinitrate isosorbide tests, hyperventilation test, psychiatrist evaluation, stress test, echocardiography, coronary angiography, electrophysiology (Graf 2008)

A4. Patient history for diagnosis of cardiac syncope (Alboni 2001; del Rosso 2008; Graf 2008; Sarasin 2003)

- Population varied
  - Three studies were in selected patients: Alboni (2001) – referrals to syncope unit; Graf (2008) – referred for unexplained syncope; Sarasin (2003) – patients with a definite cause of syncope were excluded. Del Rosso (2008) was in unselected patients
  - The Graf (2008) and Sarasin (2003) studies recorded results for cardiac *arrhythmic* syncope only
- Index test
  - Patient characteristics (e.g. age)
  - Medical history (e.g. coronary heart disease)
  - TLoC history
  - ECG status
  - Predisposing / precipitating factors (e.g. hot/warm place; stress)

  - Prodromal symptoms before TLoC (e.g. hallucinations, nausea)
  - Signs and symptoms during TLoC (e.g. tongue biting)
  - Duration of TLoC
  - Recovery after TLoC
  - Prodromal symptoms after TLoC
- Univariate and multivariate analyses carried out
- Study design varied:
  - Cross-sectional studies
    - Unselected patients presenting to ED. Cardiac syncope versus 'other syncope' (77% neurally mediated; 12% orthostatic hypotension) (del Rosso 2008)
    - Cardiac syncope versus non-cardiac syncope in patients referred to a syncope unit (Alboni 2001)
    - Arrhythmic syncope versus non-arrhythmic syncope in patients referred to a syncope clinic for unexplained syncope (Graf 2008)
- Reference standard
  - Diagnosis following secondary tests
    - Initial ECG plus ECG monitoring or 24h Holter or during electrophysiological study (del Rosso 2008)
    - Initial evaluation plus other tests (unspecified) (Alboni 2001)
    - 12-lead ECG, positive tilt test, supine & upright CSM, continuous blood pressure measurement, adenosine triphosphate and dinitrate isosorbide tests, hyperventilation test, psychiatrist evaluation, stress test, echocardiography, coronary angiography, electrophysiology (Graf 2008)
    - Diagnostic tests performed and interpreted by cardiologists: echocardiography, ambulatory ECG (24h Holter or continuous-loop event recorder) and electrophysiological studies to detect arrhythmias in the presence of syncope or near syncope (Sarasin 2003)

A5. Patient history initial evaluation score for diagnosis of neurally mediated syncope (versus other types of syncope) (Alboni 2001; Graf 2008; Sheldon 2006)

- Population – all three studies had selected patients
  - The Sheldon (2006) study had selected patients (limited to those without structural heart disease)
  - The Graf (2008) study combined the results for people diagnosed with vasovagal syncope (23%) and psychogenic non-epileptic seizures (17%)
  - The Alboni (2001) study included patients referred to the syncope unit from the ED, inpatients and outpatients (Alboni 2001)
- Index test
  - Initial evaluation decision rules based on symptoms alone, with positive and negative scoring items
  - Rules consisted of items that were significant predictors in multivariate analyses
  - Rule 1 for prediction of vasovagal syncope - Sheldon (2006): in the absence of knowledge of the numbers and historic duration of syncope and pre-syncope
    - ◊ Scores are assigned according to the relative magnitude of the regression coefficients, and summed:
    - ◊ Score -5 points for: any one of: bifascicular block, asystole, supraventricular tachycardia, diabetes
    - ◊ -4 for: blue colour noted by bystander
    - ◊ -3 for: age at first syncope at least 35 years
    - ◊ -2 for: remembers something about the TLoC spell
    - ◊ +1 for: presyncope or syncope with prolonged standing or sitting
    - ◊ +2 for: sweating or a warm feeling before TLoC
    - ◊ +3 for: presyncope or syncope with pain or medical procedure
    - ◊ Patients are classified as having vasovagal syncope if the total points score is -2 or more

  - Rule 2 – Graf (2008) for prediction of vasovagal syncope plus PNES

    - ◊ Scores are assigned according to the relative magnitude of the regression coefficients, and summed
    - ◊ Age (term 'AgeCat'): score 1 for age 45 years and below, 2 for age over 45 and below 65 years and 3 for age over 65 years
    - ◊ Number of prodromes ('ProdCat'): score 0 for 1 or 0 symptoms, and score 1 for 2 or more symptoms
    - ◊ ECG P-wave duration ('P-waveCat'): score 0 for duration below 120 ms and 1 for duration 120 ms and above or non-sinus rhythm
    - ◊ Apply formula: 2 x ProdCat – P-waveCat – AgeCat + 2
    - ◊ If total score is 0 or above, the patient is classified as having vasovagal syncope or PNES
- Study design varied
    - Case control design: vasovagal syncope versus 'secondary causes' (84% cardiac). Patients were included if they had an apparent absence of structural heart disease, and they had a positive tilt test (vasovagal syncope) or the diagnosis was known or unknown; patients with more than one plausible cause of TLoC were excluded (Sheldon 2006)
    - Cross-sectional study: vasovagal syncope plus PNES versus other syncope in patients referred to a syncope clinic for unexplained syncope (Graf 2008)
- Reference standard
    - Diagnosis following secondary tests (as above)

A6. Patient history initial evaluation score for diagnosis of cardiac syncope or predictors of arrhythmias (Alboni 2001; del Rosso 2008; Elseber 2005; Graf 2008; Sarasin 2003)

- Population
    - Unselected for two studies (del Rosso 2008; Elseber 2005)
    - Selected in the other three studies: patients with unexplained syncope (Graf 2008) or partly unexplained cause after the initial stage (Sarasin 2003); referred to the syncope unit from the ED, inpatients and outpatients (Alboni 2001)

- Index test
  - Rule 1 (EGSYS): initial evaluation decision rule based on symptoms and history, with positive and negative scoring items for prediction of cardiac syncope (del Rosso 2008)
    - ◊ Rule consisted of items that were significant predictors in a multivariate analysis (which included all items of patient history significant in univariate analysis)
    - ◊ Scores were assigned according to the relative magnitude of the regression coefficients:
      - Palpitations preceding syncope (+4); heart disease or abnormal ECG (see Appendix D1) or both (+3); syncope during effort (+3); syncope while supine (+2)
      - Precipitating or predisposing factors or both (warm, crowded place; prolonged orthostasis; fear/pain/emotion) (-1); Autonomic prodromes (nausea and/or vomiting) (-1)
      - in a referral centre, a cut-off point of 4 is used for diagnosis

  - Rule 2 (ACEP): initial evaluation decision rule based on ACEP guidelines for a cardiac cause of syncope (Elseber 2005; retrospective)
    - ◊ High risk consisted of any one of the following: history of congestive heart failure or history of ventricular arrhythmias; TLoC with chest pain or other symptoms of acute coronary syndrome; physical signs of CCF or significant valve disease; abnormal ECG (see Appendix D1)
    - ◊ Moderate risk consisted of any one of: age over 60 years; history of coronary artery disease or congenital heart disease; family history of sudden death; exertional syncope without an obvious benign cause
    - ◊ A cardiac cause of syncope was equated with the need to admit to hospital

  - Rule 3 - Graf (2008) for prediction of arrhythmic syncope
    - ◊ Scores are assigned according to the relative magnitude of the regression coefficients, and summed

  - Age (term 'AgeCat'): score 1 for age 45 years and below, 2 for age over 45 and below 65 years and 3 for age over 65 years
  - Number of prodromes ('ProdCat'): score 0 for 1 or 0 symptoms, and score 1 for 2 or more symptoms
  - Apply formula: AgeCat - ProdCat - 2
  - If total score is 0 or above, the patient is classified as having arrhythmic cause of syncope

  - Rule 4 – Sarasin (2003) for prediction of arrhythmic syncope
    - ◊ Risk score based on multivariate analysis, scored as one point for each of:
    - ◊ Age 65 years and older
    - ◊ History of congestive heart failure
    - ◊ Abnormal ECG (conduction disorder; old myocardial infarction; rhythm abnormalities – see Appendix D1 for details)
- Reference standard
  - Diagnosis following secondary tests (including ECG) - see above
  - Elseber (2005): cardiac tests including initial ECG, plus Holter monitoring or event recording or electrophysiological testing, or cardiac catheterisation or echocardiography

A7. Full initial stage evaluation for diagnosis of particular types of syncope: cardiac (arrhythmic and structural), orthostatic hypotension, reflex; and neurological and psychiatric diagnoses (van Dijk 2008)

- Population - unselected
- Index test
  - ESC guidelines based initial evaluation
    - ◊ Based on history, physical examination, ECG (van Dijk 2008)
    - ◊ Two sets of criteria:
      - Certain diagnosis - see Appendix D1
      - Suspected diagnosis (Highly likely) – see Appendix D1

- Reference standard
  - Follow up at 2 years plus further tests plus expert review leading to final diagnoses

B) Patient history, physical examination, tests, decision rules, for predicting a serious adverse event

B1. Patient history for a serious event: death within 12 months (Colivicchi 2003)

- Population – unselected
- Index test
  - Patient characteristics (e.g. age)
  - Medical history (e.g. hypertension)
  - TLoC history
  - Prodromal symptoms and signs
  - Signs and symptoms after TLoC
- Univariate and multivariate analyses carried out
- Reference standard
  - Follow up

B2. Patient history for a serious event: death, MI, arrhythmia, PE, stroke, subarachnoid haemorrhage, significant haemorrhage/anaemia needing transfusion; procedural intervention to treat syncope cause; any condition likely to cause a return to the ED or which did cause a return to the ED; hospitalisation for related event (Birnbaum 2008; Grossman 2007; Quinn 2004; Sun 2007; Reed 2007)

- Populations – unselected
- Index test
  - Patient characteristics (e.g. age)
  - Medical history (e.g. coronary artery disease)
  - Family history (e.g. of sudden death)
  - TLoC history

  - Medication use
  - Predisposing / precipitating factors (e.g. postural change)
  - Prodromal symptoms before TLoC (e.g. hallucinations, nausea)
- Univariate analyses carried out
- Reference standard
  - Follow up
    - ◊ At 7 days (Birnbaum 2008; Sun 2007; Quinn 2004)
    - ◊ At 30 days (Grossman 2007)
    - ◊ At 3 months (Reed 2007)
- Outcome/adverse events (see above)

B3. Tests and laboratory findings for a serious event: death within 12 months (Colivicchi 2003)

- Population – unselected
- Index test
  - Abnormal ECG (see Appendix D1)
- Univariate and multivariate analyses carried out
- Reference standard
  - Follow up

B4. Tests and laboratory findings for a serious event: death, MI, arrhythmia, PE, stroke, subarachnoid haemorrhage, significant haemorrhage/anaemia needing transfusion; procedural intervention to treat syncope cause; any condition likely to cause a return to the ED or which did cause a return to the ED; hospitalisation for related event (Birnbaum 2008; Grossman 2007; Quinn 2004; Sun 2007; Reed 2007)

- Population – unselected
- Index test
  - Physical examination e.g. blood pressure
  - Abnormal ECG

  - Laboratory tests (e.g. haematocrit)
- Univariate analyses carried out
- Reference standard
  - Follow up
    - ◊ At 7 days (Birnbaum 2008; Sun 2007; Quinn 2004)
    - ◊ At 30 days (Grossman 2007)
    - ◊ At 3 months (Reed 2007)
- Outcome/adverse events (see above)

C) Risk stratification approaches

C1. Decision rules for prediction of a serious event: death (Colivicchi 2003; Crane 2002; del Rosso 2008; Quinn 2008)

- Population – unselected, although Quinn (2008) was carried out in older people
- Index test
  - **OESIL** (Osservatorio Epidemiologico sulla Sincope nel Lazio) score (Colivicchi 2003)
    - ◊ Score one point for: Age over 65 years; Clinical history of cardiovascular disease; Syncope without prodromal symptoms; Abnormal ECG (see Appendix D1 for details)
  - **EGSYS** (Evaluation of Guidelines in SYncope Study) (del Rosso 2008)
    - ◊ Scores were assigned according to the relative magnitude of the regression coefficients
    - ◊ Palpitation preceding syncope (+4); heart disease or abnormal ECG (see Appendix D1) or both (+3); syncope during effort (+3); syncope while supine (+2)
    - ◊ Precipitating or predisposing factors or both (warm, crowded place; prolonged orthostasis; fear/pain/emotion) (-1); Autonomic prodromes (nausea and/or vomiting) (-1)
    - ◊ In the ED, EGSYS should be used as a screening tool, with a cut off point of 3 determining admission

- **San Francisco Syncope Rule** (Quinn 2008)
  - ◊ Any one of: history of congestive heart failure; abnormal ECG (see Appendix D1); haematocrit below 30%; patient complaint of shortness of breath; triage systolic blood pressure less than 90 mm Hg

- Initial evaluation based on **ACP guidelines** (Crane 2002)
  - ◊ Risk stratification into 'high risk', 'moderate risk' and 'low risk' of 1 year all-cause mortality
    - High risk defined as any one of: history of coronary artery disease or congestive heart failure (CCF) or ventricular tachycardia (VT); TLoC with symptoms of chest pain; physical signs of CCF, significant valve disease, stroke or focal neurology; abnormal ECG (see Appendix D1)
    - Moderate risk defined as any one of: sudden LoC with injury, rapid heart action or exertional syncope; frequent TLoC episodes; suspicion of coronary heart disease or arrhythmia; moderate to severe postural hypotension; age over 70 years
    - Low risk (other patients – safe to discharge)

- Reference standard
  - Follow up (for death)
    - ◊ At 6 months (SFSR, Quinn 2008)
    - ◊ At 12 months (Colivicchi 2003, OESIL score; Crane 2002, ACP guidelines; SFSR, Quinn 2008)
    - ◊ At 21–24 months (mean (SD) follow-up length of 614 (73) days) (del Rosso 2008; EGSYS score)
    - ◊ Identification of high (and moderate) risk groups
    - ◊ Equated with the need for admission to hospital / discharge

C2. Decision rules for a serious event: death, MI, arrhythmia, PE, stroke, subarachnoid haemorrhage, significant haemorrhage/anaemia needing transfusion; procedural intervention to treat syncope cause; any condition likely to cause a return to the ED or which did cause a return to the ED; hospitalisation for related event (Birnbaum 2008; Grossman 2007; Hing 2005; Quinn 2004; Quinn 2005; Quinn 2006; Reed 2007; Schladenhaufen 2008; Sun 2007)

- Population - unselected
- Index test
  - **OESIL** (Osservatorio Epidemiologico sulla Sincope nel Lazio) score (Hing 2005; Reed 2007)
    - ◊ Score one point for: Age over 65 years; Syncope without prodromal symptoms; Clinical history of cardiovascular disease; Abnormal ECG (see Appendix D1 for details)
    - ◊ Various cut-off scores tested
  - **San Francisco Syncope Rule** (Birnbaum 2008; Cosgriff 2007; Quinn 2005; Quinn 2006; Sun 2007; Reed 2007)
    - ◊ Any one of: history of congestive heart failure; abnormal ECG (see Appendix D1); haematocrit below 30%; patient complaint of shortness of breath; triage systolic blood pressure less than 90 mm Hg
  - **Boston Syncope Rule** (Grossman 2007)
    - ◊ ESC guideline + San Francisco Syncope Rule + expert advice
    - ◊ Any one of: signs/symptoms of acute coronary syndrome; worrying cardiac history; family history of sudden death; valvular heart disease; signs of conduction disease; volume depletion; persistent (more than 15min) abnormal vital signs; primary CNS event
- Reference standard
  - **OESIL** score
    - ◊ Follow up events (see Appendix D1) at 3 months (Reed 2007) and 3-6 months (Hing 2005)
    - ◊ Identification of high risk group; equated with the need for admission to hospital / discharge

- **San Francisco Syncope Rule**: follow up events (See Appendix D1)
  - ◊ 7 days: Birnbaum (2008); Cosgriff (2007); Quinn (2005); Sun (2007)
  - ◊ 30 days: Quinn (2006)
  - ◊ 3 months: Reed (2007)
  - ◊ Identification of high risk group; equated with the need for admission to hospital / discharge
- **Boston Syncope Rule**: follow up events (See Appendix D1)
  - ◊ 30 days and subsequent medical records (Grossman 2007)
  - ◊ Identification of high risk group; equated with the need for admission to hospital / discharge

3.3.3.4 Comparisons

One study (Reed 2007) compared two index tests in the same patients: the San Francisco Syncope Rule versus the OESIL score.

3.3.4 Methodological quality

The methodological quality was assessed using QUADAS criteria (Appendix D2).

The following studies were found to be at risk of bias on the following criteria:

- Spectrum bias (Alboni 2001; Birnbaum 2008; Cosgriff 2007; del Rosso 2008; Graf 2008; Hing 2005; Quinn 2004; Quinn 2006; Reed 2007; Sarasin 2003; Schladenhaufen 2008; Sheldon 2002; Sheldon 2006; Sun 2008; van Dijk 2008)
  - The Sheldon (2002) study excluded patients with epilepsy not diagnosed by EEG and patients with NPES: the GDG considered this to be higher risk of bias
  - The Sheldon (2006) study was restricted to those without structural heart disease and excluded from the analysis patients with syncope of unknown cause who had negative tilt test results.
  - The Reed (2007) study reported that 62% of the eligible patients were missed and that these patients were significantly younger; the study

group was skewed towards more serious risk; GDG considered this to be unacceptable
  - The Hing (2005) study included patients only if the investigators were present; this was 22% of the possible eligible patients, but may not have consitituted spectrum bias
  - The Alboni (2001) and Graf (2008) studies included patients referred to the syncope unit from the ED, inpatients and outpatients; it was unclear why patients were referred in the Alboni (2001) study
  - The Graf (2008) and Sarasin (2003) studies were restricted to patients with unexplained syncope following initial tests
  - The Birnbaum (2008) study included large proportion of non-white people, which may not have been representative of a UK population
- Three studies were retrospective and therefore considered at risk of bias (Crane 2002; Elseber 2005; Schladenhaufen 2008)
- The reference standard in the Sheldon (2002) study was considered to be inadequate because patients with epilepsy were diagnosed using EEG only
- The reference standard in Hing (2005) was predominantly from medical records or patient accounts and not provided by a health care professional
- Verification bias: in some studies the reference standard was follow up and there were missing data as follows:
  - The Cosgriff (2007) study had more than 20% missing and the GDG considered this level to be unacceptable
  - The del Rosso (2008) study had 24% missing data, 9% of whom had died.
  - Four studies had less than 20% missing data: Crane (2002); Hing (2005); Quinn (2006); Sun (2007)
- Disease progression bias: none of the studies were considered by the GDG to have disease progression bias (too long between index and reference tests), even though the time duration was 1 to 2 years in some studies (Colivicchi 2003; van Dijk 2008)
- Partial verification bias:

  - In four studies the reference standard tests varied, with some being carried out only where a particular condition/cause was suspected. (Alboni 2001; del Rosso 2008; Graf 2008; van Dijk 2008)
  - In one of these studies, it was reported that if the initial evaluation gave a definite diagnosis, further tests were interrupted, but no numbers were given (Alboni 2001)
  - In one of the studies, if the initial evaluation gave a definite diagnosis, these patients received follow up and expert review as the reference standard (24% patients), otherwise further tests were added to follow up and expert review for the reference standard (van Dijk 2008)
- Incorporation bias: four studies included the index test as part of the reference standard (Alboni 2001; del Rosso 2008; Elseber 2005; Graf 2008)
  - In three of these, this referred only to the 12-lead ECG results, and in the other study (Alboni 2001) the reference standard also included the patient history and initial examination
- Review bias (blinding)
  - In six studies, it was unclear if the index test assessors were blinded to the reference standard results (Cosgriff 2007; Elseber 2005; Graf 2008; Sarasin 2003 (decision rule); Sheldon 2002; Sheldon 2006)
  - In two of these studies (Sheldon 2002, 2006), patients were included if they had an established diagnosis, which suggests the reference standard results were known before the index test - although this was said to be a prospective study
  - In three studies, the reference test assessors were not blinded because the index test was part of the reference standard (Alboni 2001; del Rosso 2008; Graf 2008)
  - In one study, the index test and reference standard were conducted by the same person (Cosgriff 2007)
  - In five studies it was unclear who conducted the follow up investigations for the reference standard (Colivicchi 2003; Elseber 2005; Quinn 2004; Quinn 2005; Reed 2007)

- In one study it was unclear if the reference standard assessors were blinded to the index test, but this was unimportant because the reference standard was death (Crane 2002)

Overall, the GDG considered that 23 tests in 12 studies were potentially or at risk of bias (Alboni 2001; Cosgriff 2007; Crane 2002; del Rosso 2008; Elseber 2005; Graf 2008; Hing 2005; Reed 2007; Sarasin 2003; Schladenhaufen 2008; Sheldon 2002; Sheldon 2006). The two Sheldon case control studies were probably most at risk. These studies were considered in sensitivity analyses.

3.3.5 Results

3.3.5.1 Patient history, physical examination, tests and decision rules for diagnosis

A1. Patient history, physical examination and laboratory/ECG tests for diagnosis: epileptic seizures versus syncope

One low quality study reported the value of patient history in distinguishing between epileptic seizures and syncope in selected patients. Patients were included if they had EEG diagnosed epilepsy and patients with PNES were excluded. Detailed results are reported in Appendix D3.

Firstly, univariate likelihood ratios are reported for each sign and symptom – this is the likelihood that the sign or symptom predicts seizures rather than syncope. A likelihood ratio (LR) of more than 5 or less than 0.2 is considered a good test and a LR of more than 10 or less than 0.1 is considered a strong test.

Secondly, multivariate predictors obtained using regression analysis are given as odds ratios: they represent the odds that having a particular sign or symptom will predict epileptic seizures compared with the odds of not having that sign or symptom, independent of all the other predictors.

Table 1: Univariate predictors for epilepsy versus syncope		
Strength of test	**Predictors for epilepsy**	**Predictors for syncope**
Strong predictors LR > 10; LR < 0.1	• Unusual posturing during TLoC • Cut tongue during TLoC • Head turning during TLoC	• History – coronary heart disease • TLoC with prolonged sitting or standing • Dypsnoea pre-TLoC
Good predictors 5<LR<10 or 0.2>LR>0.1	• Younger age • Limb jerking noted by others during TLoC • Blue colour observed by bystander • Bedwetting during TLoC • Long history of TLoC • Large number of previous episodes	• Presyncope with prolonged sitting or standing • Diaphoresis pre-TLoC • Palpitations pre-TLoC • Chest pain pre-TLoC • Remembered loss of consciousness
Weak predictors: statistically significant but LR < 5 or > 0.2	• TLoC associated with stress • Prodromal preoccupation • Prodromal déjà vu • Prodromal hallucinations • Prodromal trembling • Observed unresponsiveness during TLoC • Abnormal behaviour during TLoC (any of limb jerking, unusual posturing, observed unresponsiveness) • Cannot remember behaviour • Mood changes post TLoC • Post ictal confusion • Post ictal headaches • Muscle pain post TLoC	• Hypertension • Self-reported high blood pressure • Pre-syncope with hot/warm place • Pre-syncope with a needle • Pre-syncope after effort • Any pre-syncope • Prodromal vertigo • Warmth pre-TLoC • Nausea pre-TLoC • Chest pain during TLoC

Signs and symptoms that are considered to be good and strong univariate predictors are shown in Table 1 (together with weak predictors) and multivariate predictors for and against seizures are shown in Table 2.

Table 2: Multivariate predictors for and against epilepsy

Predictors for epilepsy	Predictors against epilepsy (i.e. *for* syncope)
• Waking with a cut tongue • Abnormal behaviour noted (one or more of: witnessed amnesia for abnormal behaviour, witnessed unresponsiveness, unusual posturing, limb jerking) • Loss of consciousness with emotional stress • Post-ictal confusion • Head turning to one side during TLoC • Prodromal déjà vu or jamais vu	• Any presyncope • TLoC with prolonged standing or sitting • Diaphoresis before TLoC

The GDG also considered two other studies: one low quality study (Benbadis 1995) investigated the diagnostic test accuracy of tongue biting in a highly selected population (seizure patients from an epilepsy monitoring unit, who had bilateral motor phenomena – tonic and/or clonic – and syncope patients of known cause, examined retrospectively, from a syncope clinic). In this population, the final diagnoses of the patients were made using secondary tests: EEG video monitoring; 12-lead ECG and Holter monitoring, tilt test and autonomic reflex examination. Final diagnoses were: 31% epileptic seizures; 27% pseudoseizures and 42% syncope. The sensitivity of tongue biting for diagnosis of epilepsy was 24% and the specificity 99%.

The second study (Hoefnagels 1991) investigated the diagnostic test accuracy of EEG in a group of patients referred to the neurological department, the reference standard was initial signs and symptoms – it was not stated what was the basis of deciding which signs and symptoms were predictive of

seizures, and they were not separately compared with EEG diagnoses. This list is given here for reference:

- If an eyewitness observed 'more than a few' movements during TLoC and identified clonic movements from a range imitated by the interviewer
- If an eyewitness observed automatisms, such as chewing or lip smacking, during TLoC
- If the patient reported an unequivocal aura, such as a strange smell pre-TLoC
- If the patient felt confused immediately after TLoC (inability to recognize familiar persons or environment)
- Tongue biting

A2. Initial evaluation decision rules for diagnosis of epilpsy

One low quality study reported two decision rules for diagnosing epilepsy (Sheldon 2002). Patients were included if they had EEG diagnosed epilepsy and patients with PNES were excluded. An additional moderate quality study (van Dijk 2008) also reported the diagnostic test accuracy of an initial assessment based on the European Society for Cardiology (ESC) guidelines in 503 patients (van Dijk 2008; see Appendix D1). Results were reported for people predicted to be 'certain' or 'highly likely' to have a diagnosis of epilepsy.

For Sheldon (2002), the predictive ability of a decision rule, derived from the multivariate analysis is considered. This reports, as ROC curves, pairs of sensitivity and specificity at given point scores, for each of two rules, one with knowledge of previous TLoC and the other without that knowledge.

The ROC curve is shown in Figure 1 for two rules predicting seizures, with different score thresholds; the sensitivity-specificity pairs were extracted from the authors' graph.

The authors recommended a cut-off point of ≥ 1 for the symptoms only rule, which gave a sensitivity of 94% and a specificity of 96.3% in the development cohort and 94% for both sensitivity and specificity in the validation cohort.

For the rule of symptoms plus knowledge about the number of episodes and the length of the history of TLoC, the authors recommended a cut-off point of ≥ 0, which gave a sensitivity of 96% and a specificity of 84% in the development cohort and 92% and 83% in the validation cohort.

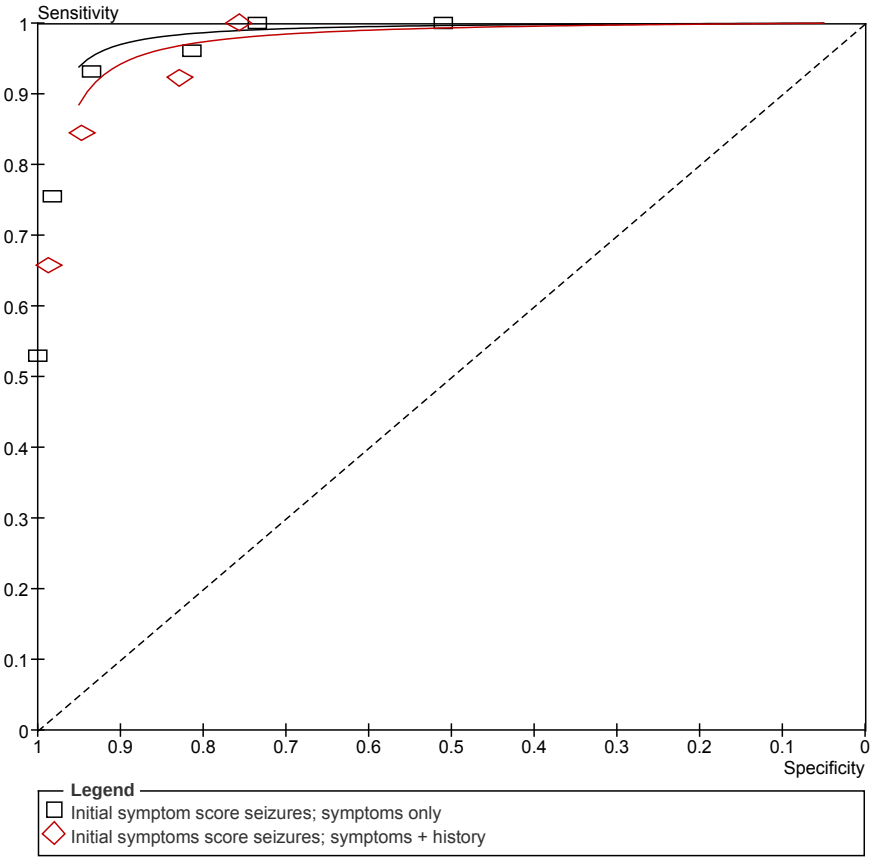
The diagnostic test accuracy results for the initial assessment rules in Sheldon (2002) and van Dijk (2008) are shown in Appendix D3; a summary is given in Table 3.

Table 3: Diagnostic test accuracy results for the prediction of epilepsy

Study	Sens (%)	Spec (%)	LR+	LR-	Diag Yield (%)
Sheldon 2002 Initial symptoms decision rule Rule 1 symptoms only Test operator: investigator	94.0	94.0	16	0.06	50
Sheldon 2002 Initial symptoms decision rule Rule 2 symptoms + TLoC history Test operator: investigator	92.2	82.5	5.3	0.09	57
van Dijk 2008 Initial evaluation based on ESC guidelines; certain only Test operator: attending physician	100.0	99.8	NA	0.00	1
van Dijk 2008 Initial evaluation based on ESC guidelines; Highly likely Test operator: attending physician	66.7	99.8	NA	0.33	1
van Dijk 2008 Initial evaluation based on ESC guidelines; certain and highly likely Test operator: attending physician	72.7	99.6	NA	0.27	2

We note that the Sheldon (2002) study is likely to overestimate the sensitivity and specificity because it was a case control study. The diagnostic yield is very low in the van Dijk (2008) study.

Figure 3.1: ROC curve for initial symptom score predicting epileptic seizures



A3. Patient history, physical examination and laboratory/ECG tests for diagnosis of cause: comparison of different types of syncope: neurally mediated syncope versus other types of syncope (Alboni 2001; Graf 2008; Sheldon 2006)

Three low quality studies reported the value of patient history in distinguishing between neurally mediated syncope and other types of syncope in selected patients. The Graf (2008) study combined the results for people diagnosed with vasovagal syncope (23%) and psychogenic non-epileptic seizures (17%). The Sheldon (2006) study was concerned with vasovagal syncope in people without structural heart disease; patients with syncope of unknown cause who

had negative tilt test results were not included in the analyses. All of the studies excluded patients with seizures to some degree: Sheldon (2006) excluded those with a known epilepsy; Graf (2008) excluded those with seizures and Alboni (2001) excluded those with a neurological or psychiatric cause. Detailed results are reported in Appendix D3.

Signs and symptoms that are considered to be good and strong univariate predictors are shown in Table 4. Where there was disagreement between studies, the predictor was not included. The symptoms identified by the Sheldon (2006) study are indicated – these are for patients who do not have structural heart disease or unexplained syncope. The symptoms identified by the Graf study are also indicated – these are predictors for vasovagal syncope or PNES.

Multivariate predictors for and against NM syncope are shown in Table 5 The Alboni (2001) study carried out two multivariate analyses separating the patients into those with and without structural heart disease after initial evaluation (history, physical examination or ECG abnormalities or a combination of these).

1

Table 4: Univariate predictors for NM syncope versus other causes of syncope

Strength of test	Predictors for NM syncope	Predictors against NM syncope
Strong predictors LR > 10; LR < 0.1	• Mood changes or preoccupation pre-TLoC (Sheldon)	• Any 1 of bifascicular block, asystole, SVT, diabetes (Sheldon)
Good predictors 5<LR<10 or 0.2>LR>0.1	• Age below 35 years (low age predicted by all 3 studies) • Longer history of TLoC (Sheldon) • With pain or medical procedure (Sheldon) • Anxiety pre-TLoC (Graf) • Headaches pre TLoC (2 studies (Sheldon and Graf) • Number of prodromes (Graf)	• Syncope during effort • Atrial fibrillation or flutter (Sheldon) • P-wave duration longer (Graf) • Cyanotic during syncope (Sheldon)
Weak predictors: statistically significant but LR < 5 or > 0.2	• History of pre-syncope • More previous episodes of TLoC (Sheldon) • Prolonged standing (2 studies) • Warm place (Sheldon) • With stress (Sheldon) • After effort (2 studies) • Duration of prodromes more than 10 seconds • Weakness pre-TLoC (Graf) • Feeling cold pre-TLoC • Numbness or tingling pre-TLoC (Sheldon) • Pallor (witness account) pre-TLoC • On way to or from the toilet (Sheldon) • Unresponsive during TLoC (Sheldon) • White or pale colour during TLoC noted by bystander (Sheldon) • Cannot remember behaviour during TLoC (Sheldon) • Sweating after TLoC • Mood changes post-TLoC (Sheldon) • Numbness or tingling post-TLoC (Sheldon) • Nausea post-TLoC	• Male gender (2 studies) • Suspected heart disease • Valvular heart disease (Sheldon) • Hypertension (Sheldon) • Syncope while supine • Absence of prodromes (Graf) • Less than 5 seconds warning (Sheldon) • No memory about TLoC (Sheldon)

2

Table 5: Multivariate predictors for neurally mediated syncope for each study

Study	Predictors for NM syncope	Predictors against NM syncope
Alboni (2001) in patients with suspected or diagnosed heart disease	• Time between 1st and last TLoC > 4years • History of pre-syncope • Nausea post TLoC	
Alboni (2001) in patients without suspected or diagnosed heart disease	• Duration of prodromes > 10s	
Graf (2008) for vasovagal syncope plus PNES	• Number of prodromes > 1	• Age Category • P-wave ≥ 120 ms or non-sinus rhythm
Sheldon (2006) for vasovagal syncope in patients without structural heart disease and with known causes of syncope	• Pre-syncope or syncope with prolonged sitting or standing • Sweating or warm feeling pre-TLoC • Pre-syncope or syncope with pain or medical procedure	• Age at first TLoC ≥ 35 years • Any 1 of bifascicular block, asystole, SVT, diabetes • Blue colour noted by bystander • Remembers something about the TLoC

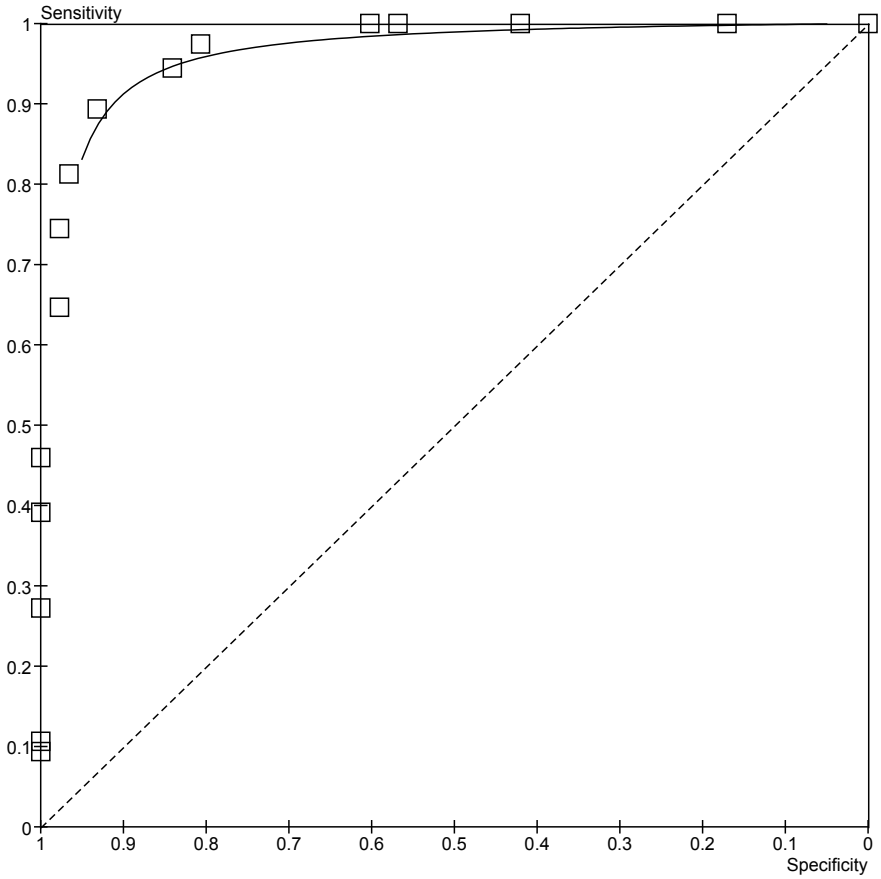
A5. Initial evaluation decision score for diagnosis of neurally mediated syncope

Two low quality studies evaluated a decision rule for the diagnosis of vasovagal syncope (Graf 2008; Sheldon 2006). Sheldon (2006) reported sensitivity-specificity pairs for different cut-off points in the development sample and Graf (2008) evaluated their rule in the derivation cohort and further tested it in 65 newly included patients. One additional, moderate

quality study evaluated an initial assessment scheme, based on the ESC guidelines in 503 patients (van Dijk 2008; see Appendix D1).

The ROC curve for the Sheldon (2006) rule is shown in Figure 2: the sensitivity-specificity pairs were extracted from the authors' graph. The authors recommended a cut-off point of > -2, which gave a sensitivity of 90% and a specificity of 93% in the development cohort. This was adjusted by modelling to represent an independent sample and gave values of 89.3% and 90.8% respectively. The authors also reported that the score alone was not usually sufficient for a diagnosis of vasovagal syncope, and state that, for such a diagnosis, the four risk factors of asystole, bifascicular block, SVT and diabetes usually need to be absent. We note that this study was carried out in a highly selected case control population and these results should be considered with caution.

Figure 3.2: ROC curve for diagnosis of vasovagal syncope in patients without structural heart disease



The Graf (2008) study reported a sensitivity of 85% and a specificity of 77% in the derivation cohort for diagnosis of vasovagal syncope and PNES, and gave values of 84% and 50%, respectively for the validation cohort.

The van Dijk (2008) study considered the predictive ability of their ESC-based initial assessment scheme for people predicted to be ‘certain’ or ‘highly likely’ to have a neurally mediated cause of syncope. The study reports the diagnostic test accuracy statistics for neurally mediated syncope, which includes vasovagal syncope and initial orthostatic hypotension and exercise-induced hypotension, but excludes orthostatic hypotension.

Full diagnostic test accuracy statistics are given in Appendix D3, with sensitivity, specificity and the likelihood ratios being summarised in Table 6 for each of these studies.

Table 6: Diagnostic test accuracy statistics for initial assessment rules for neurally mediated syncope

Study	Sens (%)	Spec (%)	LR+	LR-	Diag Yield (%)
Graf 2008c Initial symptoms decision rule VV/Psychogenic model; validation cohort. Test operator: attending physician	84.0	50.0	1.7	0.32	63
Sheldon 2006 Initial symptoms decision rule for vasovagal syncope; cut-off above -2. Test operator: investigator	89.4	90.9	9.8	0.12	67
van Dijk 2008 Initial evaluation based on ESC guidelines certain only Test operator: attending physician	97.0	99.5	NA	0.03	19
van Dijk 2008 Initial evaluation based on ESC guidelines. Highly likely only Test operator: attending physician	94.7	96.2	25	0.05	28
van Dijk 2008 Initial evaluation based on ESC guidelines certain and highly likely Test operator: attending physician	95.7	94.1	16	0.05	47

A6. Patient history, physical examination and laboratory/ECG tests for diagnosis of cause: comparison of different types of syncope: cardiac syncope versus other types of syncope (Alboni 2001; del Rosso 2008; Graf 2008)

Three low quality studies reported the value of patient history in distinguishing between cardiac and other causes of syncope. Two studies were in selected patients, with the Graf (2008) study being restricted to those with unexplained syncope and the Alboni (2001) study being in patients referred to a syncope unit. The del Rosso (2008) study was in unselected patients.

The Graf (2008) study was restricted to the diagnosis of arrhythmic syncope. Detailed results are reported in Appendix D3.

Signs and symptoms that are considered to be good and strong univariate predictors are shown in Table 7. Where there was disagreement between

studies, the predictor was not included. Multivariate predictors for and against cardiac syncope are shown in Table 8.

Table 7: Univariate predictors for cardiac syncope versus other causes of syncope

Strength of test	Predictors for cardiac syncope	Predictors against cardiac syncope
Strong predictors LR > 10; LR < 0.1	•	• Paresthesia (uncertainty)
Good predictors 5<LR<10 or 0.2>LR>0.1	• Age • Syncope while supine (borderline good, 2 studies homogeneous) • Syncope during effort (prodromal symptoms began)	• P-wave duration longer • Feeling cold pre-TLoC (uncertainty) • Anxiety pre-TLoC • Feeling cold post TLoC • Number of prodomes • Headache pre-TLoC (uncertainty)
Weak Predictors with LR not above 5 or below 0.2	• Male gender (small effect; 2 studies) • Suspected heart disease after initial assessment (2 studies) • Absence of prodromes (small effect; 2 studies) • Cardiovascular drugs •	• Diaphoresis pre-TLoC (3 studies) • Nausea or vomiting pre-TLoC (2 studies) • History of pre-syncope • During or up to 1 h after a meal • Pallor pre-TLoC
Predictors for which there is large disagreement amongst studies	• Blurred vision pre TLoC • Palpitations pre TLoC • Dyspnoea pre TLoC • Incontinence during TLoC • Light headedness/dizziness pre-TLoC	

1

Table 8: Multivariate predictors for cardiac syncope for each study

Study	Predictors for cardiac syncope	Predictors against cardiac syncope
Alboni (2001) all patients	• Suspected or certain heart disease	
Alboni (2001) in patients with suspected or diagnosed heart disease	• Time between 1st and last TLoC ≤ 4years • Supine position • Blurred vision pre-TLoC	
Alboni (2001) in patients without suspected or diagnosed heart disease	• No additional predictors	
Del Rosso (2008)	• Heart disease or abnormal ECG or both • Syncope during effort • Supine position • Palpitations pre TLoC	• Nausea or vomiting • Warm crowded place / prolonged orthostasis / fear-pain-emotion
Graf (2008) for arrhythmias	• Age Category	• Number of prodromes > 1
Sarasin (2003) arrhythmias	• Age ≥ 65 years • Abnormal ECG • History of congestive heart failure	

2

3 *A7.1. Decision rules for diagnosis of cardiac syncope (del Rosso 2008;*
4 *Elseber 2005; Graf 2008; Sarasin 2003; van Dijk 2008)*

5 Four low quality studies and one moderate quality study (van Dijk 2008)
6 evaluated a decision rule for cardiac syncope. Two studies were in selected
7 patients, with the Graf (2008) study being restricted to those with unexplained

syncope and the Sarasin (2003) study excluding patients with a definite cause of syncope. The del Rosso (2008), Elseber (2005), and van Dijk (2008) studies were in unselected patients; the Elseber (2005) study was a retrospective review of records.

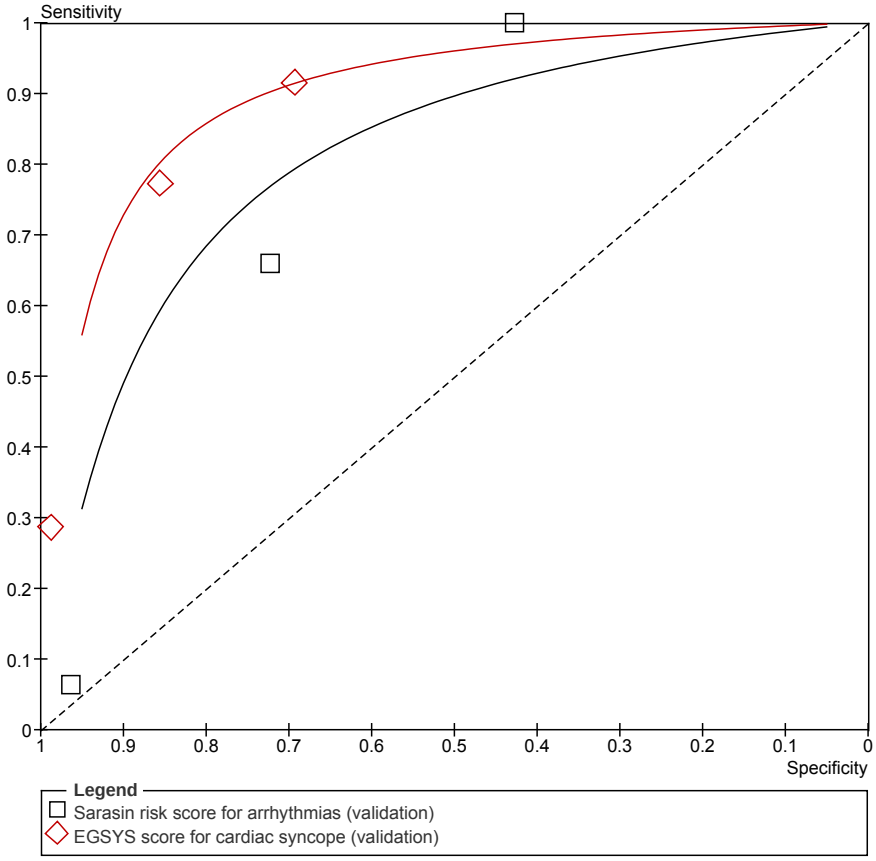
The Sarasin (2003) study was restricted to the diagnosis of arrhythmic syncope.

The Elseber (2005) study evaluated the American College of Emergency Physicians (ACEP) recommendations for admission, which was equated with a diagnosis of cardiac syncope. The van Dijk (2008) study evaluated the ESC guidelines in 503 patients (further details of both of these assessments are given in Appendix D1).

Del Rosso (2008) and Sarasin (2003) reported the percentage of patients having cardiac syncope and arrhythmias respectively for a given number of risk factors or given score, for both development and validation samples. Graf (2008) evaluated their rule in the derivation cohort and further tested it in 65 newly included patients, reporting an overall sensitivity and specificity. The Elseber (2005) study reported the overall sensitivity and specificity for the ACEP guidelines in their validation sample.

The ROC curves for the del Rosso (2008) EGSYS rule and the Sarasin (2003) scoring system are shown in Figure 3.3 for the validation cohorts. Sensitivity-specificity pairs for each cut off score were calculated from the raw data, comparing the total number of patients with cardiac syncope who had more than the cut-off score versus the total number with cardiac syncope below or with that score.

Figure 3.3: ROC curves for diagnostic rules for cardiac syncope



The EGSYS score appears to be a better diagnostic test than the Sarasin (2003) risk score.

The authors in the del Rosso (2008) study reported diagnostic test accuracy statistics for two cut-off points, ≥3 points and >4 points, these are summarised in Table 9:, along with values for the other studies. Full results are given in Appendix D3.

Table 9: Diagnostic test accuracy statistics for cardiac syncope

Study	Sens (%)	Spec (%)	LR+	LR-	Diag Yield (%)
Elseber 2005 Initial evaluation based on ACEP guidelines; ACEP level B Test operator: investigator	100.0	81.3	5.3	0.00	29
Elseber 2005 Initial evaluation based on ACEP guidelines; ACEP level B + C Test operator: investigator	100.0	33.0	1.5	0.00	71
Graf 2008b Initial symptoms decision rule Rhythmic model; validation cohort Test operator: attending physician	58.8	70.8	2	0.58	37
Sarasin 2003b Initial symptoms decision rule >0 risk factors; Validation study Test operator: research physician + investigator	93.8	41.6	1.6	0.15	65
Sarasin 2003b Initial symptoms decision rule >1 risk factor; Validation study Test operator: research physician + investigator	64.6	72.1	2.3	0.49	34
van Dijk 2008 Initial evaluation based on ESC guidelines; certain diagnosis only Test operator: attending physician	71.4	100.0	NA	0.29	1
van Dijk 2008 Initial evaluation based on ESC guidelines; highly likely diagnosis only Test operator: attending physician	73.9	98.5	51	0.26	5
van Dijk 2008 Initial evaluation based on ESC guidelines; certain and highly likely Test operator: attending physician	73.3	98.5	50	0.27	6
del Rosso 2008c EGSYS score >2; Test operator: attending physician + senior physicians (ECG)	91.4	69.2	3	0.12	39
del Rosso 2008c EGSYS score >4 Test operator: attending physician + senior physicians (ECG)	28.6	98.6	21	0.72	5

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A7.2. Decision rules for diagnosis of other types of syncope (van Dijk 2008)

The van Dijk (2008) study, which was of moderate quality, also investigated the ESC guidelines for the diagnosis of psychogenic pseudosyncope and orthostatic hypotension. The results are summarized in Table 10:, and reported in full in Appendix D3.

Table 10: Diagnostic test accuracy statistics for PNES and orthostatic hypotension

1. Psychogenic non epileptic seizures

Study	Sens (%)	Spec (%)	LR+	LR-	Diag Yield (%)
van Dijk 2008 Initial evaluation based on ESC guidelines; certain and highly likely Test operator: attending physician	85.7	100.0	NA	0.14	2
2. Orthostatic hypotension					
van Dijk 2008 Initial evaluation based on ESC guidelines; certain diagnosis only Test operator: attending physician	100.0	99.0	99	0.00	3
van Dijk 2008 Initial evaluation based on ESC guidelines; Highly likely only Test operator: attending physician	80.0	98.8	66	0.20	3
van Dijk 2008 Initial evaluation based on ESC guidelines; certain and highly likely Test operator: attending physician	88.9	97.7	39	0.11	5

3.3.5.2 Patient history, physical examination, tests and decision rules for risk stratification and prediction of adverse events

B1. Patient history for a serious event: death within 12 months (Colivicchi 2003)

One moderate quality study (Colivicchi 2003) in 270 patients investigated signs and symptoms, physical examination and laboratory tests and ECG for their ability to predict death within 12 months. These signs and symptoms are reported as the relative risk of death for the symptom present versus not present. The results are given in Appendix D3 and significant risk factors, univariate and multivariate are summarised in Table 11.

Table 11: multivariate and univariate risk factors for death in people who have had a TLoC

Multivariate risk factors for death at 12 months	Univariate risk factors for death at 12 months
• Age > 65 years • Cardiovascular disease in clinical history • Abnormal ECG findings • Syncope without prodromes (small effect)	• Age > 65 years • Cardiovascular disease in clinical history • Hypertension • Diabetes mellitus • Abnormal ECG • Absence of prodromes • Syncope-related traumatic injuries

C1. Decision rules for a serious event: death (Colivicchi 2003; Crane 2002; del Rosso 2008; Quinn 2008)

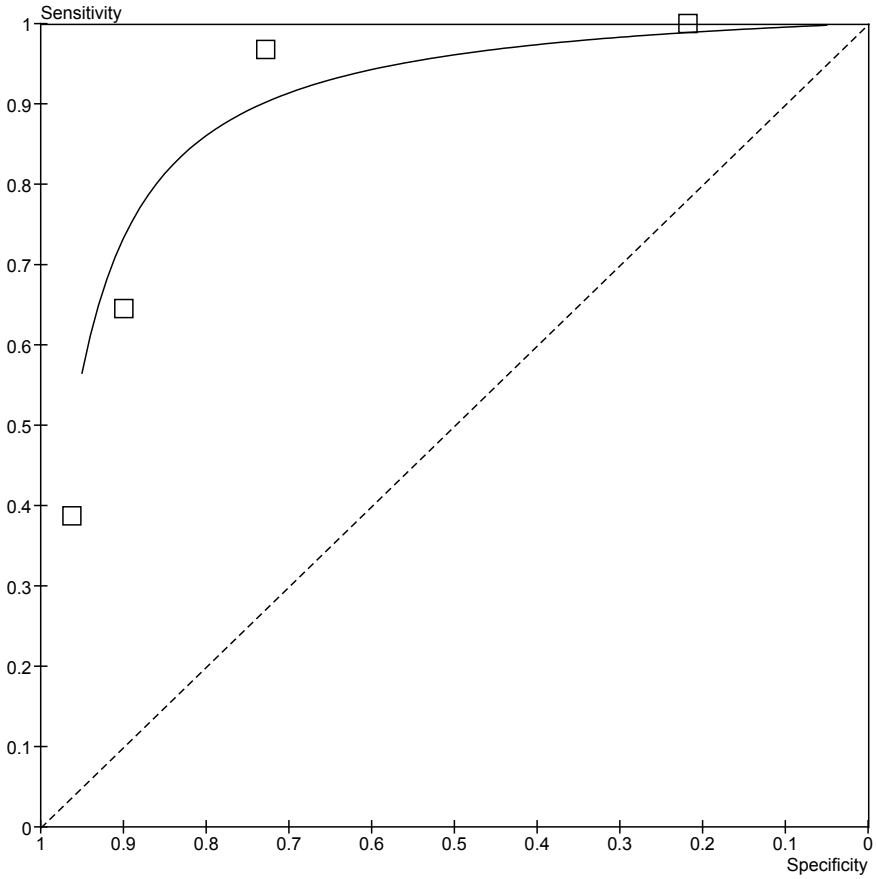
Two moderate quality studies (Colivicchi 2003; Quinn 2008) and two low quality studies (Crane 2002; retrospective; del Rosso 2008) examined different risk stratification rules for death. The follow up time was 12 months for all studies except del Rosso (2008), which followed the patients at 21-24 months. The Quinn (2008) study also had two physicians consider if the death

was related to TLoC, and results were reported for TLoC related and all-cause death at 6 months and 1 year.

Colivicchi (2003) reported the percentage of patients who died by a given number of risk factors or given score (OESIL score), for both development and validation samples; however there were insufficient data in the validation study and so the derivation cohort was used. The other studies evaluated the American College of Physicians (ACP) guidelines (Crane 2002), which defined 'high', 'medium' and 'low' risk groups (see Appendix D1); the San Francisco Syncope Rule (Quinn 2008); and the EGYS score (del Rosso 2008), each reporting an overall sensitivity and specificity.

The ROC curve for the Colivicchi (2003) OESIL scoring system is shown in Figure 3.4. Sensitivity-specificity pairs for each cut off score were calculated from the raw data.

Figure 3.4: ROC curve for the OESIL score for death at 12 months



Diagnostic test accuracy statistics for the various risk stratification tools are reported in Appendix D3 in full and summarised in Table 12.

Table 12: Diagnostic test accuracy for risk stratification tools for death

Study	Sens (%)	Spec (%)	LR+	LR-	Diag Yield (%)
ACP guidelines					
Crane 2002 Initial evaluation based on ACP guidelines, high risk group; death 12 months Test operator: investigator	66.70	83.00	3.9	0.40	23
Crane 2002 Initial evaluation based on ACP guidelines; moderate risk; death 12 months Test operator: investigator	33.30	70.30	1.1	0.95	30
Crane 2002 Initial evaluation based on ACP guidelines, high + moderate risk; 12 months Test operator: investigator	100.00	53.30	2.1	0.00	53
Crane 2002 Initial evaluation based on ACP guidelines; low risk group; death 12 months Test operator: investigator	0.00	46.70	0	2.14	47
San Francisco Syncope Rule					
Quinn 2008 San Francisco Syncope Rule deaths related to syncope at 6 months Test operator: attending physician	100.00	52.50	2.1	0.00	49
Quinn 2008 San Francisco Syncope Rule all cause deaths at 6 months Test operator: attending physician	89.10	53.10	1.9	0.21	49
Quinn 2008 San Francisco Syncope Rule deaths related to syncope at 12 months Test operator: attending physician	92.90	53.00	2	0.13	49
Quinn 2008 San Francisco Syncope Rule all cause deaths at 12 months Test operator: attending physician	83.00	54.10	1.8	0.31	49

OESIL score	Sens (%)	Spec (%)	LR+	LR-	Diag Yield (%)
Colivicchi 2003 OESIL score > 1 at 12 months Test operator: attending physician	96.80	72.80	3.6	0.04	35
EGSYS score					
del Rosso 2008b EGSYS score ≥ 3; at 21-24 months Test operator: attending physician + senior physicians (ECG)	82.40	82.00	4.6	0.22	24

B2-B4. Patient history for a serious event:

Four moderate quality studies and two small, low quality studies (Hing 2005; Reed 2007) reported signs and symptoms, physical examination and laboratory and ECG tests that gave an increase risk of an adverse event (i.e. death, MI, arrhythmia, PE, stroke, subarachnoid haemorrhage, significant haemorrhage / anaemia needing transfusion; procedural intervention to treat syncope cause; any condition likely to cause a return to the ED or which did cause a return to the ED; hospitalisation for related event). The duration of follow up varied, with Reed (2007) reporting results at 3 months, Hing (2005) at 3 to 6 months, Grossman (2007) at 30 days and the other studies at 7 days.

These signs and symptoms are reported as the relative risk of adverse events for the symptom present versus not present. The results are given in Appendix D3 and significant univariate risk factors are summarised in Table 13; also reported are non-significant results where there is agreement between two or more studies. The lower quality studies findings are reported only if there is no other evidence. Disagreement between studies is indicated in Table 13. None of the studies reported values for multivariate risk factors and these were incorporated in the various risk stratification tools developed.

Table 13: Univariate risk factors for serious events

Signs and symptoms, tests	Sign / symptom is a risk factor for serious adverse outcomes	Protective factor
Significant risk factors	• Age over 40 years (2 studies) and age over 60 years (2 studies) for 7 day outcomes • Male gender (3 agreed, 1 disagreed for 7 & 30 days) • Coronary artery disease (2 studies, 7 & 30 days) • Congestive heart failure (5 studies, slight heterogeneity; at 7 and 30 days and 3-6 months) • Ischaemic heart disease (3-6 mo, 1 low quality study) • Hypertension (borderline effect - 2 studies, 7 days and 3-6 months) • Arrhythmia (7 days) • Diabetes (2 studies; 7 days and 3-6 months) • Diuretics (7 days) • Dyspnoea (4 studies, 7 and 30 days) • Systolic blood pressure < 90 mm Hg – some heterogeneity, 4 studies (7 and 30 days) • Oxygen saturation < 95% (1 study, 7 days) • Rales (1 study, 7 days) • Abnormal heart sounds (1 study, 7 days) • Heart murmur (systolic or diastolic; 1 study, 7 days) • Carotid bruits (1 study, 7 days) • Profound dehydration (1 study, 30 days) • Abnormal rhythm (non sinus) (1 study, 7 days) • Troponin T levels (1 low quality study, 3-6 months)	Vagal symptoms (borderline, 1 study at 7 days)
Evidence for no significant effect		Prodromes (2 studies at 7 days and 3-6 months)
Signs and symptoms, tests	Sign / symptom is a risk factor for serious adverse outcomes	
Predictors for which there is large disagreement amongst studies	• Age over 80 years (2 studies at 7 days) • Antiarrhythmic medication very large heterogeneity (2 studies at 7 and 30 days) • Palpitations (2 studies at 7 and 30 days) • Chest pain (2 studies at 7 and 30 days) • Pulse rate < 50bpm or > 100-110bpm (2 studies at 7 and 30 days) • Respiratory rate > 24 breaths / min (1 study showed no events at 30 days and the other showed this to be a strong risk factor for adverse events at 7 days) • Heart murmur (7 versus 30 days) • Abnormal ECG: 3 of 4 studies showed an effect at 7 days, 1 study at 30 days did not; 1 low quality study showed an effect at 3-6 months • Haematocrit < 30%: 3 of 4 studies showed an effect at 7 days, 1 study at 30 days did not • Higher glucose level (1 study, 7 days)	

1

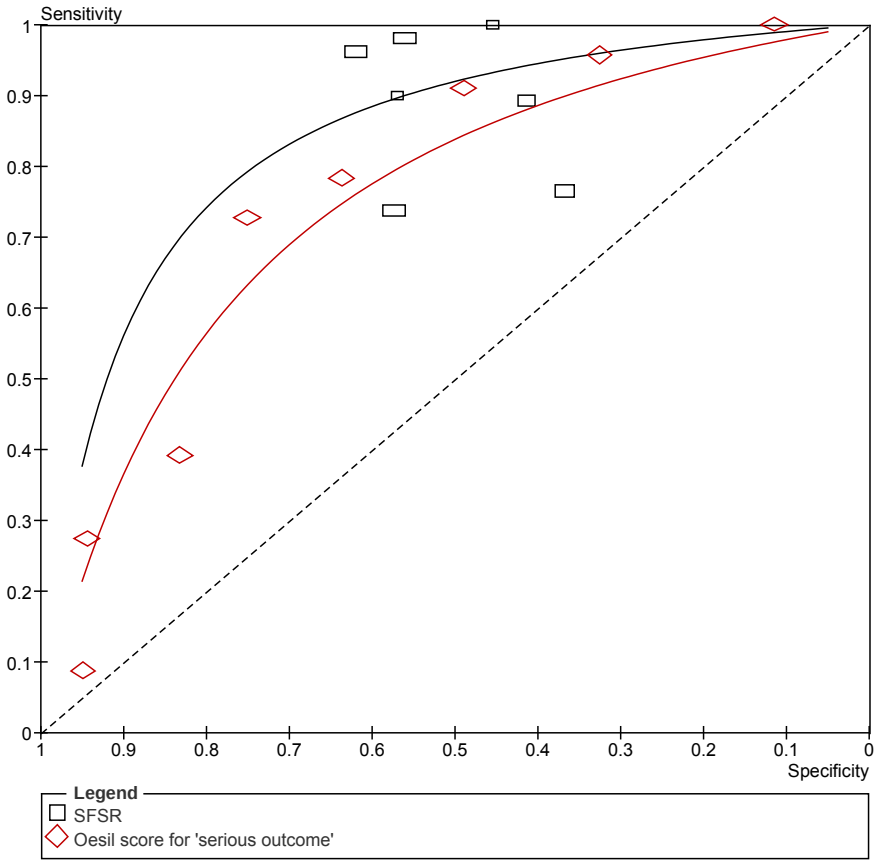
C2. Risk stratification tools for a serious event

Five moderate quality studies (Birnbaum 2008; Grossman 2007; Quinn 2005; Quinn 2006; Sun 2007) and four low quality studies (Cosgriff 2007; Hing 2005; Reed 2007; Schladenhaufen 2008 (retrospective)) examined different risk stratification rules for serious adverse events. The follow up time was 7 days for all studies except for Reed (2007) at 3 months, Hing (2005) at 3-6 months and Grossman (2007) and Quinn (2006) at 30 days.

Decision rules examined were the OESIL score (Hing 2005; Reed 2007); the San Francisco Syncope Rule (Birnbaum 2008; Cosgriff 2007; Quinn 2005; Quinn 2006; Sun 2007; Reed 2007; Schladenhaufen 2008) and the Boston Syncope Rule (Grossman 2007).

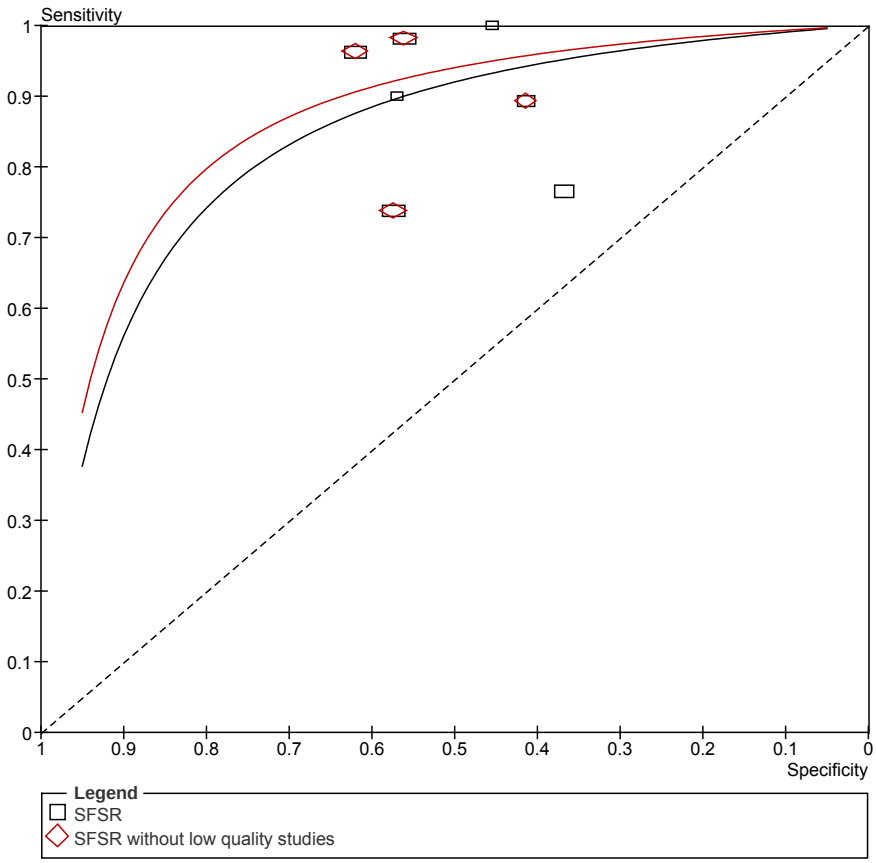
Hing (2005) and Reed (2007) each reported the number of patients who had an adverse event by the risk points score, in 99 and 100 patients respectively, allowing a combined ROC curve to be constructed (Figure 3.5). The SFSR was reported by seven studies in different populations and the sensitivity-specificity pairs are also plotted on the ROC curve.

Figure 3.5: ROC curve for risk stratification tools for adverse events



There is clearly heterogeneity amongst the SFSR studies. In the absence of the low quality studies, a slightly improved result was found (Figure 3.6).

Figure 3.6: sensitivity analysis for San Francisco Syncope Rule



The Grossman (2007) study reported overall sensitivity and specificity statistics for the Boston Syncope Rule. The diagnostic test accuracy statistics for each of the risk stratification rules are given in Appendix D3 and summarised in Table 14. A range of values is reported for the SFSR studies (higher quality only) and the optimum OESIL score is used.

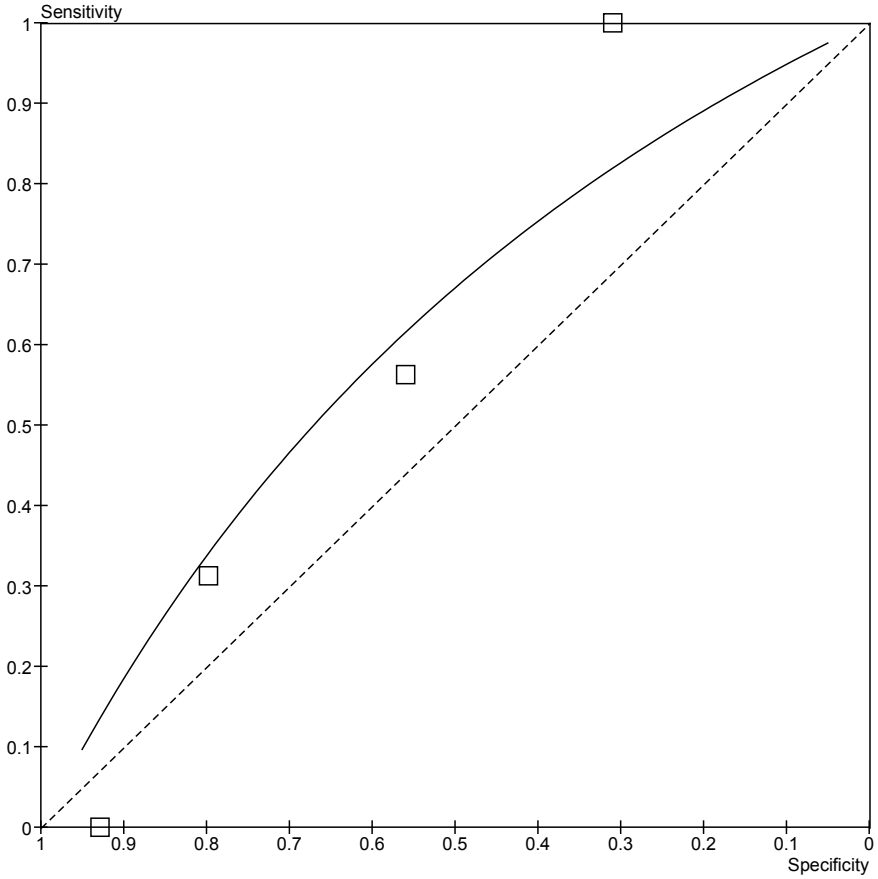
Table 14: Decision rules for adverse outcomes

Study	Sens (%)	Spec (%)	LR+	LR-	Diag Yield (%)
OESIL score					
Hing 2005 and Reed 2007 OESIL score >1 3 months follow up Test operator: attending physician	Range 78.3 to 90.9	Range 48.9 to 63.6	Range 1.8 to 2.2	Range 0.19 to 0.34	Range 46 to 56
San Francisco Syncope Rule					
Range for higher quality studies San Francisco Syncope Rule 7, 30 days and 3 month outcomes Test operator: attending physician	Range 73.8 to 98.1 (7days: 73.8 to 96.2)	Range 41.4 to 62.0 (7days: 57.0 to 62.0)	Range 1.5 to 2.5 (7days: 1.7 to 2.5)	Range 0.03 to 0.46 (7days: 0.06 to 0.46)	Range 45 to 64 (7days: 45-48)
Boston Syncope Criteria					
Grossman 2007 Boston Syncope Criteria 30 days Test operator: treating physician	97.10	62.20	2.6	0.05	52

Risk stratification tools for recurrence of syncope

One low quality study (Hing 2005) also reported the number of patients with recurrence of syncope after 3 to 6 months follow up. The diagnostic test accuracy of the OESIL score for this outcome was reported, by the risk points score, and the ROC curve is given in Figure 3.7. The summary curve is very close to the diagonal, indicating that this is not a good test for recurrence of syncope.

Figure 3.7: Risk stratification tools for the recurrence of syncope



3.4 Health Economics

None of the health economic evidence identified in our search was relevant to the initial assessment.

3.5 Evidence Statements

The evidence is summarised as follows:

3.5.1 Diagnosis of epileptic seizures versus non-seizures (syncope)

3.5.1.1 Signs and symptoms of epileptic seizures

There was low-quality evidence from two studies concerning the investigation of suspected epilepsy in selected patients. One study showed that tongue

biting had high specificity (99%) and low sensitivity (24%) in a highly selected population. The other study showed the following:

Signs and symptoms that are predictors **for** epilepsy

- Multivariate predictors (M) and/or strong univariate predictors (SU):
  - Waking with a bitten tongue (M & SU)
  - Abnormal behaviour noted, i.e. one or more of: witnessed amnesia for abnormal behaviour (M), witnessed unresponsiveness (M), unusual posturing (M & SU), limb-jerking (M)
  - TLoC with emotional stress (M)
  - Post-ictal confusion (M)
  - Head-turning to one side during TLoC (M & SU)
  - Prodromal déjà-vu or jamais-vu (M)
- Other good univariate predictors:
  - younger age
  - blue colour observed by bystander
  - bedwetting during TLoC
  - long history of TLoC
  - large number of episodes
- Other weak univariate predictors:
  - TLoC associated with stress
  - Prodromal signs: preoccupation, hallucinations, trembling
  - Mood changes after TLoC
  - Post-ictal headaches
  - Muscle pain after TLoC

A ‘strong’ univariate predictor is a likelihood ratio of more than 10 and a ‘good’ predictor is more than 5. Multivariate predictors are independent risk factors.

Signs and symptoms that are predictors **against** epilepsy being the cause of the TLoC:

- Multivariate predictors or strong univariate predictors against epileptic seizures:
  - Any pre-syncope (M)

  - TLoC with prolonged standing or sitting (M & SU)
  - Sweating before TLoC (M)
  - Coronary heart disease (SU)
  - Breathlessness preceding TLoC (SU)
- Other good univariate predictors against epileptic seizures:
  - Pre-syncope with prolonged sitting or standing
  - Palpitation before TLoC
  - Chest pain before TLoC
  - Remembered loss of consciousness
- Other weak univariate predictors against seizures:
  - Hypertension; self-reported high blood pressure
  - Pre-syncope precipitants: hot/warm place, needle
  - Pre-syncope after effort
  - Prodromal symptoms before TLoC: warmth, nausea; prodromal vertigo
  - Chest pain during TLoC

3.5.1.2 Decision rules for Epilepsy

One low-quality study with two decision rules, and one moderate quality study of initial evaluation based on the ESC guidelines (2001) showed high sensitivity and specificity for predicting epileptic seizures rather than syncope, based on the following features:

- Rule 1 (low-quality) TLoC is classified as due to epilepsy if the total symptom score is 1 or more, calculated by summing the following, if present:
  - Waking with a bitten tongue (+2)
  - Abnormal behaviour noted (one or more of: witnessed amnesia for abnormal behaviour, witnessed unresponsiveness, unusual posturing or limb-jerking) (+1)
  - TLoC with emotional stress (+1)
  - Post-ictal confusion (+1)
  - Head-turning to one side during TLoC (+1)
  - Prodromal déjà-vu or jamais-vu (+1)
  - Any pre-syncope (-2)

- TLoC with prolonged standing or sitting (-2)
- Diaphoresis (sweating) before TLoC (-2)

- Rule 2 (low-quality) TLoC is classified as due to epilepsy if the total symptom score is 0 or more, calculated by summing the following if present:
  - Head-turning to one side during TLoC (+2)
  - More than 30 episodes of TLoC (+1)
  - Unresponsiveness during TLoC (+1)
  - Sweating before TLoC (-1)
  - Any pre-syncope (-2)
  - TLoC with prolonged standing or sitting (-3)

- ESC guidelines (moderate quality study) presence of:
  - confusion after an attack for more than 5 minutes and/or tonic-clonic movements
  - automatism
  - tongue-biting
  - blue face or epileptic aura

3.5.2 Diagnosis of neurally mediated (NM) syncope versus other forms of syncope

3.5.2.1 Signs and symptoms of neurally mediated syncope

There is low-quality evidence in two studies investigating neurally mediated syncope in selected patients (patients with epileptic seizures or neurological causes excluded) and in one study investigating patients with vasovagal syncope or psychogenic non-epileptic seizures (PNES), which showed the following:

Signs and symptoms that are predictors **for** NM syncope or VVS / PNES (indicated by V/P)

- Multivariate predictors and/or strong univariate predictors:
  - Time between the first and last TLoC more than 4 years (M)
  - History of pre-syncope (M)
  - Nausea after TLoC (M)
  - Duration of prodromes longer than 10 seconds (M)
  - More than one prodrome (M for V/P)
  - Pre-syncope or syncope with prolonged sitting or standing (M)
  - Sweating or warm feeling before TLoC (M)
  - Pre-syncope or syncope with pain or medical procedure (M)
  - Mood changes or preoccupation before TLoC (SU)
- Other good univariate predictors:
  - Age below 35 years (also V/P)
  - Longer history of TLoC
  - Headaches before TLoC (also V/P)
  - Anxiety before TLoC (V/P only)
- Other weak univariate predictors:
  - More previous episodes of TLoC
  - Person was in a warm place
  - TLoC with stress
  - TLoC after effort
  - Feeling cold before TLoC
  - Numbness or tingling before TLoC
  - weakness before TLoC (V/P only)
  - TLoC on way to or from the toilet
  - Pallor (witness account) before TLoC
  - White or pale colour during TLoC noted by bystander
  - Unresponsive during TLoC
  - Cannot remember behaviour during TLoC
  - Sweating after TLoC
  - Mood changes after TLoC
  - Numbness or tingling after TLoC

Signs and symptoms that are predictors **against** NM syncope

- Multivariate predictors or strong univariate predictors against:
  - Age at first TLoC over 35 years (M and also age as continuous variable for multivariate V/P)
  - Any one of bifascicular block, asystole, SVT, diabetes (M & SU)
  - Blue colour noted by bystander (M)
  - Remembers something about the TLoC (M)
  - P-wave more than 120 ms or non-sinus rhythm (multivariate V/P only)
- Good univariate predictors against:
  - Syncope during effort
  - Atrial fibrillation or flutter
- Weak univariate predictors against::
  - Male gender
  - Suspected heart disease
  - Valvular heart disease
  - Hypertension
  - Syncope whilst supine
  - Less than 5 seconds warning
  - No memory about TLoC
  - Absence of prodromes (V/P only)

3.5.2.2 Decision rules

One low-quality study of a decision rule and one moderate-quality study of initial evaluation based on the ESC guidelines (2001) showed high sensitivity and specificity for predicting vasovagal syncope rather than other forms of syncope, based on the following features:

- **Rule 1** (low-quality): TLoC is classified as a vasovagal syncope if the total symptom score is -2 or more, calculated by summing the following if present:
  - Pre-syncope or syncope with pain or medical procedure (+3)
  - Sweating or warm feeling before TLoC (+2)
  - Pre-syncope or syncope with prolonged sitting or standing (+1)

  - Remembers something about the TLoC (-2)
  - Age at first TLoC at least 35 years (-3)
  - Blue colour noted by bystander (-4)
  - Any one of bifascicular block, asystole, supraventricular tachycardia and diabetes (-5).

The study noted that the last bullet of arrhythmia abnormalities all had to be absent (as well as positive symptoms) in order to have a diagnosis of vasovagal syncope. We note that people with epilepsy were excluded.

- **ESC guidelines** – moderate-quality study - presence of:
  - precipitating events (such as fear, severe pain, emotional distress, instrumentation, or prolonged standing) which are associated with typical prodromal symptoms.
  - We note that this study included patients with epilepsy (2%).

There was low-quality evidence of a decision rule that showed fairly high sensitivity (85%) but only moderate specificity (50%) for predicting vasovagal syncope or psychogenic non-epileptic seizures rather than other forms of syncope, based on the following features:

- **Decision rule** (classified as VVS plus PNES if score is 0 or above), TLoC is classified as a vasovagal syncope or PNES if the total symptom score is 0 or more, calculated by summing the following, if present:
  - Age (term 'AgeCat'): score 1 for age 45 years and below, 2 for age over 45 and below 65 years and 3 for age over 65 years
  - Number of prodromes ('ProdCat'): score 0 for 1 or 0 symptoms, and score 1 for 2 or more symptoms
  - ECG P-wave duration ('P-waveCat'): score 0 for duration below 120 ms and 1 for duration 120 ms and above or non-sinus rhythm.

  Then apply the formula: 2 x ProdCat – P-waveCat – AgeCat + 2

We note that this study excluded people with epilepsy.

3.5.3 Diagnosis of orthostatic hypotension versus other forms of syncope

3.5.3.1 Decision rules for orthostatic hypotension

There was moderate-quality evidence from the ESC guidelines for the diagnosis of orthostatic hypotension. The ‘certain’ diagnosis category gave very high sensitivity (100%) and very high specificity (99%). The guideline definition was a decrease in systolic blood pressure of 20 mm Hg or a decrease of systolic blood pressure to below 90 mm Hg.

3.5.4 Diagnosis of cardiac syncope versus other forms of syncope

3.5.4.1 Signs and symptoms of cardiac syncope

There was low-quality evidence investigating cardiac syncope in selected patients in two studies and unselected patients in one study, which showed the following:

Signs and symptoms that are predictors **for** cardiac syncope:

- Multivariate predictors:
  - Suspected or certain heart disease
  - Heart disease or abnormal ECG or both
  - History of congestive heart failure
  - Time between first and last TLoC less than 4 years
  - Supine position
  - Blurred vision before TLoC
  - Syncope during effort
  - Palpitations before TLoC
  - Age at least 65 years
- Other weak univariate predictors: Male gender; absence of prodromes

Signs and symptoms that are predictors **against** cardiac syncope:

- Multivariate or strong univariate predictors against :
  - Nausea or vomiting before TLoC (M)

  - Warm crowded place / prolonged orthostasis (standing upright) / fear-pain-emotion (M)
  - More than one prodrome (M)
  - Paresthesia (i.e. a sensation of tingling, pricking, or numbness of a person's skin with no apparent long-term physical effect; SU)
- Other good univariate predictors against:
  - P-wave duration (continuous variable)
  - Feeling cold before TLoC
  - Anxiety before TLoC
  - Feeling cold after TLoC
  - Headache before TLoC
- Other weak univariate predictors against::
  - Sweating before TLoC
  - History of pre-syncope
  - TLoC during or up to 1 h after a meal
  - Pallor before TLoC

Signs and symptoms for which there is **large disagreement** between studies for or against cardiac syncope:

- Sweating before TLoC
- Incontinence during TLoC
- Light headedness/dizziness before TLoC

3.5.4.2 Simple decision rules for cardiac syncope

There was low-quality evidence for cardiac syncope in selected patients in two studies and unselected patients in one study, each of which evaluated a decision rule for cardiac syncope. The ROC curves and the diagnostic test accuracy statistics suggested that the most reliable test was the EGSYS score, closely followed by the Sarasin decision rule; both rules had high sensitivity (91 and 94% respectively), but only moderate specificity (69 and 42%). The following decision rules were included:

- **EGSYS score** (low-quality) TLoC classified as cardiac syncope and equated with the need for admission if the total symptom score is 3 or more, calculated by summing the following, if present:
  - Palpitation preceding syncope (+4)
  - Heart disease or abnormal ECG or both (+3)
  - Syncope during effort (+3)
  - Syncope whilst supine (+2)
  - Precipitating or predisposing factors or both (warm, crowded place; prolonged orthostasis; fear/pain/emotion) (-1)
  - Autonomic prodromes (nausea and/or vomiting) (-1)

- **Sarasin score** for prediction of arrhythmia syncope; considered to be predicted if the patient has any one of the following:
  - Age 65 years and older
  - History of congestive heart failure
  - Abnormal ECG (conduction disorder, old myocardial infarction; rhythm abnormalities)

3.5.4.3 Guideline-based decision rules for cardiac syncope

One low-quality study evaluated a decision rule for cardiac syncope based on the **ACEP recommendations** for admission and one moderate-quality study evaluated the ESC guidelines for cardiac syncope. The former, at level B, showed very high sensitivity (100%) and fairly high specificity (81%). The latter showed high specificity (99%) and fairly high sensitivity (73%). The guideline tools can be summarised as follows:

- **ACEP level B**:
  - History of ventricular arrhythmias
  - History of congestive heart failure
  - Associated chest pain or other symptoms of acute coronary syndrome
  - Physical signs of congestive heart failure
  - Physical signs of significant valve disease
  - ECG abnormalities

- **ESC guidelines** (certain and highly-likely diagnoses):
  - ECG abnormalities
  - Presence of severe structural heart disease
  - Syncope during exertion or when supine
  - TLoC preceded by palpitation or accompanied by chest pain
  - Family history of sudden death.

3.5.5 Risk factors for death within 12 months

3.5.5.1 Features that are risk factors for death

There is moderate-quality evidence to show that the following are **factors predictive of a risk of death within 12 months:**

- Multivariate risk factors for death:
  - Age over 65 years
  - Cardiovascular disease in clinical history
  - Abnormal ECG findings
  - Syncope without prodromes
- Other univariate risk factors for death:
  - Hypertension
  - Diabetes mellitus
  - Syncope-related traumatic injuries

3.5.5.2 Simple decision rules for death within 12 months

Two moderate-quality studies and one low-quality study examined risk stratification rules for death. Diagnostic test accuracy statistics, including the ROC curve suggested that the most reliable test was the OESIL score, closely followed by the San Francisco syncope rule; both rules had high sensitivity (97 and 93% respectively), but only moderate specificity (73 and 53%). The following were included:

- **OESIL score** (moderate-quality study); the score was predictive of death if there were at least two of the following:

- Age over 65 years
- Clinical history of cardiovascular disease
- Syncope without prodromal symptoms
- Abnormal ECG

- **San Francisco Syncope Rule** (moderate quality study); the score was predictive of death at 12 months if there was any one of:
  - History of congestive heart failure
  - Abnormal ECG
  - Haematocrit below 30%
  - Patient complaint of shortness of breath
  - Triage systolic blood pressure less than 90 mm Hg.

3.5.5.3 Guideline-based decision rule for death within 12 months

There was low-quality evidence from one UK study, which evaluated the American College of Physicians (**ACP**) **guidelines**, which defined 'high'-, 'medium'- and 'low'-risk groups for death within 12 months (these corresponded to an absolute indication for admission; a probable indication for admission and no indication for admission, respectively). The high- and moderate-risk groups combined had a sensitivity of 100% and a specificity of 53%, and the decision rule was based on the following:

- ACP guidelines - high risk group:
  - History of coronary artery disease or congestive heart failure (CCF) or ventricular tachycardia (VT)
  - TLoC with symptoms of chest pain
  - Physical signs of CCF, significant valve disease, stroke or focal neurology
  - Abnormal ECG
- ACP guidelines - moderate risk group
  - Sudden TLoC with injury, rapid heart action or exertional syncope
  - Frequent TLoC episodes
  - Suspicion of coronary heart disease or arrhythmia

- Moderate to severe postural hypotension
- Age over 70 years

3.5.6 Risk factors for a serious adverse event within 7 or 30 days

A 'serious event' is defined in these studies as: death, myocardial infarction, arrhythmia, pulmonary embolism, stroke, subarachnoid haemorrhage, significant haemorrhage / anaemia needing transfusion; procedural intervention to treat cause of syncope; any condition likely to cause a return to the ED or which did cause a return to the ED; hospitalisation for a related event

3.5.6.1 Risk factors for a serious adverse event

There was moderate-quality evidence showing that the following features were statistically significant risk factors for a serious event within 7 days (3 studies):

- Univariate risk factors for a serious event:
  - Age over 40 years in one study and age over 60 years in another study
  - Male gender
  - Coronary artery disease (borderline)
  - Hypertension (borderline)
  - Congestive heart failure
  - Diabetes
  - Diuretics
  - Breathlessness
  - Systolic blood pressure below 90 mm Hg
  - Oxygen saturation less than 95%
  - Pulse rate less than 50 bpm or more than 110 bpm
  - Respiratory rate more than 24 breaths per minute
  - Chest pain
  - Râles; abnormal heart sounds; carotid bruits; heart murmur (systolic or diastolic)
  - Haematocrit less than 30%
  - Abnormal ECG

There was moderate-quality evidence showing no significant effect at 7 days for the following risk factors, but all of these were associated with imprecision in the estimates: ethnicity; nitrates, calcium channel blockers, beta blockers, alpha blockers, ACE inhibitors, nitrates; prior syncope, syncope on exertion; palpitation; sweating.

There was moderate-quality evidence for the following other risk factors for a serious event at up to 30 days:

- Statistically significant risk factors: profound dehydration
- Risk factors that were not statistically significant but had a high level of imprecision: family history of sudden death; recurrent syncope; gastrointestinal bleed; evidence of ischaemia on ECG

3.5.6.2 Simple decision rules for a serious adverse event

Five moderate-quality studies and four low-quality studies reported on the following decision rules:

- **San Francisco Syncope Rule** (3 moderate-quality and 2 low-quality studies) for predicting adverse events. For the moderate-quality studies **at 7 days** the sensitivity ranged from 74 to 96% and the specificity was 57 to 62%. At **30 days** the sensitivity was 98% and the specificity was 56%
  - Patients were considered at risk if any one of the following was present:
    - ◊ History of congestive heart failure
    - ◊ Abnormal ECG
    - ◊ Haematocrit below 30%
    - ◊ Patient complaint of shortness of breath
    - ◊ Triage systolic blood pressure less than 90 mm Hg
- **Boston Syncope Rule** (one moderate-quality study) at **30 days**: sensitivity 97%, specificity 62%. Patients were considered at risk if any one of the following was present:

  - Abnormal ECG
  - Chest pain of possible cardiac origin
  - Shortness of breath
  - History of CAD or congestive heart disease or left ventricular dysfunction or VT or pacemaker or ICD
  - Pre-hospital use of antidysrhythmic medication excluding beta-blockers or calcium channel blockers
  - Family history (first degree relative) of sudden death or HOCM or Brugada's syndrome or long QT syndrome
  - Valvular heart disease (heart murmur in history or on examination)
  - Multiple TLoC episodes within the last 6 months
  - TLoC during exercise
  - QT interval more than 500 ms
  - Gastrointestinal bleed by haemoccult or history
  - Haematocrit less than 30%
  - Dehydration not corrected in the ED
  - Persistent (more than 15 min) abnormal vital signs: respiratory rate more than 24 / min; oxygen saturation less than 90%; sinus rate less than 50 bpm or more than 100 bpm
  - Blood pressure below 90 mm Hg
  - Primary CNS event (e.g. subarachnoid haemorrhage, stroke)
- **OESIL score** (two low-quality studies) **at 3 months**: sensitivity 78 to 91% and specificity 49 to 64%. Patients were considered at risk if they two or more of:
  - Age over 65 years
  - Syncope without prodromal symptoms
  - Clinical history of cardiovascular disease
  - Abnormal ECG

3.6 Evidence to Recommendations

3.6.1 Information-gathering and recording of the event itself (recommendations 1.1.1.1 and 1.1.2)

The GDG considered all the evidence from the initial stage assessment. The guideline covers three main points of initial patient contact; the ambulance service, the emergency department and the GP surgery. Although these areas have differences, particularly in referral patterns, the GDG decided at the outset to write the recommendations such that each area could be covered by a single recommendation, with clarifying comments being added where appropriate, rather than giving three separate pathways.

It was clear from the evidence that there are two distinct types of diagnostic information about the person with TLoC that it is important to capture:

- The TLoC event itself: the symptoms experienced by the person having the TLoC and the observations made by any eye-witnesses, before during and after TLoC. This information is likely to be gathered at the initial consultation at the point of contact, but the GDG noted that sometimes it is necessary to contact any eye-witnesses at a later stage.
- History-taking, clinical examination and subsequent tests: History-taking includes the person's medical history, including their current health status, drug therapy, past medical history and family history. Initial tests may require equipment, in particular a 12-lead ECG, and may include laboratory tests on a blood sample.

Recommendation 1.1.1.1 therefore sets out the information that should be collected at the first point of contact. This list was based on the predictors described in the evidence. Recommendation 1.1.1.2 emphasises the need to take a record of this information from all sources, including the person, any witnesses and paramedics. The GDG also considered, in recommendation 1.1.1.3, the impact on the witnesses of observing somebody having TLoC, and they were particularly concerned when that witness was a child or young person or a person with learning disabilities and/or communication difficulties.

The GDG noted from their discussions that different clinicians may be involved in the two types of information gathering; for example, there may be initial contact with the ambulance service, but the second stage is carried out in the Emergency Department. The GDG considered that there was a risk that important information could be lost when different clinicians are involved, and therefore decided to recommend that the initial information is recorded clearly and that a copy of the record is transferred with the person who had a TLoC (recommendation 1.1.1.2).

The GDG decided that, before moving on to take the more detailed clinical history, it was important to decide on the basis of the initial information, whether the person had lost consciousness. If they had not, then that person would not be covered by the guideline and should be managed in other ways. However, the GDG noted that, sometimes, the person is not aware, or denies, that they have lost consciousness, so it is necessary to be definite that the person did not have TLoC. Recommendation 1.1.1.4 describes the steps that should be taken.

3.6.2 Using the information gathered about symptoms, clinical examination, 12-lead ECG and other initial tests (recommendations 1.1.3 to 1.1.5)

Decision-making was based on evidence on the following:

- people at increased risk of death or serious adverse events in the immediate future (and who require urgent admission to hospital)
- people who can safely be sent home from hospital or who need not be taken to hospital by ambulance crews or referred by GPs.
- the diagnosis of the cause of TLoC, especially neurally mediated syncope, orthostatic hypotension and cardiac syncope.

3.6.2.1 Recommendation that the person should be referred for emergency specialist assessment in cardiology (recommendation 1.1.3.2)

Quality of the evidence

There was moderate- and low-quality evidence from the review on risk factors and decision rules for serious adverse events and also on multivariate predictors for cardiac syncope. The GDG interpreted the validity of the significant risk factors in the light of their experience.

GDG discussion

The GDG were mindful of the costs of urgent hospitalisation and the potential impact of hospitalisation on the individual's quality of life. They therefore felt that it was important to target hospitalisation at those people who were more likely to experience a serious adverse event in the days following TLoC which could benefit from being managed in hospital. The GDG emphasised that the most relevant target condition was serious adverse events within 7 days, which meant that the OESIL score was indirect evidence (at 3 months). The GDG decided not to recommend using the remaining decision rule (the San Francisco Syncope Rule) because it only had moderate-high sensitivity (74-96%) and moderate specificity (57 – 62%).

The GDG chose an upper age limit of 40 years for family history of sudden cardiac death, based on the NSF guidance. This limit is pragmatic: the GDG noted that, with increasing age, coronary heart disease overtakes other, mostly inherited, conditions as the commonest cause of sudden cardiac death.

The GDG also recognised that there were other 'red flag' conditions requiring immediate attention that could occur in people who had had TLoC. Therefore, they recommended that people who have other conditions, in addition to TLoC, that require immediate treatment should be managed according to the needs for that condition, with the appropriate degree of urgency (recommendation 1.1.3.1)..

3.6.2.2 Recommendations for an uncomplicated faint (1.1.4.1)

Quality of the evidence

There was moderate- and low-quality evidence from the review on multivariate predictors and decision rules for neurally mediated syncope.

GDG discussion

The GDG included the multivariate predictors of vasovagal syncope from the evidence, and noted that the evidence also required cardiac syncope predictors to be absent. The evidence showed these were independent risk factors so only one was necessary for a diagnosis of uncomplicated faint. Based on their consensus experience, the GDG expanded the posture factor to cover recurrence of TLoC if a person sits or stands up too quickly after initial recovery, and to cover any previous similar episodes in which TLoC has been prevented by lying down. They therefore added two further diagnostic pointers to the recommendation. After the DVLA, the GDG adopted the mnemonic, 'the 6Ps' to enable easy recall of the factors.

In addition, the GDG noted, from their consensus experience, that situational syncope can be diagnosed on the basis of initial assessment, and added recommendation 1.1.4.2.

3.6.2.3 Recommendations for orthostatic hypotension (1.1.4.2)

Quality of the evidence

There was moderate-quality evidence from one study on the predictors for orthostatic hypotension.

GDG discussion

The study reported predictors for both certain and highly likely diagnoses for orthostatic hypotension. In view of the very high sensitivity (100%) and very high specificity (99%) for the certain diagnosis, these predictors were adopted by the GDG. The GDG also required that orthostatic hypotension was suggested by the history, and when describing further management following a diagnosis, took into consideration their concerns that a person with low blood pressure should be treated accordingly and not be sent home, possibly to be alone. This aspect is covered by the NICE Falls guideline and the GDG wished to cross refer to this guidance.

3.6.2.4 Recommendation for referral to a specialist in epilepsy (1.1.5.1)

Quality of the evidence

There was low-quality evidence from two studies for signs and symptoms as predictors of epilepsy as the cause of the TLoC: one study focussed only on tongue biting; the other study gave multivariate predictors and decision rules for epilepsy.

GDG discussion

The GDG interpreted these low-quality studies in the light of their experience, particularly because they were concerned that the main study excluded patients with epileptic seizures that were not supported by EEG. The GDG also noted that, although the study stated that it excluded people with psychogenic non-epileptic seizures, it did not say how this was diagnosed. The GDG decided not to include the multivariate risk factor, TLoC with emotional stress, in the recommendation because they considered this more likely to be a predictor for PNES. The GDG emphasised in this

recommendation that limb jerking should be prolonged for epilepsy to be suspected and noted that brief limb jerking can also be manifested during vasovagal syncope. As part of their consensus discussion, the GDG watched a video of an experimental study demonstrating induced syncope. The GDG's consensus, based on the evidence, is given in recommendation 1.1.5.1.

3.7 Recommendations

Hyperlink to recommendations Section 1.1.1 - Gathering information and recording of the suspected transient loss of consciousness (TLoC) event

Hyperlink to recommendations Section 1.1.2 - History-taking, clinical examination, 12-lead electrocardiogram (ECG) and other tests for people who have experienced TLoC

Hyperlink to recommendations Section 1.1.3 - Red flags

4 12-lead ECG

4.1 Clinical Questions

Q8) In people who have experienced a TLoC, which diagnostic tests should be performed, both in an unselected population and in specified subgroups (e.g. suspected syncope, epilepsy or psychogenic non-epileptic seizures).

4.2 Clinical evidence review: Introduction to the use of the standard electrocardiogram

ECG abnormalities may suggest arrhythmic syncope (e.g. bifascicular block, intraventricular conduction abnormalities, atrioventricular block, sinus bradycardia, pre-excited QRS complexes, prolonged QT interval, Brugada syndrome, right ventricular dysplasia, myocardial infarction, complete heart block, supraventricular tachyarrhythmias or ventricular tachycardia (Kapoor 1992, Task Force 2004). This test is risk-free and inexpensive (Miller 2005).

Sinus tachycardia may suggest dehydration, congestive heart failure or pulmonary embolus (Farrehi 1995). Frequent premature ventricular contractions might suggest ventricular tachycardia-induced syncope (Farrehi 1995). New pathologic Q waves or ST segment elevation may suggest an acute ischaemic syndrome (Farrehi 1995). Left ventricular hypertrophy might suggest aortic stenosis or hypertrophic cardiomyopathy (Farrehi 1995). An old myocardial infarction (suggested by Q waves) or a prolonged QT interval are both risk factors for ventricular tachycardia, the commonest cause of sudden cardiac death (Farrehi 1995, Hadjkoutis 2004). Left bundle branch block in elderly patients may suggest a cardiomyopathy or an old myocardial infarction (Farrehi 1995). In those with both a right bundle branch block and a left anterior hemiblock, there is a high incidence of coronary disease and potential to develop third-degree heart block (Farrehi 1995). An abnormal ECG obtained while the patient is at rest is key to the diagnosis of long QT syndrome (Roden 2008). The upper limits of the QT interval corrected for the heart rate (the QTc) are below 460ms for women and below 440ms for men (Roden 2008).

4.2.1 Diagnostic yield of the ECG

Overall, ECG is diagnostically useful in 5-10% of patients, including prolonged monitoring in 4% (Petkar 2007). This may represent 2–11% of the cases in which a diagnosis is made (Kapoor 1995). An abnormal ECG is found in up to 50% of patients with syncope, but in most patients it is not diagnostic (Arthur 2001).

A retrospective study of 101 hospitalised patients showed that resting ECG revealed the cause of syncope in 11% of patients in whom the history and physical examination alone had not suggested the cause, and 24-hour ECG monitoring in a further 16% of patients (Ben-Chetrit 1985).

4.2.2 Initial stages of diagnosis in patients who have had a TLoC: 12-lead ECG, introduction

The reviews in the next two sections concern the use of 12-lead ECG in the early stages of assessment for people who have had a TLoC. Section 4.4 is a continuation of chapter 3: five studies investigated the use of the 12-lead ECG for predicting serious adverse outcomes, including death (Colivicchi 2003; Grossman 2007; Quinn 2004, Reed 2007, Sun 2008), and one of these studies also addressed the dependence of the diagnostic test accuracy on the health care professional carrying out the ECG assessment and also considered the effect of patient age (Sun 2008). Section 4.5 compares results of automatic 12-lead ECGs with those of an expert clinician for the detection of life threatening arrhythmias, not necessarily in patients with TLoC (Charbit 2006, Christov 2001, Denny 2007, Fatemi 2008, Hulting 1979, Kaneko 2005, Taha 2000). This review is supplemented by an unpublished study in patients with epilepsy (Petkar 2009; pers. comm.) – section 4.6.

4.3 Clinical Evidence Review: 12-lead ECG for predicting serious adverse outcomes in people who have had a TLoC

4.3.1 Methods of the review – selection criteria

4.3.1.1 Types of participants

Adult patients who have had a TLoC presenting to emergency departments or general practice surgeries. Participants are not expected to have had any prior tests.

4.3.1.2 Reference standard

Follow up.

4.3.1.3 Target condition

The target condition was to be adverse events, which could be death only, death plus cardiac events, or any serious adverse event. The GDG defined a 'serious adverse event' to be death, any cardiac event, any cerebral event and serious injury.

4.3.2 Description of studies

Six studies were included (Colivicchi 2003; Grossman 2007; Hing 2005; Quinn 2004; Reed 2007; Sun 2008) and these have been described in chapter 3. The Sun (2008) study was a further report of the Sun (2007) study.

4.3.2.1 Index test

The index test in each study was an abnormal ECG, described fully in Appendix D1, and summarised in Table 15:

1

Table 15: Index tests		
Study	**ECG details**	**Assessed by**
Colivicchi 2003	Atrial fibrillation or flutter Supraventricular tachycardia multifocal atrial tachycardia Frequent or repetitive premature supraventricular or ventricular complexes Sustained or non-sustained ventricular tachycardia Paced rhythms Bundle branch block Complete atrioventricular block; Mobitz I or II atrioventricular block; Intraventricular conduction delay	Attending physician
Grossman 2007	Sinus rate below 50 beats/min or above 100 bpm VT, VF, SVT, rapid AF QT interval longer than 500 ms new STT wave change 2nd or 3rd degree heart block or intraventricular block	Treating physician
Hing 2005	Abnormal ECG (no details)	Not stated
Quinn 2004	Abnormal ECG result (any non-sinus rhythm or any new changes) – no further details	Attending physician
Reed 2007	Sinus bradycardia below 50 beats per minute Sinoatrial block Sinus pause longer than 3 seconds QTc longer than 450 ms New T wave/ST segment changes New ST elevation ventricular tachycardia Brugadas (ST segment elevation V1-V3) Arrhythmogenic right ventricular dysplasia Mobitz type II heart block; Wenkebach heart block; Bifascicular block; Complete heart block	Not stated
Sun 2008	Sinus bradycardia below 50 beats per minute Any non-sinus rhythm Left or right bundle branch block Abnormal conduction interval excluding 1st degree block Q/ST/T changes consistent with acute or chronic ischaemia Left axis deviation Left or right ventricular hypertrophy	Main study: emergency medicine physicians with 2-4 years experience. Sub study in a convenience sample of 230 patients: resident physician (2-4 years experience) and attending physician

2

3 *4.3.2.2 Target condition*

4 The target conditions for the six studies were:

5 • Death only, at 12 months (Colivicchi 2003)

6 • Death and cardiac outcomes only: sudden death, myocardial infarction,
7 arrhythmias (VT>3, sick sinus disease, etc) structural heart disease (aortic
8 outflow obstruction, cardiomyopathy, heart transplant complications); acute

cardiac intervention (e.g. pacemaker) (Hing 2005 at 3 to 6 months; Sun 2008 at 14 days)

- Short term serious outcomes: death, myocardial infarction, arrhythmias, pulmonary embolism, stroke, subarachnoid haemorrhage, significant haemorrhage/anaemia needing transfusion; procedural intervention to treat syncope cause; any condition likely to cause a return to the ED or which did cause a return to the ED (Grossman 2007 at 30 days; Quinn 2004 at 7 days; Reed 2007 at 3 months)

4.3.3 Methodological quality

Of the six studies, the GDG considered the Reed (2007) study to be at higher risk of bias because 62% of the eligible patients were missed and these patients were significantly younger, and also the study group was skewed towards more serious risk. The Hing (2005) study was also considered at higher risk because the reference standard was predominantly by reference to medical records and patient accounts, and had limited input from health care professionals (chapter 3).

4.3.4 Results

4.3.4.1 12-lead ECG as a predictor for adverse events

Four moderate quality studies (Colivicchi 2003; Grossman 2007; Quinn 2004; Sun 2008) and two low quality studies (Hing 2004; Reed 2007) reported the effect of ECG abnormalities as predictors for adverse outcomes. The relative risks are reported in Appendix D3. The diagnostic test accuracy statistics for each of the studies are given in Appendix D3 and summarised in Table 16 and Table 17.

We note that some studies reported separately individual ECG abnormalities, but the diagnostic test accuracy statistics were determined with a reference standard of any adverse event, not just the ones likely to ensue from that ECG abnormality (Grossman 2007; Quin 2004).

One study also reported the prevalence of the false positive findings for different ECG components (Sun 2008). These were as follows (some patients had more than one finding):

Any abnormal ECG findings	20%
Non-sinus rhythm	3%
Bundle branch block	7%
Left axis deviation	3%
Ventricular hypertrophy	2%
Abnormal intervals	3%
Chronic/acute ischaemia	4%
Sinus bradycardia (pulse rate below 50 bpm)	1%
Non-specific ST/T changes	7%

False negative results were not reported.

Table 16: 12-lead ECG as predictor for adverse outcomes

Study	Sens (%)	Spec (%)	LR +	LR-	Pre test prob	Post test prob	Diag Yield (%)
All adverse events							
Quinn 2004; 7 days Test operator: attending physician	65.8	72.6	2.4	0.47	12	24	32
Reed 2007 3 months follow up Test operator: not stated / unclear	81.8	45.5	1.5	0.40	11	16	58
Death and Cardiac outcomes only							
Sun 2008 14 days follow up Test operator: resident physician	72.4	73.6	2.7	0.37	10	26	32
Hing 2004 3 to 6 months follow up Test operator unclear	73.9	68.8	2.4	0.38	23	42	41
Death only							
Colivicchi 2003 death 12 months Test operator: attending physician	61.3	73.6	2.3	0.53	12	23	30

Table 17: 12-lead ECG individual components as predictors for adverse outcomes

Study	Sens (%)	Spec (%)	LR+	LR-	Diag Yield (%)
All adverse events					
Grossman 2007 ischaemic ECG; all adverse events; 30 d Test operator: treating physician	1.5	97.8	0.7	1.01	2
Grossman 2007 QT interval > 500ms; all adverse events; 30 days Test operator: treating physician	0.0	100.0	NA	1.00	0
Grossman 2007 heart block; all adverse events; 30 days Test operator: treating physician	1.5	97.8	0.7	1.01	2
Grossman 2007 abnormal sinus rate; 30 days Test operator: treating physician	5.9	95.1	1.2	0.99	5
Quinn 2004 Abnormal rhythm (non sinus); 7 days Test operator: attending physician	43.0	81.3	2.3	0.70	21
Quinn 2004 abnormal ECG, new changes Test operator: attending physician	55.7	82.5	3.2	0.54	22

4.3.4.2 12-lead ECG as a test for adverse events – dependence on age

One moderate quality study (Sun 2008) recorded separately the diagnostic test accuracy statistics for different age groups. These are given in detail in Appendix D3 and summarised in Table 18

Table 18: 12-lead ECG as a predictor for adverse outcomes (death and cardiac events at 14 days) – effect of age

Age group	Sens (%)	Spec (%)	LR+	LR-	Pre test prob (%)	Post test prob +ve (%)	Post test prob –ve (%)	Diag Yield (%)
age 18-39y	50.0	87.7	4.1	0.57	2.0	8.0	1.1	13
age 40-59y	90.0	87.6	7.3	0.11	10.0	45.0	1.3	20
age 60-79y	71.4	67.0	2.2	0.43	12.0	23.0	5.5	38
age 80 and above	72.2	60.4	1.8	0.46	17.0	27.0	8.6	45

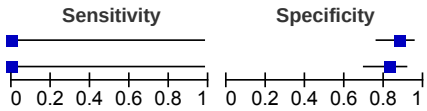
4.3.4.3 12-lead ECG as a predictor for adverse events – dependence on interpreting physician

One moderate quality study (Sun 2008) recorded separately the diagnostic test accuracy statistics for different age groups, as recorded by both a resident physician of 2 to 4 years experience and the attending physician. These are given in detail in Appendix D3 and summarised in Table 19. The sensitivity and specificity are also recorded on a forest plot in Figure 4.1, and it can be observed that the confidence intervals are wide for sensitivity, such that the study found no significant difference between operators.

Figure 4.1: Effect of operator

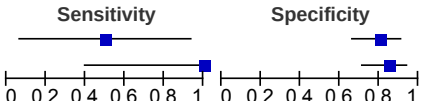
12 lead ECG cardiac outcomes, different physicians; 18-39 years

Study	TP	FP	FN	TN	Sensitivity	Specificity
Sun 2008 attending physic	0	7	1	49	0.00 [0.00, 0.97]	0.88 [0.76, 0.95]
Sun 2008 resident 2-4y	0	10	1	46	0.00 [0.00, 0.97]	0.82 [0.70, 0.91]



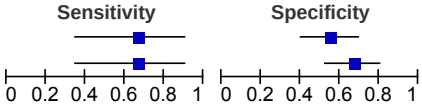
12 lead ECG cardiac outcomes, different physicians; 40-59 years

Study	TP	FP	FN	TN	Sensitivity	Specificity
Sun 2008 attending physic	2	9	2	37	0.50 [0.07, 0.93]	0.80 [0.66, 0.91]
Sun 2008 resident 2-4y	4	7	0	39	1.00 [0.40, 1.00]	0.85 [0.71, 0.94]



12 lead ECG cardiac outcomes, different physicians; 60-79 years

Study	TP	FP	FN	TN	Sensitivity	Specificity
Sun 2008 attending physic	8	22	4	27	0.67 [0.35, 0.90]	0.55 [0.40, 0.69]
Sun 2008 resident 2-4y	8	16	4	33	0.67 [0.35, 0.90]	0.67 [0.52, 0.80]



12 lead ECG cardiac outcomes, different physicians; 80 years & over

Study	TP	FP	FN	TN	Sensitivity	Specificity
Sun 2008 attending physic	7	18	5	33	0.58 [0.28, 0.85]	0.65 [0.50, 0.78]
Sun 2008 resident 2-4y	9	20	3	31	0.75 [0.43, 0.95]	0.61 [0.46, 0.74]

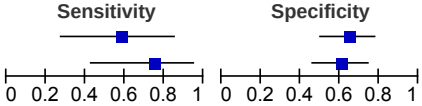


Table 19: 12-lead ECG as a test for adverse outcomes (death and cardiac events at 14 days) – effect of physician

Study	Sens (%) (95% CI)	Spec (%)	LR+	LR-	Diag Yield (%)
all ages Test operator: resident physician	72.4	73.6	2.7	0.37	32
all ages Test operator: attending physician	58.6	72.1	2.1	0.57	32
age 18-39y Test operator: resident physician	0.0 (0-98)	82.1	0	1.22	18
age 18-39y; Test operator: attending physician	0.0 (0-98)	87.5	0	1.14	12
age 40-59y; Test operator: resident physician	100.0 (40-100)	84.8	6.6	0.00	22
age 40-59y; Test operator: attending physician	50.0 (7-93)	80.4	2.6	0.62	22
age 60-79y; Test operator: resident physician	66.7 (35-90)	67.3	2	0.49	39
age 60-79y; Test operator: attending physician	66.7 (35-90)	55.1	1.5	0.60	49
age over 80y; Test operator: resident physician	75.0 (43-95)	60.8	1.9	0.41	46
age over 80y; Test operator: attending physician	58.3 (28-85)	64.7	1.7	0.64	40

4.4 Clinical Evidence Review: Automatic 12-lead ECG in diagnosing life threatening arrhythmias in people who may or may not have had a TLoC

4.4.1 Methods of the review - selection criteria

The following inclusion criteria were used for this review:

4.4.1.1 Types of participants

Adult patients, not necessarily restricted to those who have had a TLoC (indirect population).

4.4.1.2 The index test

Automated 12-lead ECG. Potential advantages of a fully automated system of measurement may include 100% reproducibility; however, such systems may not be able to recognise rarer T wave morphologies, resulting in inaccurate measurements, e.g. of QT dispersion.

4.4.1.3 The reference standard

Second stage diagnostic tests or follow up. In the absence of these, the GDG accepted clinician-read 12-lead ECG as a reference standard, recognising the limitations of this approach.

4.4.1.4 The target condition

Life threatening arrhythmias such as long QT syndrome, Torsade de Pointes, ventricular tachycardia, junctional rhythms, etc.

4.4.2 Description of studies

Fifty-seven studies were identified as being potentially relevant. Fifty studies were excluded: these are listed in Appendix F, along with reasons for exclusion.

Seven studies of diagnostic test accuracy were initially included in this review (Charbit 2006, Christov 2001, Denny 2007, Fatemi 2008, Hulting 1979, Kaneko 2005, Taha 2000). However, the GDG excluded Hulting (1979) because the technology had changed substantially since that time.

4.4.2.1 Study Design

Two studies were prospective (Charbit 2006, Fatemi 2008); three were retrospective (Christov 2001, Denny 2007 and Taha 2000) and one was unclear (Kaneko 2005). The prospective studies had a cross sectional design.

The number of patients in the prospective studies varied from 108 to 440, whilst the database population in the retrospective studies varied from 329 to 44,808.

4.4.2.2 Population

The inclusion and exclusion criteria for each of the studies are shown in Appendix D1.

The population and setting differed across studies.

- Three examined a more general population, at least partly using database records:
  - Denny (2007) used a database of 44,808 ECGs generated from all inpatients admitted for 2-30 days from 1999-2003.
  - Kaneko (2005) studied 97 ECGs from 27 patients with Brugada syndrome, plus 21,524 other ECGs (10,564 from population health checkups; 9740 from university hospital; 1220 CSE database)
  - Taha (2000) used a database of 4172 ECGs.
- One study examined patient database records from a cardiology department (Christov 2001)
  - this included 329 records from an annotated atrial flutter-fibrillation database: ECGs were collected routinely in a cardiology department and over 80% were abnormal. ECGs with intensive noise in V1 signals preventing accurate detection of P-wave onset and T-wave end were excluded.
- One study assessed patients admitted to a Coronary Care Unit (CCU)
  - In Fatemi (2008), 200 patients were admitted to a Coronary Care Unit (CCU) or a Cardiac Emergency Ward
- One study (Charbit 2006) assessed 108 patients (mean age 45 (SD 16) years; 57% female) in a recovery room after anaesthesia (mainly general anaesthesia); those with known cardiac arrhythmias or bundle branch block were excluded.

4.4.2.3 Index tests and Target conditions

- Two studies used a 12-lead ECG to record QT intervals (Charbit 2006; Denny 2007)
  - Charbit (2006) used a standard 12 lead ECG using Pagewriter M1770 (Hewlett Packard); corrected QTc was calculated using the Bazett or

Fridericia formula. The target condition was a prolonged QT interval (defined as over 450ms for women and 440ms for men).

- Denny (2007) used machine calculated QT intervals and heart rate (automated QT and QTc) to assess a QTc over 450ms versus probable or possible QT prolongation identified by cardiologist

- Two studies investigated atrial flutter or fibrillation (Christov 2001; Taha 2000)
  - Christov (2001) used an algorithm to calculate an 'atrial flutter/fibrillation parameter' (the mean value of the differentiated filtered and rectified signal); a threshold of 0.35% was used as the cut-off value to define a case. Atrial flutter/fibrillation was compared with a normal ECG
  - Taha (2000) used time-based criteria for detecting atrial flutter or fibrillation (each correctly classified) versus neither of these; no further details were given.
- One study investigated ST segment abnormalities defined as characteristic of Brugada syndrome (Kaneko 2005) in patients with Brugada syndrome (type 1 or 2 or 3) or having suspected Brugada type ECGs.
- The remaining study (Fatemi 2008) observed abnormal arrhythmias generally (see target condition below)
  - Fatemi (2008) used a 3-channel digital ECG device (GE industry of Germany) to assess ischaemic disorders (acute myocardial infarction/ischaemic heart disease); arrhythmias (premature atrial/ventricular contractions, atrial fibrillation, paroxysmal supraventricular tachycardia); structural disorders (enlarged atrium, ventricular hypertrophy); and conduction disorders (AV/bundle branch/sinoatrial block) in separate categories

4.4.2.4 Reference Standard

In all the studies the reference standard was interpretation by an expert clinician, although we note this is really only a comparative measure, not a true reference standard. In two studies a single clinician was used (Charbit 2006, Taha 2000). In the other studies a group of cardiologists were involved (Christov 2001, Denny 2007, Fatemi 2008, Kaneko 2005).

The following additional details were given:

- Charbit (2006) used ECGs analysed by one investigator, who was an anaesthetist and pharmacologist; RR and QT intervals were measured in the chest lead with the maximal T wave amplitude using a digitising pad (SummaSketch III Professional); QTc (Bazett or Fridericia) was averaged over 3-7 consecutive beats.
- Christov (2001) used atrial flutter-fibrillation records diagnosed and annotated by a group of cardiologists
- Denny (2007) used as the reference standard a cardiologist-generated free text impression (selected from stock phrases, or stock phrase edited by the cardiologist, or typed free text).

4.4.3 Methodological quality of included studies

Two studies were prospective (Charbit 2006, Fatemi 2008); three were retrospective (Christov 2001, Denny 2007 and Taha 2000) and one was unclear (Kaneko 2005).

Most of the studies included all eligible patients; although one study excluded patients with known cardiac arrhythmias or bundle branch block (Charbit 2006) and one study excluded ECGs with extensive noise (Christov 2001).

Outcome assessment was reported as blinded only in Fatemi (2008).

Full data were available for all participants with no attrition in any of the studies.

Studies of diagnostic test accuracy were assessed using QUADAS criteria (see Appendix D2). In all the studies, the population included was not representative of an unselected TLoC population, but some studies were less representative than others, notably the one carried out in a CCU (Fatemi 2008) and the study in the recovery room following anaesthesia (Charbit 2006). Apart from this, however, there were other methodological limitations for some studies:

- Denny (2007): the reference standard was unlikely to be independent of the index test and the cardiologist would not have been blinded to the results of that test
- Four studies were retrospective (Christov 2001, Denny 2007; Kaneko 2005 (unclear) Taha 2000)
- One study did not have an adequate reference standard: Charbit (2006) did not have a cardiologist as the assessor for clinician-read ECGs.

The overall QUADAS assessment of all the studies was "-" due to potentially non-representative patients, but the following studies were considered to be more at risk of bias than others: Charbit 2006, Denny 2007, Fatemi 2008, and these were treated with caution and considered in sensitivity analyses.

4.4.4 Results

The various papers included in the review used different algorithms for automatic reading of ECGs, looking for different target conditions.

4.4.4.1 Prolonged QT target condition

Two low quality studies looked for a prolonged QT interval (Charbit 2006, Denny 2007). The QT interval needs to be corrected for heart rate, and this can be done using different formulae such as the Bazett formula (QT_{cb} = $QT/\sqrt{RR}$) or the Fridericia formula (QT_{cf} = $QT/\sqrt[3]{RR}$). One of the studies (Charbit 2006) assessed prolonged QT using both these formulae in separate analyses; the other study (Denny 2007) did not state how the QT was corrected. Figure 4.2 shows the forest plot for sensitivity and specificity, and Figure 4.3 the ROC curve.

Figure 4.2: long QT interval

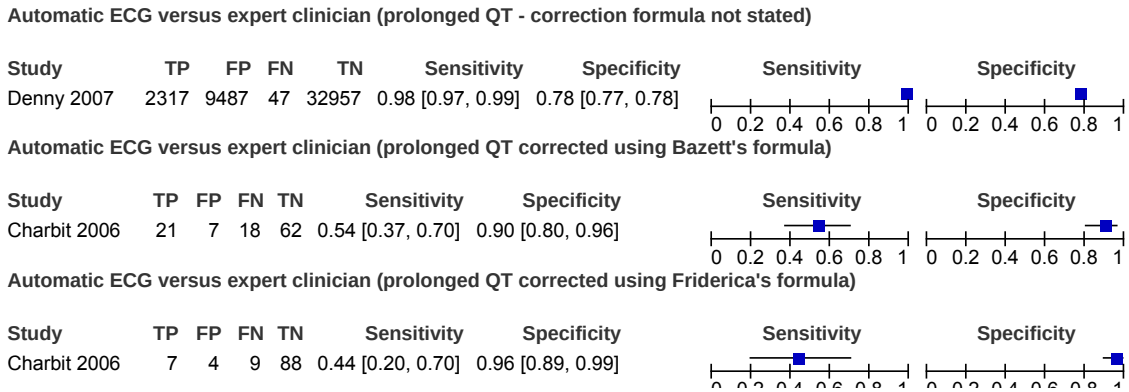
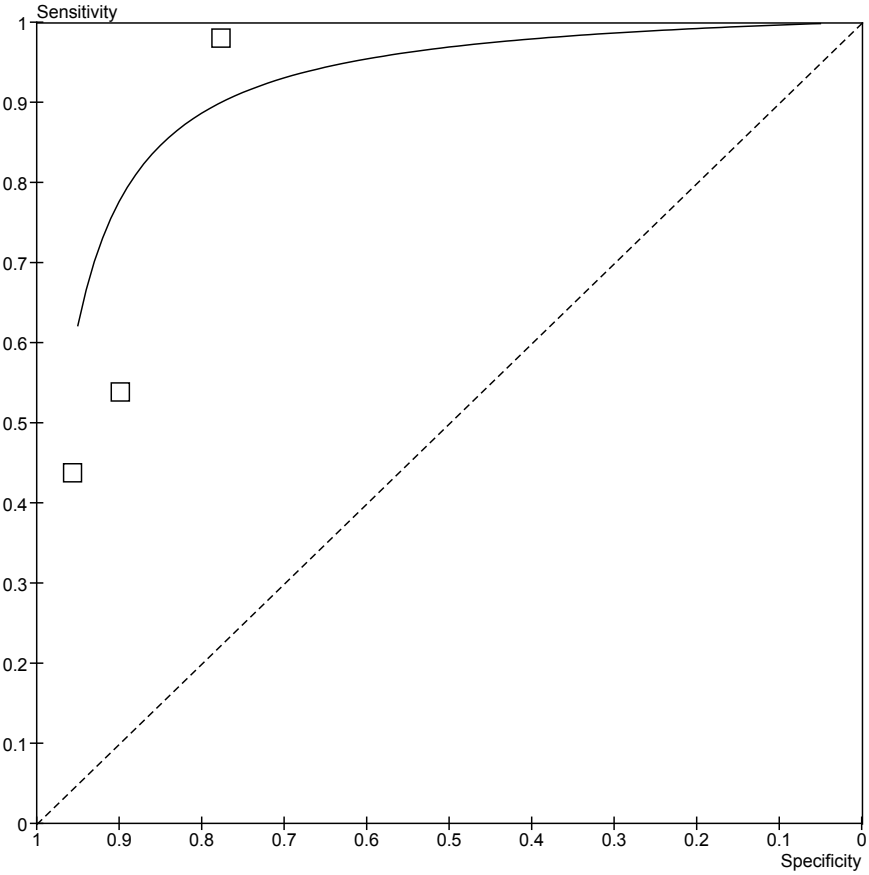


Figure 4.3. ROC curve for long QT interval

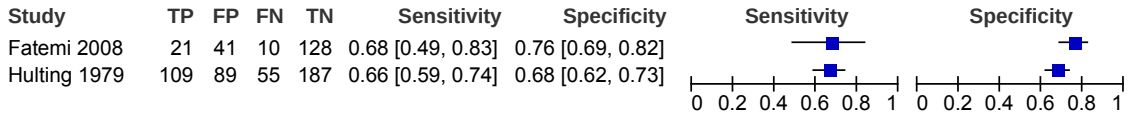


4.4.4.2 Arrhythmias (several) as the target condition

One study (Fatemi 2008) carried out in a CCU (i.e. unrepresentative) assessed arrhythmias. This study included in the definition of arrhythmia the

following conditions: premature atrial or ventricular contractions, atrial fibrillation, paroxysmal supraventricular tachycardia. Figure 4.4 shows the forest plot for sensitivity and specificity.

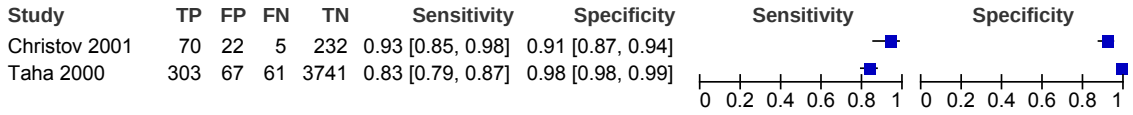
Figure 4.4: arrhythmias (several) as target condition



4.4.4.3 Specific arrhythmias: atrial flutter or fibrillation

Two retrospective studies assessed the ability of the automatic system to correctly identify atrial flutter and fibrillation (i.e. each had to be correctly classified, not one outcome category including either diagnosis): Christov (2001) and Taha (2000). Figure 4.5 shows the forest plot for sensitivity and specificity.

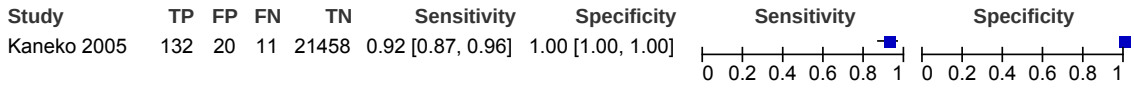
Figure 4.5: specific arrhythmias as target condition: atrial fibrillation/flutter



4.4.4.4 Specific arrhythmias: Brugada syndrome

One possibly retrospective study assessed the ability of an automatic system to identify Brugada syndrome (Kaneko 2005). Figure 4.6 shows the forest plot for sensitivity and specificity.

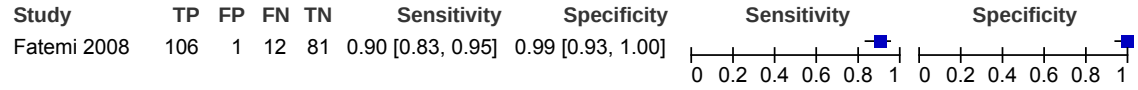
Figure 4.6: specific arrhythmias as target condition: Brugada syndrome



4.4.4.5 Myocardial infarction or ischaemia

One study carried out in a CCU (Fatemi 2008) assessed ischaemic patterns to the ECGs (acute myocardial infarction or ischaemic heart disease). Figure 4.7 shows the forest plot for sensitivity and specificity.

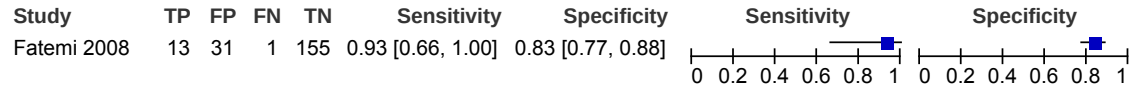
Figure 4.7: myocardial infarction or ischaemia as the target condition



4.4.4.6 Structural disorders

One study carried out in a CCU (Fatemi 2008) assessed structural disorders (enlarged atrium, ventricular hypertrophy). Figure 4.8 shows the forest plot for sensitivity and specificity.

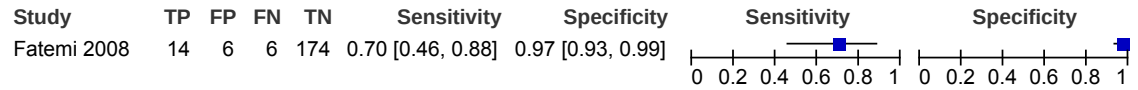
Figure 4.8: Structural disorders as target condition



4.4.4.7 Conduction disorders as the target condition

One study carried out in CCU (Fatemi 2008) assessed conduction disorders (atrioventricular block, bundle branch block, sinoatrial block). Figure 4.9 shows the forest plot for sensitivity and specificity.

Figure 4.9: conduction disorders



4.4.4.8 Overall summary: diagnostic test accuracy studies

Full diagnostic test accuracy statistics are given in Appendix D3, with sensitivity, specificity likelihood ratios and pre- and post-test probabilities being summarised in Table 20 for each of these studies. It should be recalled that the comparison is with expert clinician interpretation, so the post test probability, for example, is a measure of the number identified of those determined by the expert, and not necessarily the proportion of those who are diagnosed.

Table 20: Summary of diagnostic test accuracy statistics

	Sens	Spec	LR+	LR-	pre test prob	post test prob +ve	post test prob -ve
Target condition: long QT							
Charbit 2006 Fridericia formula long QT	43.8	95.7	10.1	0.59	14.8	63.6	9.3
Charbit 2006 Bazett formula long QT	53.8	89.9	5.3	0.51	36.1	75.0	22.5
Denny 2007; long QT	98.0	77.6	4.4	0.03	5.3	19.6	0.1
Target condition: arrhythmias							
Fatemi 2008	67.7	75.7	2.8	0.43	15.5	33.9	7.2
Target condition: atrial flutter/fibrillation							
Christov 2001	93.3	91.3	10.8	0.07	22.8	76.1	2.1
Taha 2000	83.2	98.2	47.3	0.17	8.7	81.9	1.6
Target condition: Brugada syndrome							
Kaneko 2005 automatic examination 1	93.3	99.7	NA	0.07	0.70	69.7	0.00
Kaneko 2005 automatic examination 2	88.4	99.9	NA	0.12	0.60	85.9	0.1
Kaneko 2005 automatic examination 3	92.3	99.9	NA	0.08	0.70	86.8	0.1
Target condition: cardiac abnormalities							
Fatemi 2008 conductive disorders	70.0	96.7	21	0.31	10.0	70.00	3.3
Fatemi 2008 structural disorders	92.9	83.3	5.6	0.09	7.0	29.50	0.6
Fatemi 2008 acute MI or IHD	89.8	98.8	73.7	0.10	59.0	99.10	12.9

4.5 Clinical evidence review: Correlation between automatic and manual determination of heart rate, PR interval, QT and QTc intervals in a TLoC population

4.5.1 Description of Studies

The GDG also considered an unpublished report of a study conducted by one of its members.

This UK-based, prospective study was carried out in a highly selected population: adults with long standing difficult to control epilepsy and learning disabilities. It is noted that, in the Long QT Registry, 6% of patients with the Congenital Long QT syndrome presented with seizures and prolongation of the QT interval by antiepileptic drugs is a matter for concern to clinicians. In

addition, retrospective data from patients referred to the Manchester Heart Centre by neurologists and who underwent a loop recorder implantation between 1996 and 2006, revealed that 1 in 8 patients with epilepsy were misdiagnosed and that the true diagnosis was syncope.

This report focuses on the correlation between automatic and manual determination of heart rate, PR interval, QT and QTc intervals on an ECG. Manual reading of ECG's was undertaken by cardiologists from a tertiary care centre in the UK.

Results have been reported as mean±SD, median and range. The 't test' was used to compare means. Spearman's correlation was used to correlate measured values and the Bland-Altman Test was used for calculating the Limits of Agreement. GraphPad Prism was the statistical package used for analysis.

4.5.2 Results:

A 12 lead ECG was undertaken in 214 patients during the study period. The mean age of the population was 38.1±17.6 years, (median: 33.5, range: 17-83). Sixty four percent (136/214) were male. The mean duration of epilepsy was: 33.5±17.7 years (median: 33, range: 2-73). Patients were on a mean of 4.94±2.8 (median: 4, range: 0-15) antiepileptic drugs. Sixty percent of the ECG's showed some abnormality.

4.5.2.1 Correlation of Automatic versus Manual Interpretation of ECG's:

(i) Heart Rate:

The mean heart rate calculated automatically was 79.8±13.2 beats/minute which did not differ significantly from that obtained manually i.e. 79.1±13.5 beats/minute, p=ns. There was good correlation between the results by the two methods (r=0.962). The two tests varied in their results by -6.4 to +7.5 beats/minute by the Bland-Altman test.

(ii) PR Interval:

The mean PR interval calculated automatically was 153±23.3 ms which was statistically significantly different from that obtained manually i.e. 158±21.4 ms, p=0.014. Still there was reasonably good correlation between the results by the two methods (r=0.59), with a variation in the observed results of -42.0 to +32.2 ms (Bland-Altman Test).

(iii) QT Interval:

The mean QT interval measured automatically by the machine was 354±29.8 ms, which did not differ statistically from that calculated manually i.e. 356±30.9 ms, p=ns. There was good correlation between the two methods (r=0.74), the values between the two methods varying by -43.6 to +39.1 ms (Bland-Altman Test).

QTc Interval:

There was no statistically significant difference between the two methods in the calculation of the mean QTc (Automatic: 404±26.2 ms versus 406±28.6 ms, p=ns). The correlation between the two methods was weaker than with the QT interval but nevertheless statistically significant (r=0.57). The variation in the calculation of the QTc between the two methods was -52.1 to +48.2 ms (Bland-Altman Method).

4.5.3 Discussion:

There was a discussion about the different methods of QT/QTc calculation and their accuracy. It was recognized that automatic calculation of QT/QTc uses various linear methods while manual calculation was done using the Bazett's formula. The limitations of the different methods were also discussed. Usually, automatically calculated QT/QTc's are longer, though their accuracy in the face of abnormal T waves was uncertain. It was also discussed that that there was a variation in the QT/QTc interval dependent on sex, age, and the time of the day /night when it was measured.

4.6 Health Economics

There were no papers identified that considered the cost-effectiveness of including a 12-lead ECG within the initial assessment. The NHS reference cost for a 12-lead ECG through direct access diagnostic testing is £33 (IQR £19-43) [NHS reference costs 07/08 for DA01]. This is likely to reflect accurately the cost incurred when a referral for 12-lead ECG is requested for a patient who presents to primary care having experienced a TLoC. However the cost of administering a 12-lead ECG as part of a spell of outpatient or ED care is likely to be less than this. NHS reference costs for ED are categorised according to the dominant investigation and the dominant treatment. 12-lead ECG is considered to be a category 1 investigation. If the treatment consists of nothing more complicated that verbal/written advice, then a category 1 investigation, such as ECG, would push the spell into the next cost category (from VB11Z to VB09Z, **Error! Reference source not found.** for details) increasing the cost of the spell by £20. However, simple measures such as vital sign recording are regarded as category 1 treatment and therefore the ECG would not add any further cost. If the patient requires treatment for any injury sustained, then these costs are likely to outweigh the costs of an ECG. For example, a bandage or wound cleaning would push the spell into the VB09Z category. Therefore the cost of providing an ECG within an A&E setting is likely to be fall between zero and £20.

Table 21: 12 Lead ECG

HRG code	Cost, £ (interquartile range)	Number of Finished Consultant Episodes (FCEs)
DA01 Direct Access ECG [12 lead]	33 (19 – 43)	197,527
VB09Z Not leading to admitted;cat 1 invest with cat 1-2 treat (allows for ECG, observation, vital sign recording, IV cannula, guidance/advice)	78 (66 – 88)	2,277,177
VB11Z Not leading to admitted: no sign treatment or investigation e.g no ECG, guidance/advice is only treatment	58 (39 – 71)	3,122,898
Cost attributable to ECG	VB09Z- VB11Z = 20	

The costs of different types of ECG screening to identify people with AF in a primary care setting are provided by Hobbs et al (Hobbs 2005). These are UK NHS costs for a primary care based ECG screening program using data gathered from an RCT. The estimated costs include materials, equipment and clinical time to administer and interpret the ECG as well as the costs of administrating a screening program (e.g letters to invite patients etc) so they are likely to overestimate the costs of using 12-lead ECGs in a TLoC population. Even including the costs of administering the screening program, the cost per patient screened with 12 lead ECG was £14.20, £14.85, £16.03, £16.25, when interpreted by computerised decision support software, a nurse, a GP or a consultant respectively. Uplifting these costs to reflect price increases from 2003 to 2008 gives a cost of £20 for an ECG interpreted by a consultant. This suggests that the reference costs may slightly overestimate the opportunity cost of 12-lead ECG testing. Given the low cost attributed to 12-lead ECG testing in comparison to other tests being considered within the guideline, this area was not prioritised for further economic modeling.

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4.7 Evidence Statements

4.7.1 12-lead ECG as a test for adverse events

4.7.1.1 Diagnostic test accuracy of 12-lead ECG in the emergency department

There was moderate-quality evidence to show:

- Moderate sensitivity and specificity (66 and 73%) for 12-lead ECG as a predictor of all adverse events at 7 days
- Moderate values (72 and 74%, respectively) for death and cardiac outcomes at 14 days
- Moderate sensitivity and specificity for death at 12 months (61 and 74% respectively)
- Diagnostic yields around 30%
- Pre-test and post-test probabilities of 10-12% to 24-26%

This compares with the sensitivity and specificity for death and cardiac events at 7 days for the San Francisco Syncope Rule of 74-96% and 57-62% respectively; and 59-100% and 42-100% respectively for the diagnosis of cardiac syncope.

4.7.1.2 Dependence on age of diagnostic test accuracy of 12-lead ECG

There was moderate-quality evidence to show a peak in the sensitivity with age at the group 40 - 59 years, and a decrease with age (from 18 – 39 years to age over 80 years) in the specificity of 12-lead ECG for the adverse outcomes of death and cardiac events at 14 days.

4.7.1.3 Dependence on the physician interpreting the ECG test

There was limited evidence to suggest there may have been a decreased sensitivity of ECG for detecting death and cardiac events at 14 days when the attending physician (ED consultant) read the ECG compared with the resident physician of 2 to 4 years, although there was much imprecision.

4.7.1.4 Automated ECG interpretation versus clinician-read ECG

There was low-quality evidence in a non-TLoC population that showed a large variation between studies in the test accuracy of automated ECG interpretation compared with expert-clinician-read ECGs for recognition of a long QT interval: sensitivity (43 to 98%) and specificity (78 to 96%).

There was low-quality evidence in a non-TLoC population that showed moderate sensitivity (68%) and specificity (76%) for automated ECG interpretation compared with expert-clinician-read ECGs for the detection of premature atrial or ventricular contractions, atrial fibrillation, paroxysmal supraventricular tachycardia.

There was low-quality evidence in a non-TLoC population that showed high sensitivity and specificity for automated ECG interpretation compared with expert-clinician-read ECGs for the following:

- Detection of atrial fibrillation (93% sensitivity and 91% specificity)
- Brugada Syndrome (92% and 100%)
- Myocardial infarction or ischaemia (90 and 99%)

- Structural disorders (enlarged atrium, ventricular hypertrophy); 93 and 83%

There was low-quality evidence in a non-TLoC population that showed moderate sensitivity (70%) and high specificity (97%) for automated ECG interpretation compared with expert-clinician-read ECGs for the diagnosis of conduction disorders.

4.8 Evidence to recommendations

4.8.1 12-lead ECG – items to be assessed and recorded

All of the items in the list for Recommendation 1.1.2.3 came from the evidence, mainly from the studies described in chapter 3 (Appendix D1) and these were examined carefully by the GDG. For recommendations 1.1.2.2 and 1.1.2.3, the GDG focussed on the review evidence on the usefulness of 12-lead ECG for identifying people at risk of death or serious adverse events.

Quality of the evidence

The GDG took into consideration the following evidence:

- The moderate-quality evidence, for the TLoC population, of diagnostic test accuracy statistics for 12-lead ECG as a single test to predict serious adverse events
- The moderate-quality evidence, for the TLoC population, from a single study on the effect of patient age on diagnostic test accuracy of 12-lead ECG
- The limited evidence, for the TLoC population, for the effect on diagnostic test accuracy of the clinician reading the 12-lead ECG
- The low-quality evidence, in an indirect population (no TLoC), comparing automated ECG reports and clinician-read ECGs
- The low-quality evidence from one unpublished study in an epilepsy population

GDG discussion

The GDG noted that, for the better quality studies, the 12-lead ECG was moderately sensitive (61 -72%) and specific (73 – 74%) for predicting serious adverse events. This compared with the sensitivity and specificity for death and cardiac events at 7 days for the San Francisco Syncope Rule of 74-96% and 57-62% respectively. The GDG concluded that 12-lead ECG was very important for predicting adverse events, and particularly so in primary care settings, acknowledging that its accuracy was improved if the analysis (automated or by a competent healthcare professional) is used in conjunction with other initial symptoms and signs. The 12-lead ECG has been associated with some adverse effects: the GDG advised that some people have allergic reactions to the electrodes; some people have to be shaved to allow electrode application to the chest and this could upset some people and, very rarely, causes cuts or abrasions. Furthermore, incorrect electrode connection leading to mis-interpretation of ECG evidence and inappropriate treatment is relatively common. Despite this, the test is already used in many clinical contexts and its cost is low.

The GDG considered the likely balance of costs, benefits and harms and determined that 12-lead ECG is likely to be cost-effective given the low cost and the sensitivity and specificity of the test for identifying patients who are at risk of serious adverse events.

The GDG decided that there was insufficient evidence to support restricting the 12-lead ECG test to particular age groups, and recommended that everyone with a TLoC should have a 12-lead ECG. They were concerned that conditions predisposing to life-threatening arrhythmias could be missed in young people if the test was not carried out. The GDG also made a research recommendation to investigate the usefulness of a 12-lead ECG in people who are considered to have had an uncomplicated faint on the basis of clinical history and examination.

The evidence for automated interpretation versus clinician-read ECGs was low quality, and was in a non-TLoC indirect population, but it did suggest that

automated interpretation lacked sensitivity in detecting long QT (around 50%). The GDG observed that automatically-calculated QT/QTc intervals may be over-estimated, and that their accuracy in the presence of U waves and of abnormal T waves was uncertain. The GDG noted that different ECG recorders used different algorithms for automated interpretation, so the accuracy of interpretation may vary according to the manufacturer. The GDG noted also that good quality recordings are required for accurate ECG interpretation and that artefacts due to poor recording technique are a potential source of error in ECG interpretation, both automated and by clinicians. The GDG also made a research recommendation to compare automated and expert ECG interpretation in the TLoC population

The GDG considered whether serial ECGs would be helpful, and noted that, in some patients, conduction abnormalities and other arrhythmias that cause TLoC are often paroxysmal so that serial recordings are crucial. On the other hand, in some people serial recordings would not necessarily add anything to the diagnosis. Therefore, the GDG decided to make a research recommendation on the usefulness of serial ECGs.

The GDG was keen to emphasise that ECG findings should be interpreted in full clinical context, including the detailed clinical and family history and physical signs, in order to make a full diagnosis, especially in conditions predisposing to life-threatening arrhythmias (such as the long QT syndromes and Brugada syndrome), in which the GDG was aware that a single ECG may give false negative evidence.

The GDG also took into consideration the very low quality evidence that clinicans who were not regularly intepreting ECG traces were less accurate than those who were experienced in this interpretation. This accorded with the GDG's experience, and their view was that an automated interpretation would probably be more accurate than interpretation by a non-specialist. Therefore, the GDG recommended that an automated interpretation of the ECG should be used where available and that any abnormality identified should be interpreted with the advice of an expert (recommendation 1.1.2.2). If an

automated interpretation was not available the GDG recommended that the ECG be reported by a person able to indentify a defined set of abnormalities.

The list of abnormalities was produced by the cardiology specialists on the GDG, using descriptions of abnormalities given in several studies included in the evidence reviews. The GDG discussed their definition of what constituted long QT syndrome and whether there should be a different value used for men and women. The decision reached was to use the same value for both in order to give a simpler recommendation. This is widely acknowledged in the specialist literature as a QT interval that measures between 350mm – 440 mm on a standard ECG recording. The GDG noted that some clinicians also use the QTc interval and observed that although it has some potential limitations, particularly at slower heart rates, it may have some clinical value.

4.9 Recommendations

Hyperlink to recommendations Section 1.1.2 - History-taking, clinical examination, 12-lead electrocardiogram (ECG) and other tests for people who have experienced TLoC

5 Specialist assessment and diagnosis

5.1 Clinical Question

In people who have experienced a TLoC, which diagnostic tests should be performed, both in an unselected population and in specified subgroups (e.g. suspected syncope, epilepsy or psychogenic non-epileptic seizures).

5.2 Introduction

This chapter investigates the value of further diagnostic tests for people who do not have a firm diagnosis following the initial assessment stage, i.e. those who do not definitely have orthostatic hypotension, an uncomplicated faint, or definite seizures. Instead the chapter is concerned with diagnosis of the causes of syncope for the following groups of people, those with:

- Suspected cardiac arrhythmic cause (including those requiring urgent investigation)
- Suspected NM syncope (cardioinhibitory; vasodepressor or mixed)
- Unexplained TLoC (which may include possible psychogenic seizures and possible epileptic seizures).

This chapter is concerned with which diagnostic tests are the most useful and cost effective for diagnosing the likely causes of syncope in these populations. We also consider which tests are the most useful and cost effective for directing the use of a pacemaker for people with neurally mediated syncope.

The diagnostic tests described are based on two main mechanisms: investigating what happens when TLoC is induced (tilt test, carotid sinus massage, exercise test) or when TLoC occurs spontaneously (ambulatory ECG). Each test considers symptom correlation for the TLoC event, with a view to detecting arrhythmias indicating a cardiac cause (bradycardia or tachycardia), and/or NM syncope with a cardioinhibitory response (bradycardia or asystole).

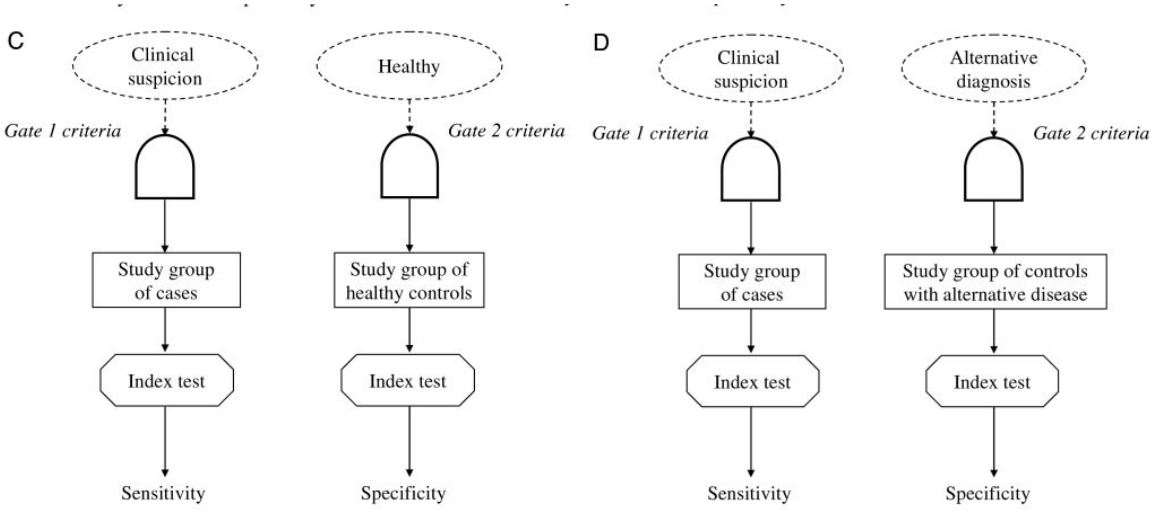
Each test records an ECG as part of the test. This may be the test itself (e.g. ambulatory ECG) or it may be supplementary information (e.g. as recorded during a tilt test). The type of rhythm found during TLoC, including normal rhythm, gives useful information, and arrhythmias in the absence of TLoC can also aid diagnosis.

For many of these second stage reviews of diagnostic test accuracy, there is difficulty in defining a reference standard. The studies have considered this in various ways:

- Some studies have used a case-control design; e.g. ‘cases’ are those suspected of having neurally mediated (NM) syncope on the basis of prior tests, history and examination, and ‘controls’ are those who are not suspected of having NM syncope - and often these people did not have TLoC at all.
- Some studies state that the reference standard is the same as the index test (e.g. ambulatory ECG) and so record only the diagnostic yield (see below)
- Some studies choose another test as the reference standard, but this is unlikely to be the best reference

The diagnostic yield is usually defined as the number of positive results as a proportion of the total number of patients, but this definition may vary (see the ambulatory ECG review, section 5.3).

For several of the reviews in this chapter, the reference standard, as defined by the GDG, is the diagnosis of an expert clinician. However, in many studies (e.g. those in the tilt test review), the study design was a case-control 2-gate approach (represented by C in the figure below).



The expert clinician diagnosis reference standard is based on prior tests defining certain individuals as ’patients‘ (i.e. with NM syncope) and ‘controls’ mainly as those without any syncope.

In terms of the population for the guideline (people with TLoC) and the purpose of the test (differentiating one form of syncope from another), the spectrum of patients in these studies is not representative, and this is liable to lead to risk of bias, e.g. inclusion of patients with NM syncope following a range of prior tests will probably generate fewer false negative test results than the inclusion of patients with a range of suspicion of NM syncope. In addition, healthy volunteers are less likely to have alternative diagnoses that will generate false positive results. Thus the representativeness of the patients in the studies is necessarily inadequate.

In case-control studies the sensitivity can be equated to the diagnostic yield in the population defined by the cases.

5.3 Clinical Evidence Review: ambulatory ECG following initial assessment for people with (i) a suspected arrhythmic cause of syncope; (ii) with unexplained syncope and (iii) with suspected neurally mediated syncope

5.3.1 Introduction

Ambulatory ECGs are used to monitor patients over a period of at least 24-hours for arrhythmias and signs of structural heart disease. The benefit of ambulatory devices is that many arrhythmias are not present all the time and a longer period of monitoring (compared with a single resting ECG) increases the chances of discovering irregularities, leading to diagnosis. People who have had a TLoC are likely to have arrhythmias that are related to cardiac conditions or those that are an indication of cardioinhibitory neurally mediated syncope (typically manifested as bradycardia and asystole longer than 3 seconds).

Once one or more arrhythmias have been detected in a patient, the particular cause of TLoC can be more easily ascertained, leading to further diagnostic work-up and/or treatment.

The ability of a particular ECG device to detect arrhythmias in a particular patient is expected to depend on the frequency of their episodes of TLoC and features of the monitoring device. The latter includes the duration of monitoring and how the device is triggered. The GDG subdivided the frequency of TLoC episodes into: highly frequent (daily or every few days), frequent (every week or two) and infrequent (several weeks or months between events).

This review considers three types of ambulatory ECG recorder: the Holter monitor, an external event recorder and an implantable event recorder.

- The Holter monitor records the person's ECG continuously for 24 or 48 hours, providing various types of information, including rhythms (normal or abnormal) during TLoC and abnormal rhythms not during TLoC.
- External event recorders (EER) are of two types, one of which is worn continuously by the person and is activated by them, and one which is used only if the person activates it after placing it on their chest. This review is concerned only with the former device, which records the ECG continuously until the device is activated by the person when they have symptoms, at which time the ECG recording is 'frozen' for analysis. Typically, the EER is in place for two to four weeks.
- The implantable event recorder (IER) is a continuous ECG recorder that is implanted in the body under the skin. The patient or a bystander uses a small hand-held activator to communicate through the skin with the IER to 'freeze' the ECG trace associated with an event. Minimally invasive subcutaneous placement of the IER in the chest area can be performed with local anaesthesia.

Both the EER and the IER devices may have an automatic feature, in which case they can be automatically activated by events (e.g. set to detect asystole more than 3 seconds) and programmed to save the rhythm for a certain period before and after the trigger.

Section 5.3 examines the usefulness of various types of ambulatory ECG device in detecting any type of relevant arrhythmia in patients with different possible causes of TLoC.

5.3.2 Methods of the review – selection criteria

The GDG was interested in two reviews of diagnostic test accuracy, which varied according to the patient population. For these reviews the inclusion criteria were:

5.3.2.1 ***Population***

There were to be two populations, which defined the separate reviews:

- Those in whom a cardiac arrhythmia is a suspected, but not definitive, cause of TLoC after the initial assessment (12-lead ECG normal or any

identified abnormality not likely to be the cause of TLoC). This would include patients with structural heart disease or a past history of arrhythmias, but who do not have any resting ECG abnormalities at the time of measurement (post TLoC).

- Those in whom there is a history of recurrent syncope which remains unexplained after the initial assessment (12-lead ECG normal or any identified abnormality not likely to be the cause of TLoC). This would exclude patients who have a positive diagnosis of cardiac causes of syncope or orthostatic hypotension on the basis of initial tests or neurally mediated syncope on the basis of patient history. The GDG defined 'recurrent' as occurring more than once.

5.3.2.2 Index and comparator tests

The index test was to be any ambulatory ECG method, including Holter monitors, external event recorders (continuously placed), and implantable event recorders. Studies were to be included if they compared two or more tests or if they only investigated one test.

5.3.2.3 Target condition

- The target condition was originally defined to be arrhythmias as follows:
  - Sinus node disease
  - AV block
  - Pacemaker malfunction
  - Drug-induced
- Tachyarrhythmias
  - Ventricular tachycardia
  - Torsades de pointes
  - Supraventricular tachycardia

5.3.2.4 Reference Standard

This review examined ambulatory ECG for the detection of arrhythmias, and for this the reference standard is abnormalities on an ECG (i.e. the same as is measured in the index test).

5.3.2.5 Outcomes

The reference standard is the same as the index test. Therefore, sensitivity and specificity are not appropriate outcome measures and what can be determined is how likely it is that the test captures an event, i.e. the diagnostic yield.

The following test outcomes were to be recorded:

- Number of patients with no TLoC during ambulatory ECG
- Number of patients with an ECG showing normal rhythm and rate during TLoC
- Number of patients with an ECG showing arrhythmia recorded during TLoC
- Number of patients with an arrhythmia recorded but not during TLoC
- Number of patients with no ECG recorded during TLoC (technology failed)

The following outcomes were also to be reported:

- Number of patients started on therapy
- Time to first recurrence
- Proportion of all arrhythmias found that are bradyarrhythmias
  - Arrhythmias during TLoC
  - Arrhythmias not during TLoC
  - Any arrhythmias detected
- Adverse events
- Number of patients who died

The GDG observed that the outcome, number of people with no TLoC during recording, was related only to the population (i.e. frequency of TLoC) and the duration of recording. It was not dependent on the nature of the device, or on how the ECG is interpreted. The outcome, number of people with normal rhythm during TLoC, is also related to population characteristics; and the number with abnormal rhythm during TLoC is related both to population characteristics and the device used for recording arrhythmias. The outcomes

were to be considered in the above order to build up an understanding of the evidence.

5.3.2.6 Sensitivity analyses

Sensitivity analyses were to be carried out according to the types of arrhythmias recorded. For this purpose, the GDG defined which arrhythmias were most appropriate to enable a diagnosis of the cause of syncope. These were:

- Symptom correlation (any arrhythmia)
- Complete AV block or sustained VT not connected with symptoms
- Asystole greater than 3 seconds even if there were no symptoms

Studies reporting non-sustained VT without symptoms were regarded as at risk of bias.

Where possible, we extracted data on the number of people with arrhythmias in the above list, but when these were not reported separately from other arrhythmias, the studies were considered to have a mixture of 'good' and 'bad' arrhythmias and the studies were considered in sensitivity analyses. The different types of arrhythmias recorded in each study are given in Appendix D1 and the proportion of bradycardias noted.

5.3.2.7 Subgroup analyses

If there was heterogeneity amongst studies, the GDG identified *a-priori* subgroup analyses that were to be carried out to try to explain the heterogeneity:

- Over 65 years versus under 65 years
- Over 35 years versus under 35 years (category for young sudden cardiac deaths)
- Gender (heart disease more common in men and neurally mediated syncope more common in women).
- Frequency of events (e.g. events per month): highly frequent TLoC (daily or every few days; more than 50/year); versus frequent (every week or two;

25-50/year) versus infrequent (several weeks or months between events; 1-24 events/year).

- The test duration (e.g. less than 6 months; 6 to 12 months; more than 12 months for IERs)
- The product of duration of recording in time units multiplied by frequency of TLoC (number per time unit), e.g. Holter 48-hour and frequency 104/year: 2 (days) x 104/365 days = 0.55; subgroups of (a) less than 0.1; (b) 0.1 to 0.99; (c) 1 to 10; (d) more than 10.
- Patient activation versus patient plus automatic activation
- Year of study (older devices in earlier studies), i.e. generation of devices (digital versus tape)
- Funding – whether the company making the device was directly involved in the research (e.g. name on publication) or grant to university/free devices – declaration of whether restricted or unrestricted/conflict of interest statement).

5.3.3 Description of studies

We initially evaluated 200 papers for inclusion: 148 studies were excluded. Details are given in Appendix F with reasons for exclusion. In November 2009, an update search was carried out. This identified a further 49 papers that were evaluated, of which one was included (Kabra 2009).

Fifty-two studies were included (Aronow 1993; Arya 2005; Ashby 2002; Boersma 2004; Boudoulas 1979; Boudoulas 1983; Brembilla-Perrot 2001; Brembilla-Perrot 2004a; Brembilla-Perrot 2004b; Brignole 2001; Brignole 2005; Brignole 2006; Comolli 1993; Cumbee 1990; Deharo 2006; Donateo 2003; Farwell 2006; Fitchet 2003; Fogel 1997; Garcia-Civera 2005; Gibson 1984; Kabra 2009; Kapoor 1991; Krahn 1998; Krahn 1999; Krahn 2000; Krahn 2001; Krahn 2002; Krahn 2004; Kuhne 2007; Lacroix 1981; Linzer 1990; Lombardi 2005; Mason 2003; Menozzi 2002; Morrison 1997; Moya 2001a; Moya 2001b; Nierop 2000; Pezawas 2007; Pierre 2008; Porterfield 1999; Ringqvist 1989; Rockx 2005; Rothman 2007; Sarasin 2001a; Sarasin

2001b; Sarasin 2005; Saxon 1990; Schernthaner 2008; Schuchert 2003; Seidl 2000; Zeldis 1980).

5.3.3.1 Study Design

Four studies comparing different tests were included, three were RCTs (Farwell 2003; Krahn 2001; Rockx 2005) and one was a non-randomised comparative study (Krahn 2000). The rest of the studies were case series, although the Fitchet (2003) study compared tilt test and Holter monitoring in the same patients in a prospective way.

Eleven studies (Ashby 2002; Cumbee 1990; Gibson 1984; Kabra 2009; Krahn 2000; Kuhne 2007; Mason 2003; Morrison 1997; Porterfield 1999; Schernthaner 2008; Zeldis 1980) were retrospective and the rest were prospective.

The studies were conducted in various countries:

- 2 in the UK (Farwell 2006; Fitchet 2003)
- 15 in the USA (Aronow 1993; Boudoulas 1979; Boudoulas 1983; Cumbee 1990; Fogel 1997; Gibson 1984; Kabra 2009; Kapoor 1991; Linzer 1990; Mason 2003; Morrison 1997; Porterfield 1999; Rothman 2007; Saxon 1990; Zeldis 1980)
- 9 multinational (Boersma 2004; Brignole 2001; Brignole 2006b; Krahn 1999; Krahn 2002; Menozzi 2002; Moya 2001a; Moya 2001b; Seidl 2000)
- 6 in Canada (Krahn 1998; Krahn 2000; Krahn 2001; Krahn 2004; Lacroix 1981; Rockx 2005),

The rest were carried out in other countries.

Four studies received some funding from Medtronic, the manufacturers of the Reveal Plus implantable event recorder (Brignole 2006b; Farwell 2006; Mason 2003; Pierre 2008) and one (Rothman 2007) had funding from Cardionet, the manufacturers of the mobile cardiac outpatient telemetry system. Eleven studies were funded by educational foundations (Boersma 2004; Boudoulas 1979; Cumbee 1990; Krahn 1998; Krahn 1999; Krahn 2000; Krahn 2001;

Krahn 2002; Krahn 2004; Linzer 1990; Rockx 2005); and the rest did not state a funding source.

The study size ranged from 25 to 1512 patients:

- 13 included studies had fewer than 50 patients (Ashby 2002; Arya 2005; Boersma 2004; Cumbee 1990; Deharo 2006; Donateo 2003; Krahn 1998; Lombardi 2005; Mason 2003; Menozzi 2002; Moya 2001; Nierop 2000; Schuchert 2003)
- 17 studies had more than 50, but fewer than 100 patients (Boudoulas 1983; Brembilla-Perrot 2004; Brignole 2001; Fogel 1997; Garcia-Civera 2005; Kabra 2009; Kapoor 1991; Krahn 1999; Krahn 2001; Krahn 2004; Linzer 1990; Morrison 1997; Moya 2001; Pezawas 2007; Pierre 2008; Ringqvist 1989; Schernthaner 2008)
- 23 studies had more than 100 patients (Aronow 1993; Boudoulas 1979; Brembilla-Perrot 2001; Brembilla-Perrot 2004; Brignole 2005; Brignole 2006; Comolli 1993; Farwell 2006; Fitchet 2003; Gibson 1984; Krahn 2000; Krahn 2002; Kuhne 2007; Lacroix 1981; Porterfield 1999; Rockx 2005; Rothman 2007; Sarasin 2001a; Sarasin 2001b; Sarasin 2005; Saxon 1990; Seidl 2000; Zeldis 1980).
- Of the comparative studies, the number of patients per arm ranged from 30 to 103.

5.3.3.2 Population

Setting

The studies took place in various settings:

- 29 took place in cardiology departments of hospitals (Arya 2005; Boersma 2004; Boudoulas 1979; Boudoulas 1983; Brembilla- Perrot 2001; Brembilla-Perrot 2004a; Brembilla-Perrot 2004b; Brignole 2005; Brignole 2006; Cumbee 1990; Deharo 2006; Fitchet 2003; Fogel 1997; Garcia-Civera 2005; Gibson 1984; Kabra 2009; Krahn 1998; Krahn 2000; Krahn 2001; Krahn 2004; Kuhne 2007; Mason 2003; Nierop 2000; Pezawas 2007; Pierre 2008; Rockx 2005; Rothman 2007; Saxon 1990; Schernthaner 2008)

- 3 were in an emergency department setting (Morrison 1997; Sarasin 2001a; Sarasin 2001b)
- 19 were in a range of hospital departments (Aronow 1993; Brignole 2001; Comolli 1993; Donateo 2003; Farwell 2006; Kapoor 1991; Krahn 1999; Krahn 2002; Lacroix 1981; Linzer 1990; Lombardi 2005; Menozzi 2002; Moya 2001a; Moya 2001b; Ringqvist 1989; Sarasin 2005; Schuchert 2003; Seidl 2000; Zeldis 1980);
- 1 was in a blackout clinic or syncope unit (Ashby 2002)
- 1 did not state the setting (Porterfield 1999).

Further details are given in Appendix D1. The GDG regarded the emergency department patients as possibly representing a different population so that these studies were to be considered in sensitivity analyses.

Age and gender

The studies varied in the ages of patients included:

- 21 had adults with a mean age of 65 years or over (Aronow 1993; Ashby 2002; Brembilla-Perrot 2001; Brembilla-Perrot 2004a; Brignole 2001; Brignole 2005; Brignole 2006; Comolli 1993; Donateo 2003; Farwell 2006; Krahn 2001; Krahn 2004; Kuhne 2007; Menozzi 2002; Morrison 1997; Nierop 2000; Ringqvist 1989; Sarasin 2001a; Sarasin 2001b ; Sarasin 2005; Saxon 1990)
- 32 had a mean age 35 to 65 years (Arya 2005; Boudoulas 1979; Brembilla-Perrot 2004b; Boersma 2004; Cumbee 1990; Deharo 2006; Fitchet 2003; Fogel 1997; Garcia-Civera 2005; Kabra 2009; Kapoor 1991; Krahn 1998; Krahn 1999; Krahn 2000; Krahn 2002; Lacroix 1981; Linzer 1990; Lombardi 2005; Mason 2003; Moya 2001a; Moya 2001b; Pezawas 2007; Pierre 2008; Porterfield 1999; Rockx 2005; Rothman 2007; Sarasin 2001a; Sarasin 2001b; Schernthaner 2008; Schuchert 2003; Seidl 2000; Zeldis 1980).
- No studies had a mean age below 35 years
- 2 did not state the age range (Boudoulas 1983 and Gibson 1984).

No studies were carried out solely in female patients or solely in male patients. The proportion of male patients ranged from 30% to 89%. Ethnicity was not reported in any study.

Definitions of TLoC

The studies described TLoC in various ways:

- 11 reported that the patients had had a TLoC, defined as 'sudden transient loss of consciousness with inability to maintain postural tone and spontaneous recovery' (Aronow 1993; Cumbee 1990; Kapoor 1991; Krahn 1999; Kuhne 2007; Linzer 1990; Porterfield 1999; Sarasin 2001a; Sarasin 2001b; Sarasin 2005; Seidl 2000)
- 5 stated that the patients had 'syncope' without definition (Donateo 2003; Kabra 2009; Krahn 2001; Lombardi 2005; Pezawas 2007)
- 6 included patients with either syncope or near syncope (Ashby 2002; Boudoulas 1979; Fogel 1997; Krahn 2000; Rothman 2007; Rockx 2005). Patients with syncope or presyncope were counted as a single category.
- 2 defined TLoC as 'a short loss of consciousness' (Brembilla-Perrot 2004a; Brembilla-Perrot 2004b)
- One (Nierop 2000) defined TLoC as 'temporary and reversible loss of consciousness'
- One (Fitchet 2003) included patients with 'blackouts suggestive of vasovagal syncope'
- One (Saxon 1990) included patients with 'cerebral symptoms possibly due to cardiac arrhythmias (includes dizziness)'
- The rest stated that patients had had a TLoC but did not define it.

The Saxon (1990) study was treated with caution because the definition was not necessarily consistent with TLoC; this study was to be considered in sensitivity analyses.

Previous TLoC episodes and recurrence rates

Patients in the studies varied in their reporting of whether the patients had recurrent TLoC:

- 36 reported that patients had recurrent TLoC (Arya 2005; Ashby 2002; Boersma 2004; Brembilla-Perrot 2004a; Brembilla-Perrot 2004b; Brignole 2001; Brignole 2005; Brignole 2006; Cumbee 1990; Deharo 2006; Donateo 2003; Farwell 2006; Fitchet 2003; Garcia-Civera 2005; Kapoor 1991; Krahn 1998; Krahn 1999; Krahn 2001; Krahn 2002; Krahn 2004; Lacroix 1981; Linzer 1990; Lombardi 2005; Mason 2003; Menozzi 2002; Moya 2001a; Moya 2001b; Nierop 2000; Pezawas 2007; Pierre 2008; Ringqvist 1989; Rockx 2005; Sarasin 2005; Schernthaner 2008; Schuchert 2003; Seidl 2000)
  - The mean number of episodes ranged from 2.4 to 50, and across all studies the number of episodes ranged from 1 to 100
  - The median duration of TLoC, where reported, varied from 6.5 to 18 months, with a range of 0.02 to 60 years.
  - Sarasin (2005) reported that 52% patients had a single episode; Ringqvist (1989) had 35% patients and Krahn (2001) had 13% single episodes; Kapoor (1991) stated that 58% patients had multiple episodes, suggesting that the rest may have had single or 2 episodes
- 17 did not say if the TLoC was recurrent (Aronow 1993; Boudoulas 1979; Boudoulas 1983; Brembilla-Perrot 2001; Comolli 1993; Fogel 1997; Gibson 1984; Kabra 2009; Krahn 2000; Kuhne 2007; Morrison 1997; Porterfield 1999; Rothman 2007; Sarasin 2001a; Sarasin 2001b; Saxon 1990; Zeldis 1980).

Fourteen of the 37 studies reporting recurrent TLoC also gave the frequency of TLoC:

- 5-10 events per year: 6 studies (Boersma 2004; Deharo 2006; Krahn 1999; Nierop 2000; Schuchert 2003; Seidl 2000)

- 1-5 events per year: 8 studies (Cumbee 1990; Farwell 2006; Garcia-Civera 2005; Krahn 1988; Menozzi 2002; Moya 2001a; Moya 2001b; Schernthaner 2008)

Both these categories would be classified as infrequent. Further details are given in Appendix D1.

Prior tests

All studies except seven reported that the patients had received prior tests and these seven did not mention prior tests (Boudoulas 1979, Ermis 2003; Fitchet 2003; Gibson 1984; Krahn 2000; Kuhne 2007; Porterfield 1999). Of the studies reporting prior tests:

- 42 were considered to have performed an extensive set of prior tests (defined as including secondary tests such as 24-hour Holter monitoring, EER, EPS, tilt table, carotid sinus massage): Aronow 1993, Ashby 2002, Boersma 2004, Boudoulas 1983, Brembilla-Perrot 2001, Brembilla-Perrot 2004, Brignole 2001, Brignole 2005, Brignole 2006, Cumbee 1990, Deharo 2006, Donateo 2003, Farwell 2006, Fogel 1997, Garcia-Civera 2005, Kabra 2009; Kapoor 1991, Krahn 1998, Krahn 1999, Krahn 2001, Krahn 2002, Krahn 2004, Kuhne 2007, Lacroix 1981, Linzer 1990, Lombardi 2005, Mason 2003, Menozzi 2002, Morrison 1997, Moya 2001, Moya 2001b, Nierop 2000, Pezawas 2007, Pierre 2008, Rockx 2005, Rothman 2007, Sarasin 2001, Sarasin 2001b, Schernthaner 2008, Schuchert 2003, Seidl 2000, Zeldis 1980)
- Five were considered to have performed basic prior tests (history and 12-lead ECG only: Arya 2005, Comolli 1993, Ringqvist 1989, Sarasin 2005, Saxon 1990)

History of heart disease

Patients in the studies varied in their history of heart disease:

- 5 had all included patients with heart disease (Boudoulas 1979; Brembilla-Perrot 2001; Brembilla-Perrot 2004a; Brembilla-Perrot 2004b; Menozzi 2002)
- 39 had some patients with heart disease (Aronow 1993; Arya 2005; Ashby 2002; Boersma 2004; Boudoulas 1983; Brignole 2001; Brignole 2005; Brignole 2006; Donateo 2003; Farwell 2006; Fitchet 2003; Fogel 1997; Garcia-Civera 2005; Kabra 2009; Krahn 1998; Krahn 1999; Krahn 2001; Krahn 2002; Krahn 2004; Kuhne 2007; Lacroix 1981; Linzer 1990; Lombardi 2005; Mason 2003; Moya 2001a; Moya 2001b; Nierop 2000; Pezawas 2007; Pierre 2008; Ringqvist 1989; Rockx 2005; Rothman 2007; Sarasin 2001a; Sarasin 200b; Sarasin 2005; Saxon 1990; Schernthaner 2008; Seidl 2000; Zeldis 1980).

  The proportions with heart disease ranged from 14 to 92%

  - 15 studies had over 50% of the patients with heart disease (Arya 2005, Boudoulas 1979; Boudoulas 1983; Brembilla-Perrot 2001; Brembilla-Perrot 2004a, Brembilla-Perrot 2004b; Brignole 2001; Garcia-Civera 2005; Krahn 1999; Mason 2003; Menozzi 2002; Ringqvist 1989; Rothman 2007; Sarasin 2005; Saxon 1990)
- 2 reported no history of heart disease (Deharo 2006; Schuchert 2003)
- 7 did not state if the patients had heart disease (Comolli 1993; Cumbee 1990; Gibson 1984; Kapoor 1991; Krahn 2000; Morrison 1997; Porterfield 1999)

Of the studies reporting heart disease:

- 2 also stated that initial tests and history did not confirm a cardiac cause of TLoC (Boudoulas 1979; Brembilla-Perrot 2001)
- 7 reported that the cause of TLoC was unexplained by initial tests and further ambulatory ECG tests (Brignole 2005; Fogel 1997; Krahn 1999; Krahn 2004; Linzer 1990; Saxon 1990; Zeldis 1980)
- 34 had an unexplained cause, i.e. not explained by a range of initial and second stage tests, including carotid sinus massage and tilt table tests (Aronow 1993; Arya 2005; Ashby 2002; Boersma 2004; Boudoulas 1983; Brembilla-Perrot 2004a; Brembilla-Perrot 2004b; Brignole 2001; Brignole

2005; Brignole 2006; Donateo 2003; Farwell 2006; Fitchet 2003; Garcia-Civera 2005; Krahn 1998; Krahn 2001; Krahn 2002; Kuhne 2007; Lacroix 1981; Lombardi 2005; Mason 2003; Menozzi 2002; Moya 2001a; Moya 2001b; Nierop 2000; Pezawas 2007; Pierre 2008; Ringqvist 1989; Rockx 2005; Rothman 2007; Sarasin 2001a; Sarasin 2001b; Sarasin 2005; Schernthaner 2008; Seidl 2000)

Of the studies in patients without a history of heart disease or with no information on history:

- One (Deharo 2006) had a positive test result on the tilt table test
- 2 (Comolli 1993; Kapoor 1991) reported that the cause of TLoC was unexplained by initial tests and further ambulatory ECG tests
- 2 (Cumbee 1990; Schuchert 2003) had an unexplained cause, i.e. not explained by a range of initial and second stage tests, including carotid sinus massage and tilt table tests
- 4 studies did not give any information (Gibson 1984; Krahn 2000; Morrison 1997; Porterfield 1999).

Population groups

We decided to separate the studies into different population groups. Some studies defined the patients as having 'suspected neurally mediated syncope' on the basis of the initial assessment, and this was treated as a separate category to 'unexplained syncope'. In order to be classified as suspected neurally mediated syncope, the study had to state that initial assessment indicated the likelihood of a positive diagnosis of NM syncope (in addition to the absence of evidence of other forms of syncope); in one study (Moya 2001a) this was on the basis of a positive tilt test. The classification of studies is summarised in Appendix D1 and below. Studies that did not state if the patients had recurrent syncope were grouped with studies in patients with recurrent syncope.

A) Suspected arrhythmic cause:

- with recurrent syncope or TLoC history not stated
  - more than 50% of patients with heart disease (Arya 2005, Brembilla-Perrot 2001, Brembilla-Perrot 2004a, Brembilla-Perrot 2004b, Brignole 2001, Boudoulas 1979, Boudoulas 1983, Garcia-Civera 2005, Krahn 1999, Mason 2003, Menozzi 2002, Saxon 1990)
  - stated to have 'suspected arrhythmic cause after initial assessment': Ringqvist (1989): clinical examination had ruled out other causes of symptoms than arrhythmia; Rothman 2007: around 49% hypertension; 20% coronary artery disease; 5% MI, 5% congestive heart failure and high clinical suspicion of malignant arrhythmia; Kabra (2009): ‘potentially arrhythmic symptoms’; TLoC history not stated; 24% coronary artery disease; 42% hypertension; 28% structural heart disease; 10% left ventricular ejection fraction <50%.
- without recurrent syncope (Sarasin (2005): unexplained syncope and a high likelihood of arrhythmias (neurological examination and tests for orthostatic hypotension negative; typical history of vasovagal/ situational syncope excluded))

B) Suspected neurally mediated syncope (on the basis of the initial assessment)

- with recurrent syncope or TLoC history not stated: Brignole 2006, Deharo 2006, Fitchet 2003, Moya 2001b
  - The Brignole (2006) study was in patients with a severe clinical presentation: inclusion criteria were a high number of previous TLoCs that had affected the patient’s quality of life or put them at high risk of physical injury due to unpredictable recurrence
- without recurrent syncope (no studies)

C) Unexplained cause on the basis of the initial assessment

- with recurrent syncope or TLoC history not stated: Comolli 1993, Ermis 2003, Gibson 1984, Kapoor 1991; Krahn 2000, Porterfield 1999

- without recurrent syncope (no studies)

D) Unexplained cause following secondary tests.

- with recurrent syncope or TLoC history not stated: (Aronow 1993; Ashby 2002; Boersma 2004; Brignole 2005; Cumbee 1990; Donateo 2003; Farwell 2006; Fogel 1997; Krahn 1998; Krahn 2001; Krahn 2002; Krahn 2004; Kuhne 2007; Lacroix 1981; Linzer 1990; Lombardi 2005; Morrison 1997; Moya 2001a; Nierop 2000; Pezawas 2007; Pierre 2008; Rockx 2005; Sarasin 2001a; Sarasin 2001b; Schernthaner 2008; Schuchert 2003; Seidl 2000; Zeldis 1980).
- without recurrent syncope (no studies)

In the group of studies including patients with ‘unexplained syncope after secondary tests’, some studies excluded patients who had a positive result on a secondary test (e.g. a positive tilt test which excluded patients from the current test), whilst in other studies, such patients were not excluded. We therefore also looked at subgroups of studies within ’unexplained syncope after secondary tests’ as:

  - (i) those with positive prior tests excluded: Aronow 1993, Ashby 2002; Brignole 2005; Cumbee 1990; Farwell 2006; Fogel 1997; Krahn 1998; Krahn 2001; Krahn 2002; Krahn 2004; Kuhne 2007; Lacroix 1981; Linzer 1990; Lombardi 2005; Moya 2001a; Pezawas 2007; Pierre 2008; Rockx 2005; Sarasin 2001a; Sarasin 2001b; Schuchert 2003; Seidl 2000; Zeldis 1980
  - (ii) those in which patients were not excluded on the basis of prior tests (although we note that this population may be more akin to the population ‘unexplained after initial tests’): Boersma 2004; Donateo 2003; Morrison 1997; Nierop 2000; Schernthaner 2008.

In practice, the studies with a high proportion of patients with a single or first episode were labelled as such in forest plots, to distinguish them from studies

in patients with recurrent syncope, and all studies were combined in analyses, with these single episode studies being treated in sensitivity analyses.

5.3.3.3 Index tests

The index tests were:

- Holter 24-hour monitoring: 16 studies (Aronow 1993; Arya 2005; Boudoulas 1979; Boudoulas 1983; Brembilla-Perrot 2001; Brembilla-Perrot 2004; Comolli 1993; Gibson 1984; Krahn 2000; Kuhne 2007; Lacroix 1981; Morrison 1997; Sarasin 2001; Sarasin 2005; Saxon 1990; Zeldis 1980)
  - Avionics: 1 study (Aronow 1993; Boudoulas 1979; Boudoulas 1983; Gibson 1984; Zeldis 1980)
  - VISTA: 1 study (Arya 2005)
  - Analysed with Elatec system (Brembilla-Perrot 2001; Brembilla-Perrot 2004a; Brembilla-Perrot 2004b)
  - Kontron tape (Comolli 1993)
  - Schiller (Kuhne 2007)
  - Holter two-lead monitor in 94 patients and bedside 24-hour monitoring in 6 patients (Lacroix 1981)
  - 3 channels of ECG Del Mar Avionics: (Sarasin 2005)
  - no further details (Morrison 1997; Sarasin 2001; Saxon 1990)
- Holter 48-hour monitoring: 4 studies (Fitchet 2003; Krahn 2000; Ringqvist 1989; Rockx 2005)
  - No further details for Fitchet (2003); Marquette Electronics (Krahn 2000); portable 1 or 2 channel FM cassette recorders (SRA-Helige); also patient activated for Ringqvist (1989); 2 channel ambulatory tape recorder, with time stamp for symptom correlation (Marquette Electronics) (Rockx 2005)
- Holter 72 hour monitoring: 1 study (Kapoor 1991)
  - Holter up to 3 x 24-hours (more than 80% of patients on consecutive days)
- Transtelephonic external event monitor, patient or automatically activated: 1 study (Rothman 2007)

- External event recorder; patient activated (Cumbee 1990 [Instant Replay]; Fogel 1997 [Instromedix instant replay or King of Hearts or WristRecorder]; Krahn 2000 [King of Hearts]; Linzer 1990 [Instromedix instant replay or King of Hearts]; Porterfield 1999 [no further details]; Sarasin 2001 [R Test Evolution]; Schuchert 2003 [CardioCall]; Rockx 2005 [King of Hearts Express or Cardiocall ST80])
  - Up to 1 week: 1 study (Sarasin 2001): patients had a mean duration of recording of 160 (40) hours; the authors reported that 9 patients had technical problems with the procedure (e.g. allergic reactions) and 8 stopped the recording prematurely, but they did not state whether the duration was pre-planned or patients stopped recording once an event occurred.
  - 1 week to 1 month: 5 studies (Cumbee 1990: monitoring terminated when diagnostic recording obtained or when physician thought further recording unlikely to be diagnostic; Fogel 1997: usually 4 weeks; less if an event; extended if no event; Linzer 1990: recording stopped if diagnostic event; Porterfield 1999: only states ‘30 day monitoring period’; Rockx 2005: worn until 2 clinical episodes occurred or 1 month elapsed)
  - more than 1 month: 2 studies (Krahn 2000: median 30 days; range 5-96 days; retrospective - no further details; Schuchert 2003: routinely given for 8 weeks; extended if no event and patient wanted to continue; patients seen earlier if experienced event; mean 7 (3) weeks; range 1-10 weeks)
- Implantable event recorder - automatically activated only: no studies
- Implantable event recorder - patient activated: 13 studies (Ashby 2002; Brignole 2001; Donateo 2003; Garcia-Civera 2005; Krahn 1998; Krahn 1999; Krahn 2001; Krahn 2002; Menozzi 2002; Moya 2001a; Moya 2001b; Nierop 2000; Seidl 2000)
  - Less than 6 months: 3 studies (Brignole 2001: median 48 days (IQR 16 to 100); seen every 3 month, until an event or until battery ran down; Krahn 1998: up to 12 months; mean 4.6 (3.8) months; device explanted if diagnosis made or no event in 2 years (battery life); Krahn 2002: mean

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

- 6 months to 1 year: 7 studies (Garcia-Civera 2005: mean 9.2 (5.9) months; seen every 3 months; followed yup until diagnosis reached, battery expired or patient died; Krahn 1999: mean 10.5 (4) months; follow up after each event; device in until syncope/presyncope; 18 months follow up; end of battery life; or patient or investigator chose to remove it sooner; Krahn 2001: follow up at 1 week, 1, 2, 3, 6, 9 and 12 months and after event (aimed for full 1 year monitoring); Moya 2001a: mean 9 (5) months; seen every 3 months until diagnosis, battery ran down or end of study (maximum 36 months); Moya 2001b: mean 10 (5) months; seen every 3 months until diagnosis, battery ran down or end of study (maximum 36 months); Nierop 2000: 11 (8) months; seen every 3 months; no further details; Seidl 2000: mean 10.8 (4.3) months; device implanted until syncope/presyncope or patient or investigator wanted to remove it)
- 1-2 years: 3 studies (Ashby 2002: mean 5.6 (5.7) months (to diagnostic event or end of battery life i.e. 14 months); Donateo 2003: mean 18 (9) months; 1st syncopal event analysed; follow up every 3 months to maximum of 36 months; Menozzi 2002: mean 16 (11) months; seen every 3 months until diagnosis, end of battery life or patient died)
- more than 2 years: no studies

- Implantable event recorder - patient and automatically activated: 12 studies (Boersma 2004; Brignole 2005; Brignole 2006b; Deharo 2006; Farwell 2006; Kabra 2009; Krahn 2004; Lombardi 2005; Mason 2003; Pezawas 2007; Pierre 2008; Schernthaner 2008)
  - Less than 6 months: no studies
  - 6 months to 1 year: 7 studies (Brignole 2006b: mean 12 (8) months; device interrogated every 3 months or after event to maximum of 24 months; Kabra 2009 mean 10 (7) months; routine follow up every 1-3 months; Krahn 2004: follow up at 1, 2, 4, 8, 12 weeks and every 3 months thereafter to event or 1 year of end of battery life (14-20 months); Lombardi 2005: mean 7 (4) months, range 1-14 months; device

explanted after diagnosis made or if no syncope after 14 months; Mason 2003: mean 11.1 (10.4) months; minimum 7 months; maximum 36 months; all followed until IER explanted or end of study; Pierre 2008: mean 10.2 (5.2) months; seen every 3 months until diagnosis or end of battery life (14 months); Schernthaner 2008: mean 9 (8) months to first recorded event; range 1-27 months; seen every 3-6 months)

- 1-2 years: 5 studies (Boersma 2004: median 18 months (range 1-18 months); device interrogated every 3 months and after an event; Brignole 2005: mean follow up 14 months (10 months); device interrogated every 3 months or after event; if battery ran down, pt could have 2nd IER; Deharo 2006: planned duration 18 months; device interrogated after 1 month then every 3 months and after event; all followed to 18 months except 2 explanted (infection/neoplasia); Farwell 2006: median 17 months (IQR 9-23 months); maximum 34 months; Pezawas 2007: mean 16 (8) months; seen every 3 months to diagnosis or end of IER life)
- more than 2 years: no studies

Product of frequency of TLoC and duration of recording

For the studies reporting both the frequency of TLoC and the duration of measurement, we calculated the product of the two and noted the following:

- The product of duration of recording in time units multiplied by frequency of TLoC (number per time unit): studies were divided into the following subgroups
  - (a) product less than 0.1: Fitchet (2003), Lacroix (1981); Rockx (2005 Holter);
  - (b) 0.1 to 0.99: Brignole (2001), Linzer (1990), Rockx (2005 ELR), Schuchert (2003);
  - (c) 1 to 10: Boersma (2004), Brignole (2006), Deharo (2006), Donateo (2003), Farwell (2006), Garcia-Civera (2005), Krahn (1998), Krahn (1999), Krahn (2001), Krahn (2004), Lombardi (2005), Menozzi (2002), Moya (2001a), Moya (2001b), Nierop (2000), Seidl (2000);

- (d) more than 10: none.

5.3.3.4 Comparisons

Two studies compared ambulatory ECG with a conventional testing approach, as follows:

- Implantable event recorder versus conventional testing (Farwell 2006' Krahn 2001).
  - The control group comprised 'conventional investigation and management' (Farwell 2006) or 'conventional plus external event recorder (duration 2-4 weeks) plus tilt and electrophysiological testing' (Krahn 2001)
  - The Farwell (2006) study did not give details of what tests the control group received, but stated in the cost-effectiveness analyses that the following numbers of tests were carried out post-randomisation for the IER versus conventional groups: CT 4 versus 8; MRI 1 versus 1; EEG 0 versus 2; Carotid Doppler 3 versus 5; Echo 12 versus 15; 24-hour Holter 4 versus 11; external event recorder 5 versus 28; electrophysiology 0 versus 1.

Two other studies compared two or more ambulatory ECG index tests as follows:

- External event recorder versus Holter monitoring: 1 RCT (Rockx 2005; 48-hours of Holter); 1 non-randomised comparative study (Krahn 2000; 24 or 48-hour Holter monitoring)
  - Tests in the Rockx (2005) study were in two stages: patients were first randomised to the EER or Holter monitoring and then, if there was no recurrence of symptoms (or the EER was not activated), patients were offered crossover to the other test. Thus this was a comparison of two strategies.

One other prospective study compared Holter monitoring 48-hours with tilt testing in the same patients, the test order was not stated, but the two tests were carried out within 3 months of each other (Fitchet 2003).

One other RCT was identified that compared ambulatory ECG with other tests not included in the guideline (telemetry), and the GDG decided not to consider this further as a comparative study (Rothman 2007).

5.3.3.5 Outcomes

All studies aimed to record symptom-rhythm correlation (i.e. arrhythmia during TLoC) although some also recorded arrhythmia not during TLoC and/or normal rhythm during TLoC.

Many studies reported a 'diagnostic yield', which was defined in different ways by different authors, which led to inconsistencies amongst studies. In practice, we found the most useful information to extract was the separate outcomes, rather than an overall diagnostic yield, so the latter was not recorded.

5.3.4 Methodological quality

5.3.4.1 RCTs

There were three RCTs (Farwell 2006, Krahn 2001, Rockx 2005).

The method of sequence generation was adequate in two studies (random number tables - Farwell 2006; computer-generated sequence - Rockx 2005) and unclear in one study (Krahn 2001).

The method of allocation concealment was adequate in one study (sealed envelopes held in study centre; Farwell 2006) and unclear in the other studies.

Neither patients not outcome assessors were blinded. All patients were followed up and baseline comparability was demonstrated (e.g. comparable on age, gender, previous ischaemic heart disease, duration of symptoms, previous episodes in Farwell 2006; comparable on age, sex, baseline ECG,

heart diseasee, left ventricular ejection fraction, number of syncopal episodes, syncope duration in Krahn 2001).

One study carried out a power calculation (sample size 200 appropriate to detect 18% improvement in diagnosis with 90% power; Farwell 2006).

Two studies had no missing data, while in the third study (Farwell 2006), data were missing on two of 103 IER patients and one of 98 on usual care.

All the studies had potential for bias due to the lack of blinding, and there was a lack of allocation concealment in two studies (Farwell 2006, Krahn 2001).

5.3.4.2 Non-randomised studies

Fifty non-randomised studies were included in the review, one was comparative (Krahn 2000) and the rest were case series. In some of the latter, patients were given more than one test and these were compared directly (Brignole 2006; Farwell 2006; Fitchet 2003).

The non-randomised comparative study (Krahn 2000) was retrospective and assessed two groups of patients (not matched) that had had the two tests during a one-year period.

Twenty-four studies reported that all eligible patients were included (Ashby 2002; Boersma 2004; Brembilla-Perrot 2004; Brignole 2001; Comolli 1993; Cumbee 1990; Deharo 2006; Fogel 1997; Garcia-Civera 2005; Gibson 1984; Kapoor 1991; Krahn 2004; Kuhne 2007; Lacroix 1981; Linzer 1990; Lombardi 2005; Mason 2003; Morrison 1997; Porterfield 1999; Ringqvist 1989; Sarasin 2001; Saxon 1990; Schuchert 2003; Zeldis 1980).

Brignole (2005) reported that only one-third of patients with unexplained syncope were given an IER, while Brignole (2006) reported that 6% of eligible patients declined. Sarasin (2005) reported that 140/155 (90%) of eligible patients were enrolled; non-participants (no reason was given) were older (mean 77 years) than participants (mean 68 years). In the other studies it was unclear whether all eligible patients were enrolled.

Twelve studies were retrospective (Ashby 2002; Cumbee 1990; Gibson 1984; Kabra 2009; Krahn 2000; Kuhne 2007; Mason 2003; Morrison 1997; Porterfield 1999; Saxon 1990; Schernthaner 2008; Zeldis 1980).

In 41 studies all patients were followed, there was less than 20% missing data in two studies (Deharo 2006 [two patients had the device prematurely explanted, one due to breast cancer and one due to infection]; Seidl 2000 [3 patients were lost to follow up]) and in 2 studies (Brignole 2005; Donateo 2003) missing data were unclear.

Several of the studies did not report all outcomes; some had missing data on some patients and/or the numbers reported in tables and text did not agree.

In Seidl (2000), 3 patients with adverse events, 3 who were lost to follow up and 3 who died were not included in the analysis.

Overall, the studies were considered to be of acceptable quality for non-randomised studies, except for the retrospective studies.

5.3.5 Results – non comparative studies

5.3.5.1 Plan of this section

We decided to exclude the retrospective studies (Ashby 2002; Cumbee 1990; Gibson 1984; Kabra 2009; Krahn 2000; Kuhne 2007; Mason 2003; Morrison 1997; Porterfield 1999; Saxon 1990; Schernthaner 2008; Zeldis 1980) because of their poorer quality and because there were several prospective studies.

We report the results in different ways, in all cases reporting the series of review outcomes as the proportion of the total number of patients in that study. Firstly, different tests are reported for each of the four population groups. Then different populations are compared indirectly for each test. Finally studies comparing different tests head-to-head are described.

Where there was more than one study in a particular subgroup, meta-analysis was carried out to give an indication of statistical heterogeneity, not in order to obtain a pooled result; and the range was quoted in the summary results.

Self consistent studies

The studies variously reported the number of patients with a particular outcome. Each patient could have different outcomes: they either did or did not have a TLoC during the recording period. If they did have a TLoC, this could be accompanied by the device recording an arrhythmia or normal rhythm or not recording at all (equipment failure or human error). Then if the person did not have a TLoC, some of the devices could still record arrhythmias. The proportions for the following outcomes should total 1 for each study: no TLoC; arrhythmia during TLoC; normal rhythm during TLoC; no ECG recorded during TLoC. Therefore, results for each study were checked, where possible, to ensure consistency. The following studies did account for all the patients and were self-consistent (Brignole 2001; Brignole 2005; Brignole 2006; Comolli 1993; Donateo 2003; Ermis 2003; Farwell 2006; Fogel 1997; Garcia-Civera 2005; Kapoor 1991; Krahn 1998; Krahn 1999; Krahn 2001; Krahn 2002; Krahn 2004; Linzer 1990; Lombardi 2005; Menozzi 2002; Moya 2001a; Moya 2001b; Nierop 2000; Rockx 2005; Rothman 2007; Sarasin 2005; Schuchert 2003; Seidl 2000). The other studies had at least one missing outcome.

'Good' arrhythmias

As mentioned earlier, studies were assessed according to whether or not they met the GDG's criteria for acceptable arrhythmias recorded; further details are given in Appendix D1. The criteria for 'good' arrhyhmias were: any arrhythmia with symptom correlation; complete AV block or sustained VT not connected with symptoms; and asystole greater than 3 seconds even if there were no symptoms. Where the studies reported separately the numbers of patients with 'good' and 'bad' arrhythmias, we extracted only the data on the 'good' arrhythmias. Otherwise the studies were considered to be potentially biased.

- Three studies were considered to be potentially biased (Brembilla-Perot 2001, Brembilla-Perot 2004a, Brembilla-Perot 2004b)
- For three studies it was possible to extract only the 'good' arrhythmias (Brignole 2006; Fitchet 2003; Kapoor 1991)
- Four were unclear on what was recorded (Arya 2005, Boudoulas 1979, Boudoulas 1983, Lacroix 1981)
- And the rest appeared to be of acceptable quality

5.3.5.2 Results for a suspected arrhythmic cause of TLoC – subgroup comparisons of tests

Thirteen studies in patients with a suspected arrhythmic cause of syncope (after initial assessment) were divided into those: a) with recurrent TLoC (or TLoC history not stated) and b) without recurrent TLoC

- Eight studies had patients with recurrent TLoC (Arya 2005, Brembilla-Perrot 2004a, Brembilla-Perrot 2004b, Brignole 2001, Garcia-Civera 2005, Krahn 1999, Menozzi 2002, Ringqvist 1989)
- One study had a high proportion of patients with a first episode (Sarasin 2005; 52% first episode)
- Four studies did not state the TLoC history (Boudoulas 1979, Boudoulas 1983, Brembilla-Perrot 2001, Rothman 2007).

The Brembilla-Perrot (2004) study had two parts: (a) labelled 'cd' on forest plot: patients with coronary disease with a history of myocardial infarction and/or multiple coronary stenoses on angiography and an LVEF below 40%; (b) labelled 'dcm' on forest plot: patients with idiopathic dilated cardiomyopathy, normal coronary angiogram, left ventricular ejection fraction (LVEF) below 40%.

The following devices were investigated for this patient group:

- Six studies used Holter 24-hour monitoring (Boudoulas 1979, Boudoulas 1983, Brembilla-Perrot 2001, Brembilla-Perrot 2004a, Brembilla-Perrot 2004b, Sarasin 2005)
- Two studies used Holter 48-hour monitoring (Arya 2005, Ringqvist 1989)
- One study used an external event recorder (Rothman 2007)
- Four studies used an IER (Brignole 2001, Garcia-Civera 2005, Krahn 1999, Menozzi 2002)

All included all the relevant outcomes (self consistency).

The following studies were excluded in sensitivity analyses for the outcome of 'arrhythmia not during TLoC' (see Appendix D1) as they did not report only 'good' arrhythmias, or, if they reported both 'good' and 'bad' arrhythmias, these could not be separated (Brembilla-Perrot 2001, Brembilla-Perrot 2004a, Brembilla-Perrot 2004b, Lacroix 1981, Rothman 2007, Sarasin 2001).

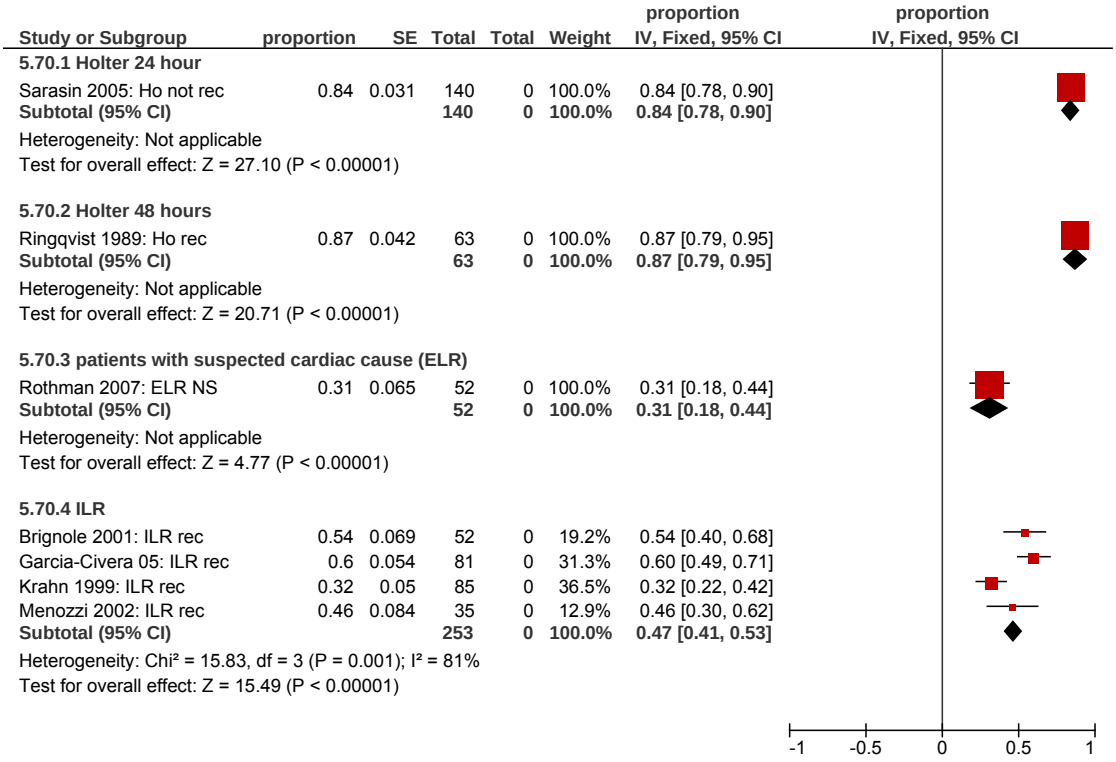
A1. No TLoC during recording period

Seven studies reported the outcome of no TLoC during the recording period in 508 patients. One study (Sarasin 2005) assessed 24-hour Holter; one study (Ringqvist 1989) assessed 48-hour Holter; and one study assessed EER (Rothman 2007). Four studies (Brignole 2001; Garcia-Civera 2005; Krahn 1999; Menozzi 2002) assessed implantable event recorders; all patients in these studies had recurrent TLoC except the Sarasin (2005) study, which had 52% of patients with a single episode and so this study is treated separately.

The populations differed across studies in terms of their frequency of TLoC, however: the Rothman (2007) study reported that median time to diagnosis was 10 days for patients given an EER, where the time to diagnosis applied to those patients with a clinically significant arrhythmia. The frequency of previous TLoCs and the time to event in the study were respectively (Appendix D1): Brignole (2001) median 1.5/year and 48 days in patients given an IER; Garcia-Civera (2005) mean 3.5/year and 85 days; Krahn (1999) mean 5.1/year and 71 days; and Menozzi (2002) median of 1/year and 180 days.

This matching of duration of monitoring and time to event might explain the lower proportion of patients without a TLoC in the Rothman (2007) study, but we note that this study also included pre-syncopal events.

Figure 5-1: No TLoC during the recording period by type of device

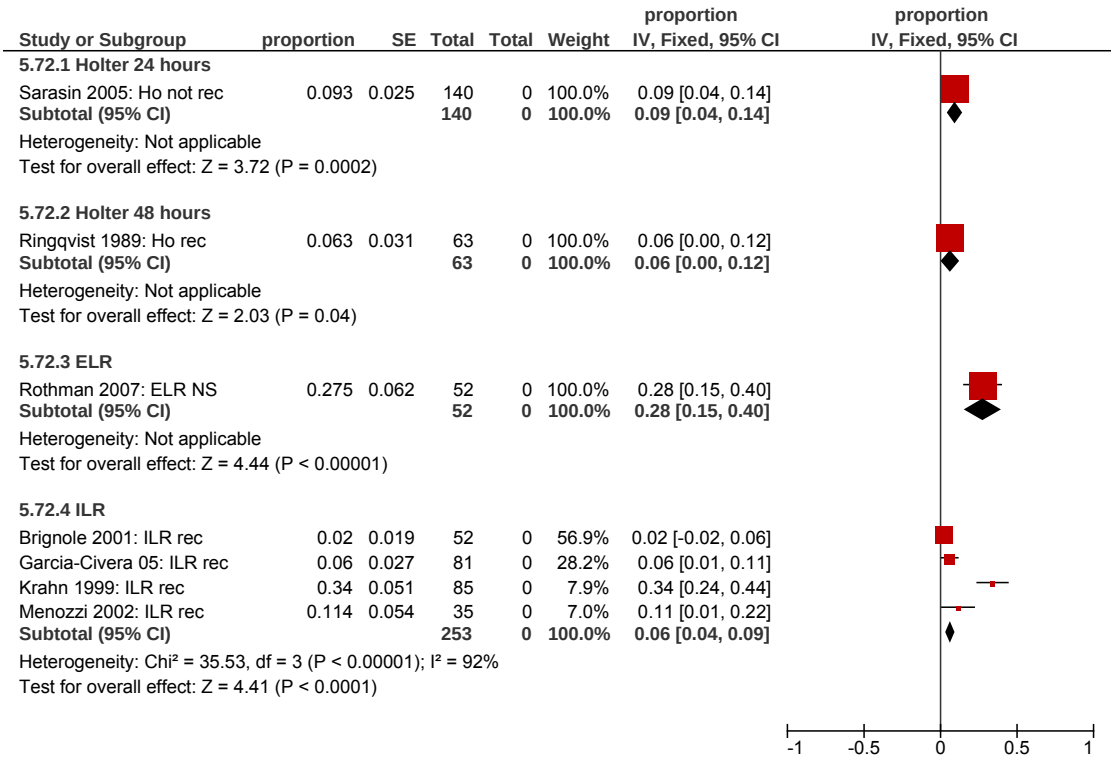


The likelihood of having no TLoC during the recording period appears to be high for Holter monitoring and lower for EER or IER (as might be expected for the longer duration of monitoring). There was significant heterogeneity for the IER studies.

A2. Normal rhythm during TLoC

Seven studies reported this outcome. One study assessed 48-hour Holter (Ringqvist 1989); one of the studies assessed 24-hour Holter and had 52% of patients with a single episode of TLoC (Sarasin 2005); and one assessed EER (Rothman 2007). Four studies (Brignole 2001; Garcia-Civera 2005; Krahn 1999; Menozzi 2002) reported normal rhythm during TLoC for implantable event recorders; all patients had recurrent TLoC.

Figure 5-2: normal rhythm during TLoC; subgroup by type of device



Test for subgroup differences: Chi² = 11.74, df = 3 (P = 0.008), I² = 74.5%

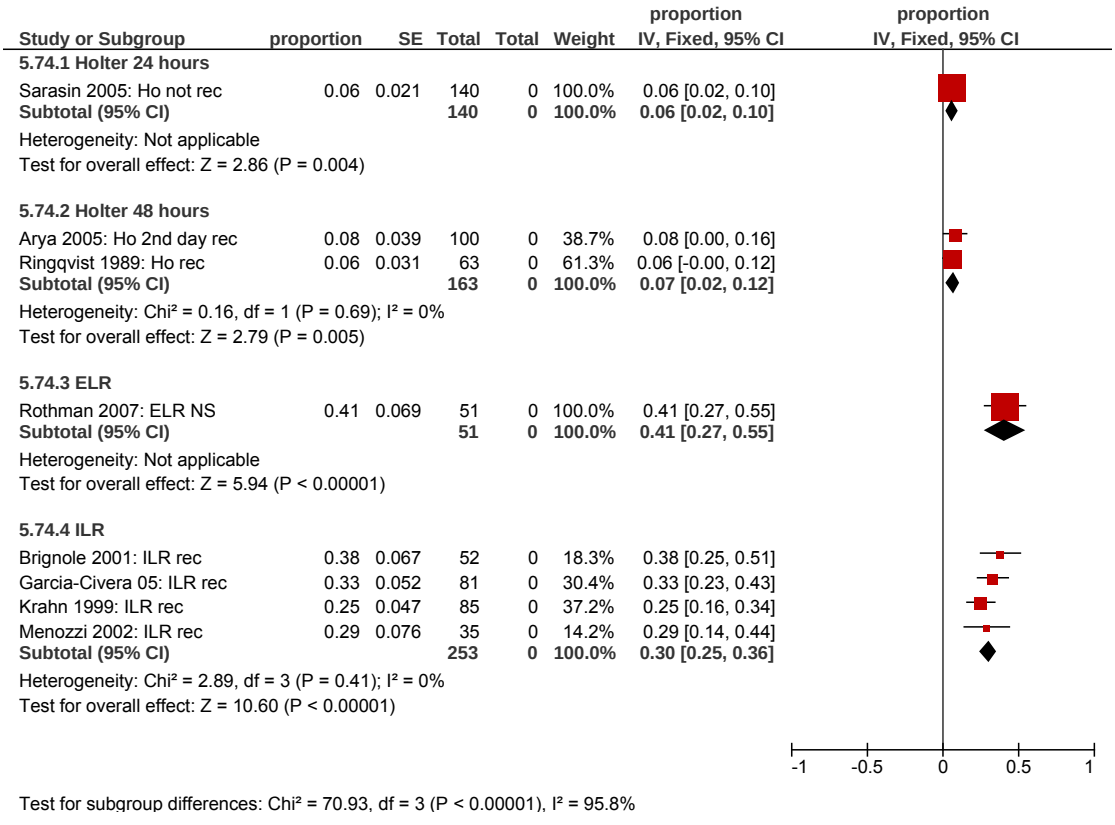
The likelihood of capturing normal rhythm during TLoC was small for Holter (as most people did not have a TLoC within the monitoring period). Again there was significant heterogeneity across the IER studies.

A3. Arrhythmia recorded during TLoC

One study (Sarasin 2005) reported the number of patients for whom an arrhythmia was recorded during TLoC for Holter 24-hour monitoring; this had 52% patients with a first episode of TLoC. One other study (Boudoulas 1979) reported 'dysrrhythmias considered as the cause of TLoC' but did not say if there was symptom correlation, so this outcome was not included in the analysis. One study (Ringqvist 1989) reported arrhythmia during TLoC for Holter 48-hour monitoring; it had 63 patients who had recurrent TLoC; one study (Arya 2005) reported arrhythmia during TLoC for the total of the 48-hour monitoring period but not each 24-hours separately; patients had recurrent TLoC. One study (Rothman 2007) assessed EER and reported arrhythmia

during TLoC; for this outcome clinically significant and clinically insignificant arrhthmias were included. Four studies (Brignole 2001; Garcia-Civera 2005; Krahn 1999; Menozzi 2002) reported arrhythmia during TLoC for implantable event recorders; all patients had recurrent TLoC. We note that the Arya (2005) and Ringqvist (1989) studies were not self consistent.

Figure 5-3: Arrhythmia during TLoC; subgroup by type of device



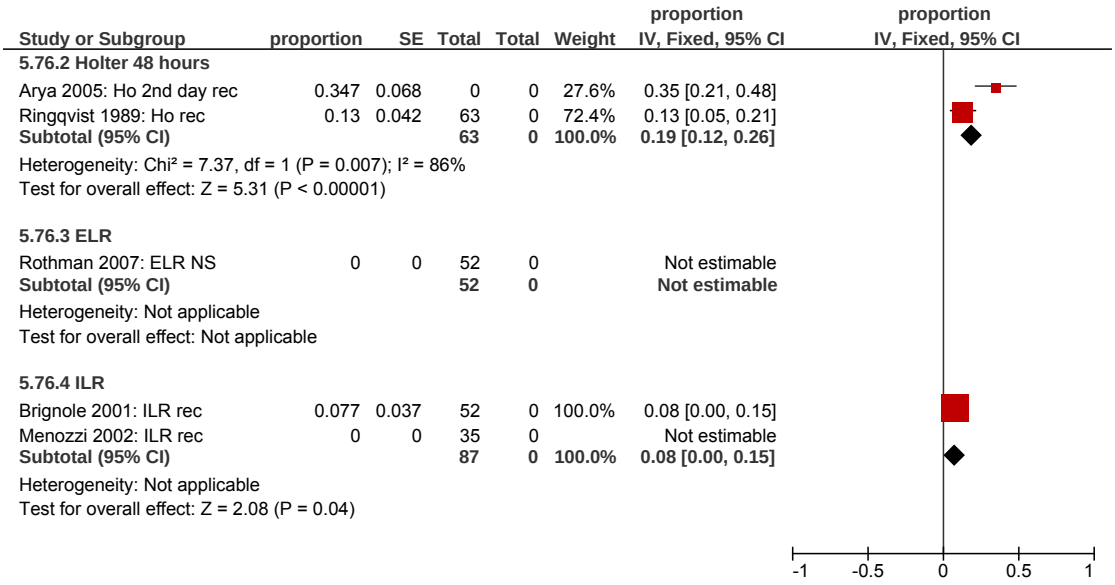
The diagnostic yield for capturing an arrhythmia during TLoC is higher for IER (30%) and EER (41%) than Holter monitoring (7%), and there was no heterogeneity amongst the IER studies.

A4. Arrhythmia recorded not during TLoC

One study (Ringqvist 1989) reported arrhythmia not during TLoC for Holter 48-hour monitoring; it had patients who had recurrent TLoC. One study (Rothman 2007) reported arrhythmia not during TLoC for EER, but none were significant arrhythmias, so these were not counted. One study (Brignole 2001)

reported arrhythmia not during TLoC for implantable event recorders; patients had recurrent TLoC. One study (Menozzi 2002) examined this outcome for patients with recurrent TLoC on IER but there were no events.

Figure 5-4: Arrhythmia recorded, but not during TLoC; subgroup by type of device

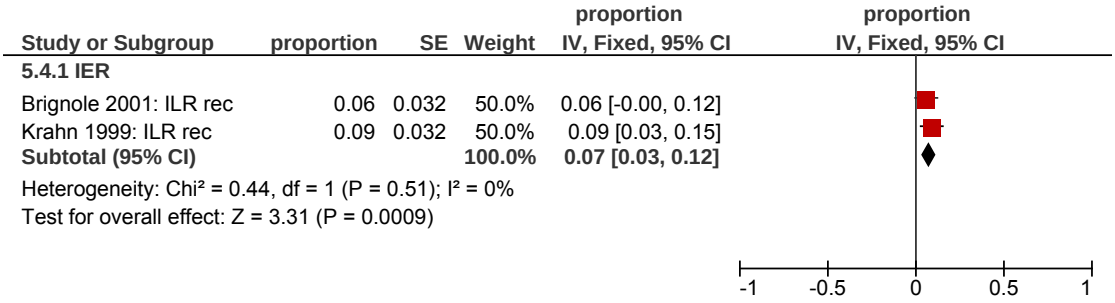


Test for subgroup differences: Chi² = 4.82, df = 1 (P = 0.03), I² = 79.3%

A5. No ECG recorded

Two studies (Brignole 2001; Krahn 1999) reported the outcome, no ECG recorded during TLoC, for implantable event recorders; all patients had recurrent TLoC. Two other studies had no patients with no ECG recorded (Menozzi 2002; Rothman 2007).

Figure 5: No ECG recorded

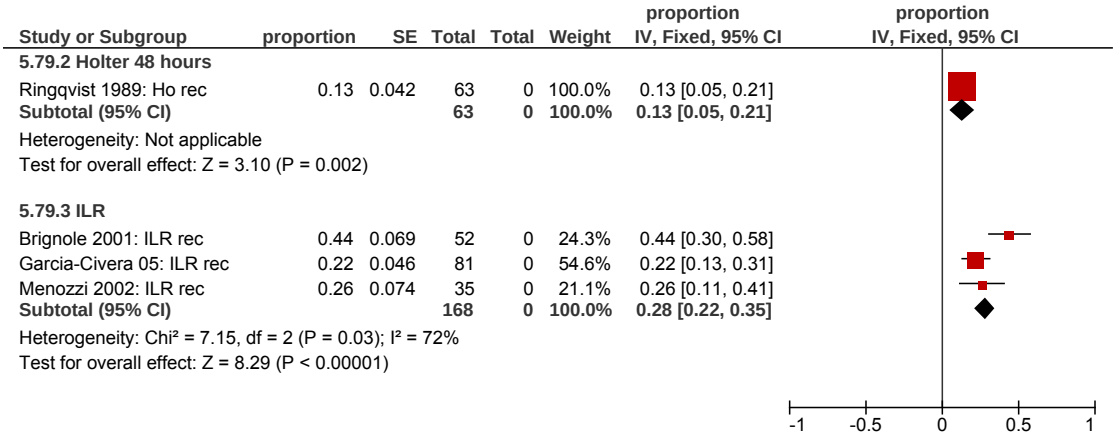


Test for subgroup differences: Not applicable

A6. Number of patients started on therapy

One study assessing Holter 48-hours (Ringqvist 1989; recurrent TLoC) and 3 assessing implantable event recorders (Brignole 2001; Garcia-Civera 2005; Menozzi 2002; all patients had recurrent TLoC) reported the number of patients started on therapy. The therapy included pacemakers, implantable defibrillators and antiarrhythmic drugs.

Figure 5-6: number of patients started on therapy by type of device



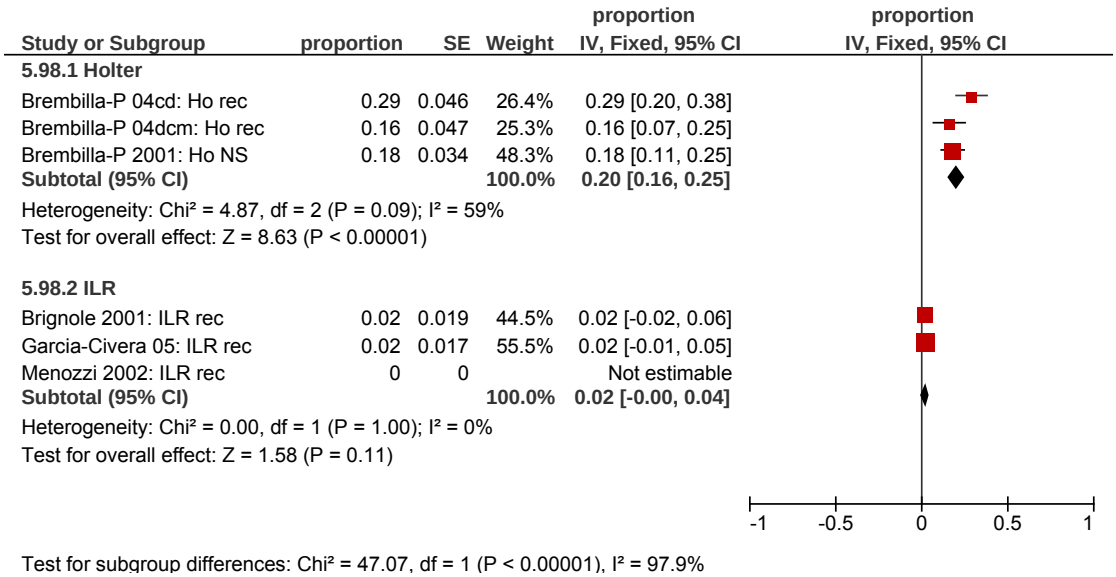
A7. Adverse events

One study (Krahn 1999) reported 4 adverse events in 85 people with implantable event recorders; 3 patients had infections and one had pain.

A8. Death

Three Holter studies (Brembilla-Perrot 2001; Brembilla-Perrot 2004a; Brembilla-Perrot 2004b) and three IER studies (Brignole 2001; Garcia-Civera 2005; Menozzi 2002) reported this outcome. The results are more likely to be due to the patient characteristics than the type of device.

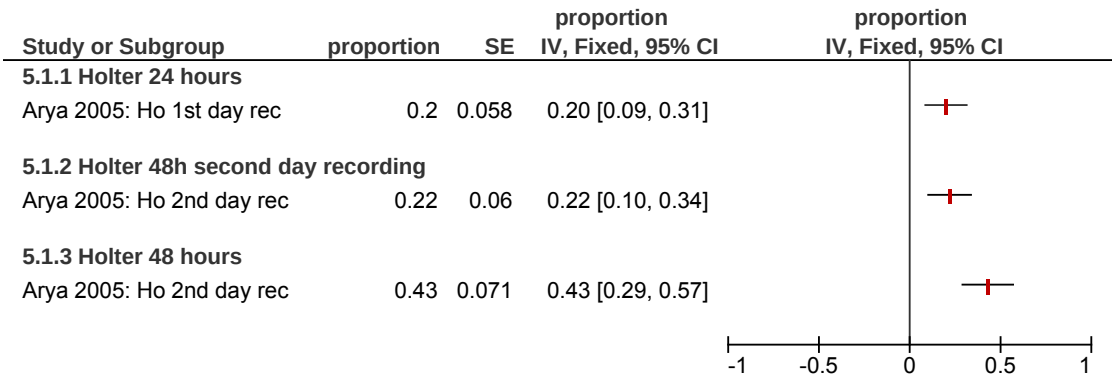
Figure 5-7. Number of patients who died



A9. Holter 24h versus Holter 48h

One study (Arya 2005) compared the total number of arrhythmic events, rather than the number of patients (with and without TLoC) diagnosed after 24h and 48h Holter monitoring in the same patients. This indicates that additional information can be obtained by using the Holter monitor for a second day.

Figure 5-8: 24h versus 48h Holter monitoring: all arrhythmic events



5.3.5.3 Results for suspected neurally mediated syncope – subgroup comparisons of tests

Four studies included patients with suspected NM syncope on the basis of initial assessment. All reported recurrent TLoC (Brignole 2006, Deharo 2006, Fitchet 2003, Moya 2001b); Brignole (2006) included only patients with a severe presentation.

We note that the Brignole (2006) study was funded by Medtronic Inc, who also provided a study manager.

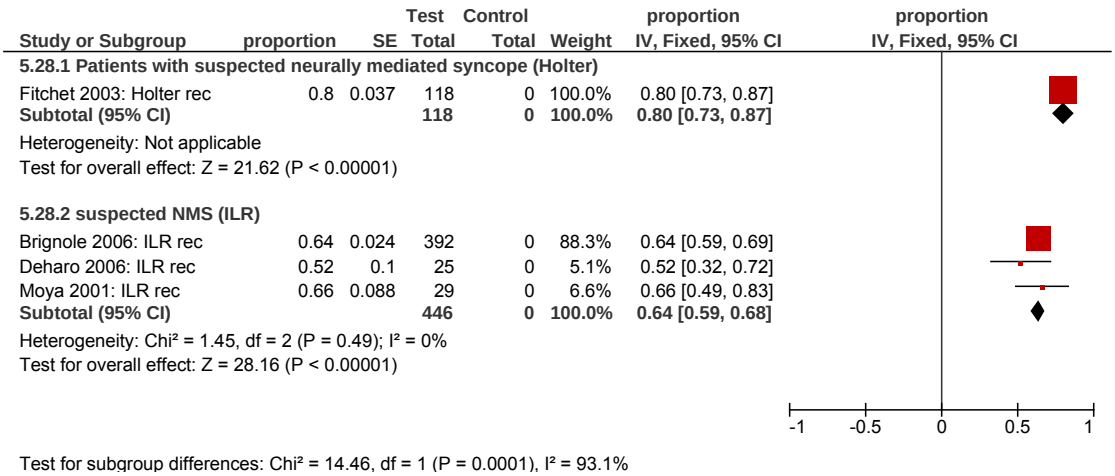
The following devices were investigated for this patient group:

- One study assessed Holter 48-hour monitoring (Fitchet 2003)
- Three studies assessed implantable event recorders (Brignole 2006, Deharo 2006, Moya 2001b)

B1. No TLoC during recording period

Four studies reported this outcome in 562 patients (Brignole 2006, Deharo 2006, Fitchet 2003, Moya 2001). The Moya (2001) and Brignole (2006) studies were self consistent.

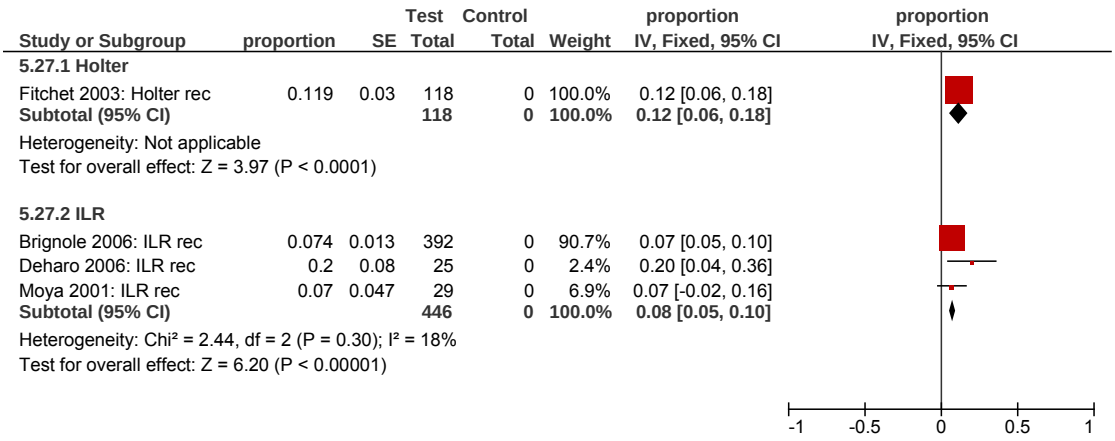
Figure 5-9. No TLoC during recording period. Subgroups by type of device



B2. Normal rhythm during TLoC

Four studies reported this outcome (Brignole 2006, Deharo 2003, Fitchet 2003, Moya 2001). A single study reported a yield of 12% for 48-hour Holter monitoring and three studies reported 8% for IER, with no significant heterogeneity.

Figure 5-10. Normal rhythm during TLoC (suspected NM syncope)

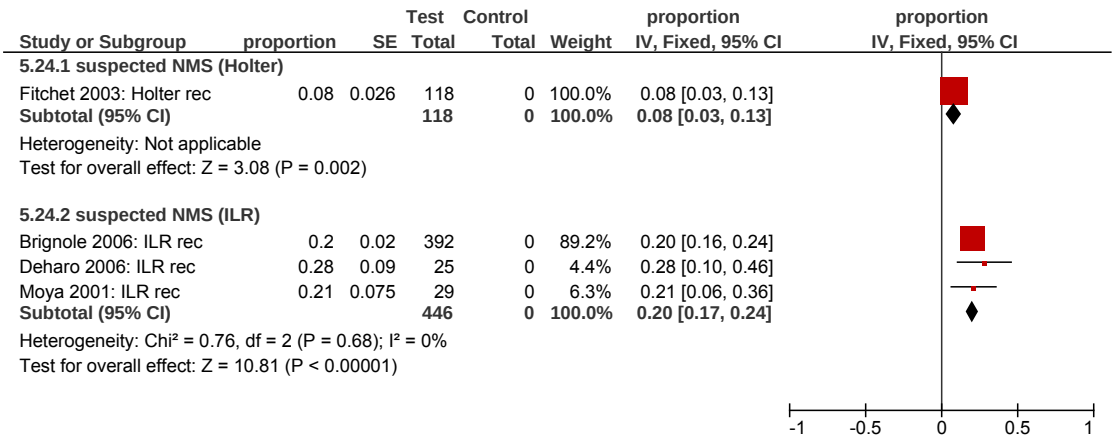


Test for subgroup differences: Chi² = 1.70, df = 1 (P = 0.19), I² = 41.0%

B3. Arrhythmia during TLoC

Four studies assessed this outcome (Brignole 2006, Deharo 2006, Fitchet 2003, Moya 2001). A single study reported a yield of 8% for 48-hour Holter monitoring and three studies reported 20% for IER, with no heterogeneity.

Figure 5-11. Arrhythmia during TLoC by type of device in patients with suspected NM syncope

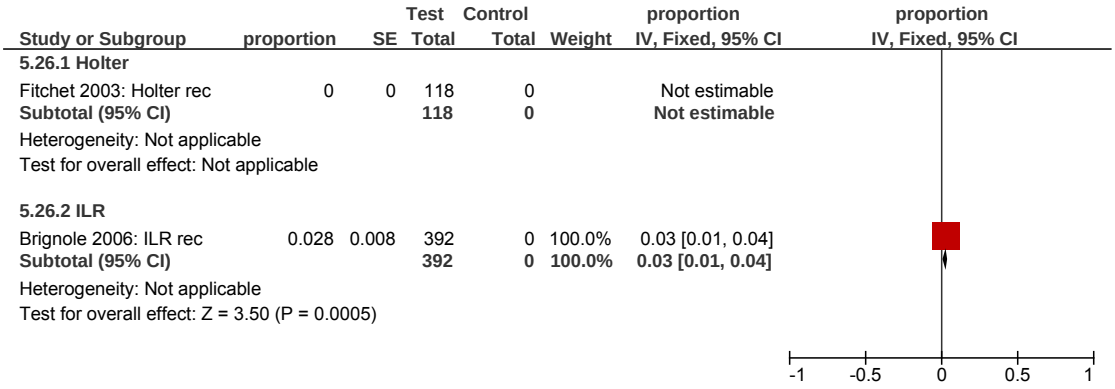


Test for subgroup differences: Chi² = 14.92, df = 1 (P = 0.0001), I² = 93.3%

B4. Arrhythmia not during TLoC

Two studies (Brignole 2006, Fitchet 2003) assessed this outcome. Results are reported only for 'good' arrhythmias. A single study reported no asymptomatic arrhythmias for the Holter monitor and a large single study reported 3%.

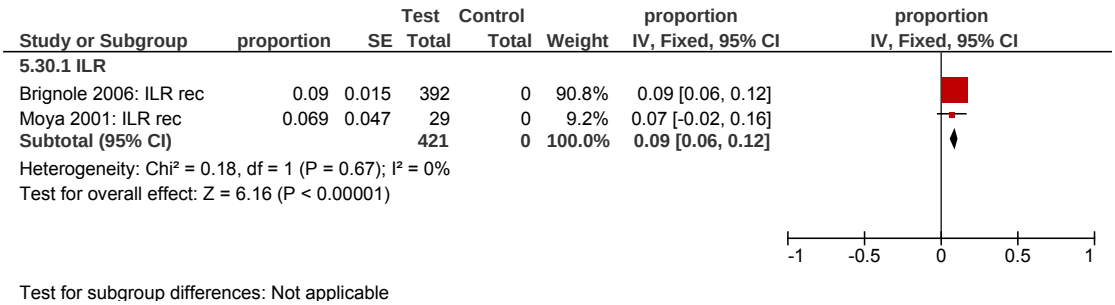
Figure 5-12. Arrhythmia not during TLoC (suspected NM syncope)



B5. No ECG during TLoC

Two studies (Brignole 2006, Moya 2001) reported this outcome for an IER and had a yield of 9%.

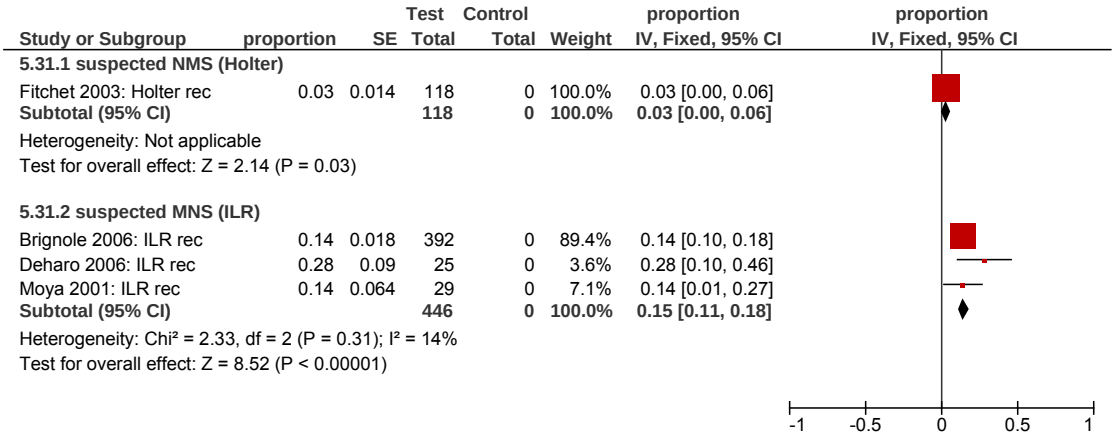
Figure 5-13: No ECG during TLoC (suspected NM syncope)



B6. Number of patients started on therapy

Four studies reported this outcome (Brignole 2006, Deharo 2006, Fitchet 2003, Moya 2001).

Figure 5-14: Patients started on therapy (suspected NM syncope), by type of test



B7. Adverse events

Two studies (Brignole 2006, Deharo 2006) reported adverse events: Brignole (2006) reported 4 pocket infections of 392 implantable event recorders, and Deharo (2006) reported one patient had an infection (out of 25 patients) and the implantable event recorder was explanted after 6 months.

B8. Number of patients who died

One study (Moya 2001) reported that no patients died during the study period.

5.3.5.4 Results for unexplained syncope on the basis of the initial assessment – subgroup comparisons of tests

Three studies included patients with unexplained syncope after an initial assessment.

Two of the studies did not state the TLoC history (Comolli 1993, Ermis 2003), and the other study (Kapoor 1991) reported that 55/95 patients had had multiple syncopal episodes. All the studies had self consistent outcomes.

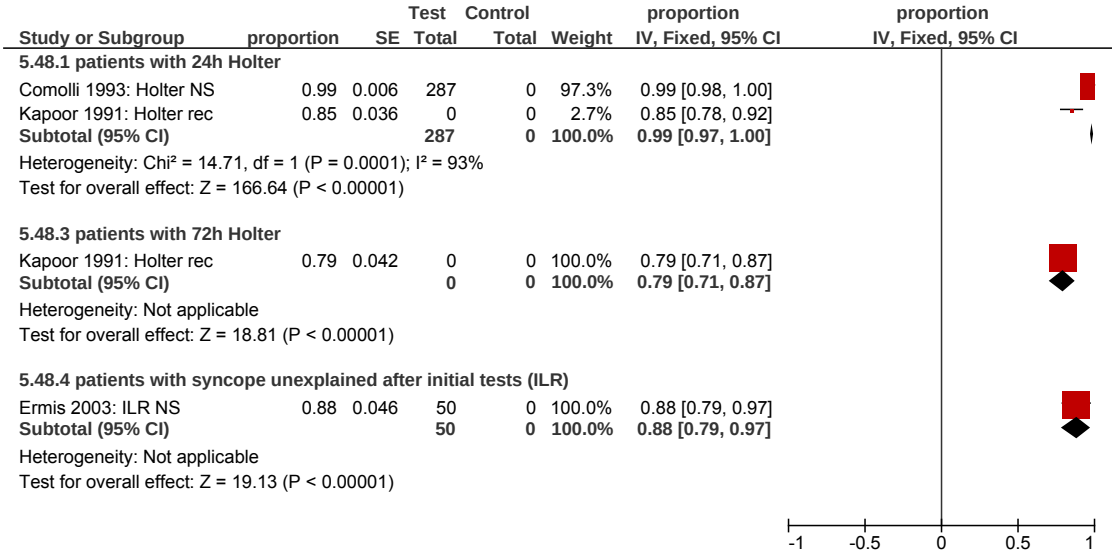
The following devices were investigated for this patient group:

- Two studies assessed Holter 24-hour monitoring (Comolli 1993), Kapoor 1991)
- Kapoor (1991) also examined cumulative Holter 48h and 72h monitoring
- One study assessed an implantable event recorder (Ermis 2003).

C1 No TLoC during recording period

Three studies reported this outcome (Comolli 1993, Ermis 2003, Kapoor 1991).

Figure 5-16. No TLoC during recording period in patients with syncope unexplained after initial tests; subgroup by type of device

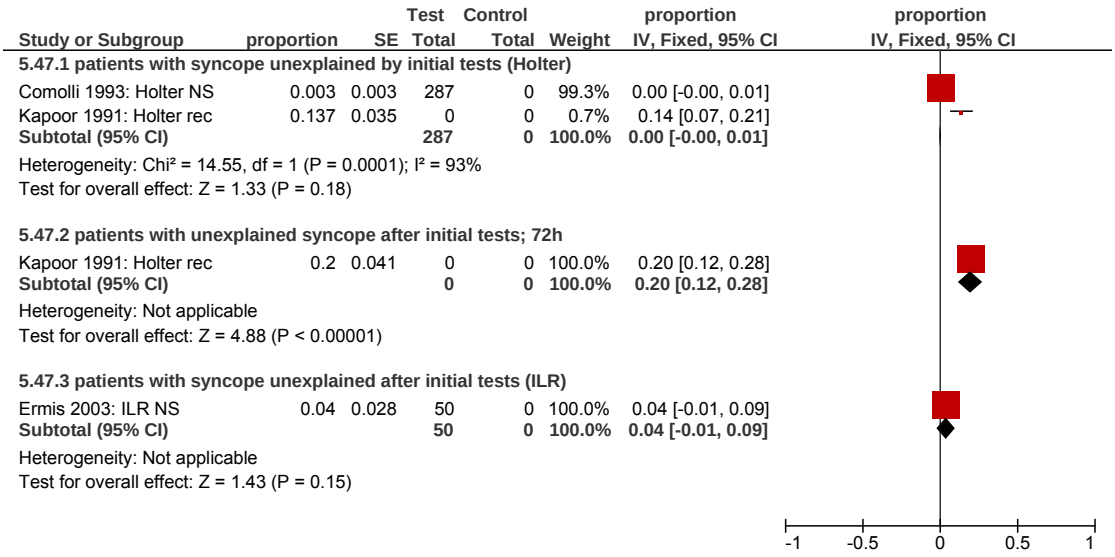


Test for subgroup differences: Chi² = 26.28, df = 2 (P < 0.00001), I² = 92.4%

C2 Normal rhythm during TLoC

Three studies reported this outcome (Comolli 1993, Ermis 2003, Kapoor 1991).

Figure 5-17. Normal rhythm during TLoC in patients with syncope unexplained after initial tests; subgroup by type of test

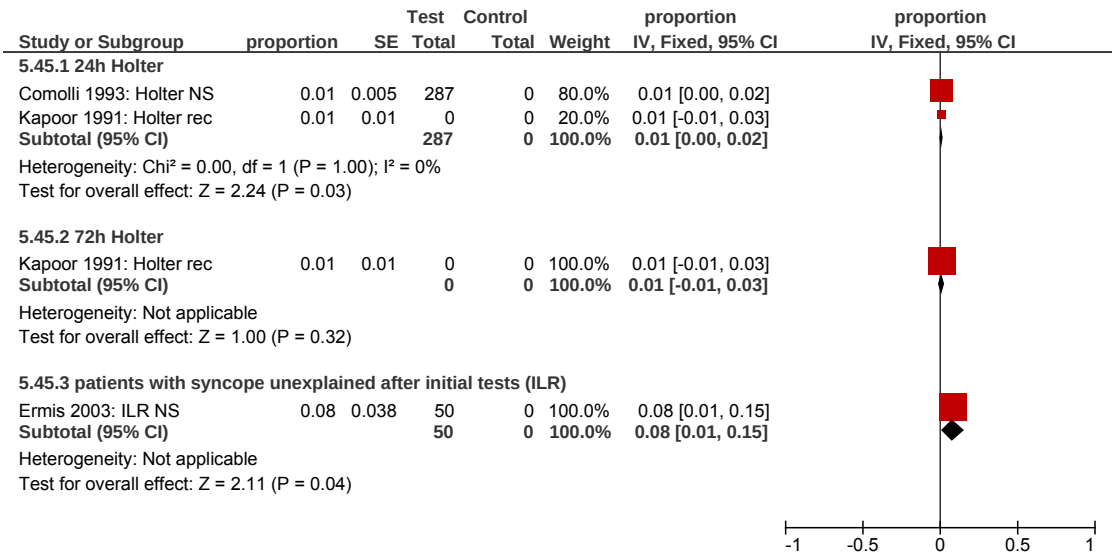


Test for subgroup differences: Chi² = 24.28, df = 2 (P < 0.00001), I² = 91.8%

C3 Arrhythmia during TLoC

Three studies reported this outcome (Comolli 1993, Ermis 2003, Kapoor 1991).

Figure 5-18. Arrhythmia during TLoC in patients with syncope unexplained after initial tests; subgroup by type of device

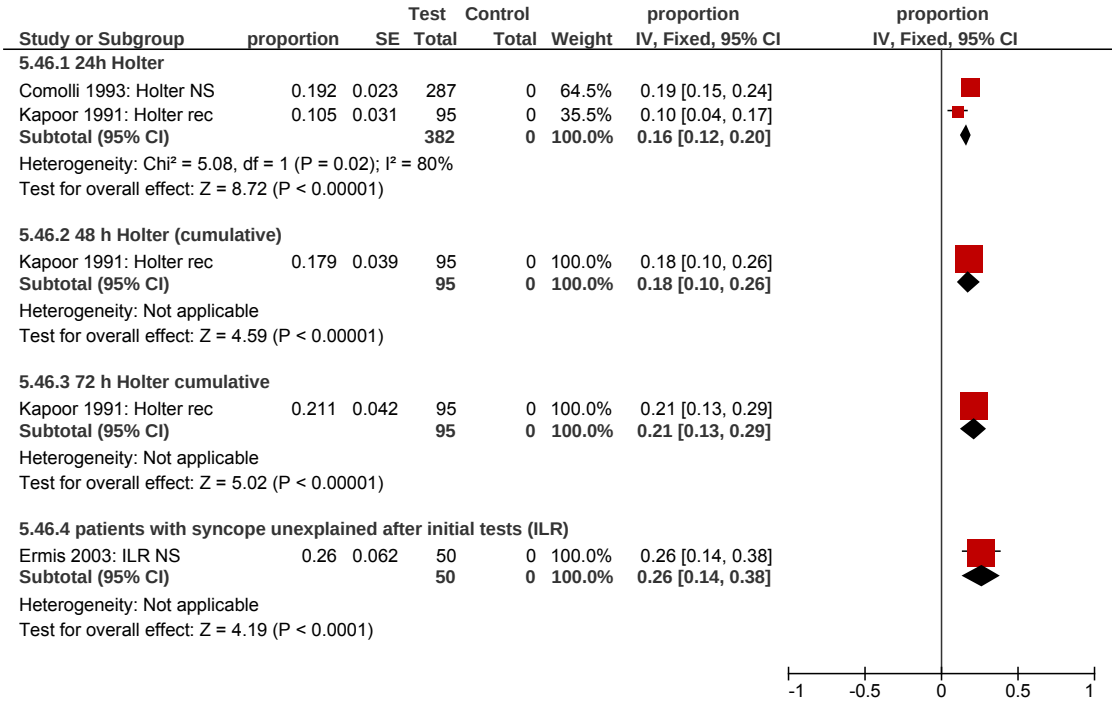


Test for subgroup differences: Chi² = 3.35, df = 2 (P = 0.19), I² = 40.4%

C4 Arrhythmia not during TLoC

Three studes reported this outcome (Comolli 1993, Ermis 2003; Kapoor 1991). For the Comolli (1993) and Kapoor (1991) studies we only considered the 'good' arrhythmias, and the Ermis (2003) study was assessed to be 'good' arrhythmias if grades 0 and I were considered only.

Figure 5-19. Arrhythmia not during TLoC in patients with syncope unexplained after initial tests; subgroup by type of device

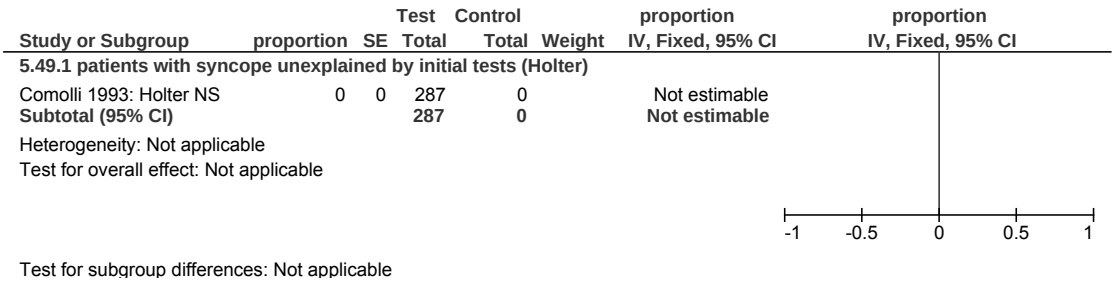


Test for subgroup differences: Chi² = 3.19, df = 3 (P = 0.36), I² = 5.8%

C5 No ECG during TLoC

One study reported this outcome (Comolli 1993).

Figure 5-20. No ECG during TLoC in patients with syncope unexplained after initial tests; subgroup by type of test



C6 Number of patients started on therapy

One study (Ermis 2003) reported that 16 out of 50 patients were started on therapy.

C7 Number with Adverse events

No study reported this outcome.

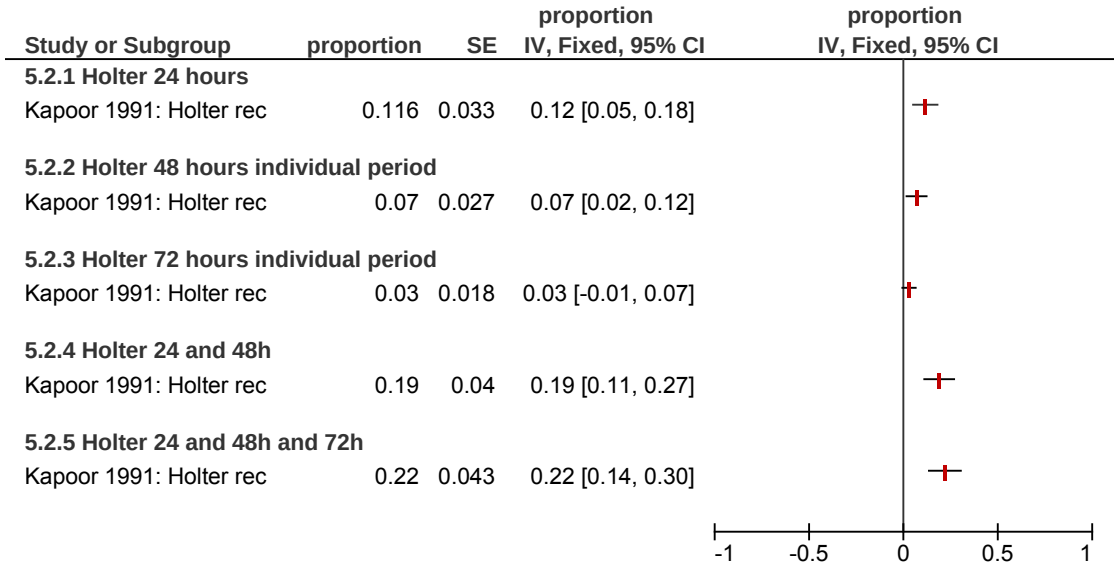
C8 Number of patients who died

One study (Ermis 2003) reported that 3 out of 50 patients died.

C9. All arrhythmias for 24h versus 48h versus 72h Holter monitoring.

One study (Kapoor 1991) gave patients a Holter monitor for up to three 24-hour periods. Patients who had no arrhythmias detected in the first 24-hours were given the monitor for a further 24-hour period and so on. The total number of patients with arrhythmias recorded (with and without TLoC) for each period and the cumulative results are shown in Figure 5-20.

Figure 5-20: Holter monitoring for 24 versus 48 versus 72h



5.3.5.5 *Results for unexplained syncope following secondary tests – subgroup comparisons of tests*

Twenty-two studies included patients with unexplained syncope after secondary tests (Aronow 1993, Boersma 2004, Brignole 2005, Donateo 2003, Farwell 2006, Fogel 1997, Krahn 1998, Krahn 2001, Krahn 2002, Krahn 2004, Lacroix 1981, Linzer 1990, Lombardi 2005, Moya 2001, Nierop 2000, Pezawas 2007, Pierre 2008, Rockx 2005, Sarasin 2001, Sarasin 2001, Schuchert 2003, Seidl 2000).

Four studies did not state the TLoC history (Aronow 1993, Fogel 1997, Sarasin 2001a, Sarasin 2001b); the others included patients with recurrent TLoC. There were no studies that stated that TLoC was not recurrent.

The following devices were investigated for this patient group:

- Three studies assessed Holter 24-hour monitoring (Aronow 1993, Lacroix 1981, Sarasin 2001)
- One study assessed Holter 48-hours (Rockx 2005)
- Five studies assessed an external event recorder (Fogel 1997, Linzer 1990, Rockx 2005, Sarasin 2001, Schuchert 2003)

- Fourteen studies assessed an implantable event recorder (Boersma 2004, Brignole 2005, Donateo 2003, Farwell 2006, Krahn 1998, Krahn 2001, Krahn 2002, Krahn 2004, Lombardi 2005, Moya 2001, Nierop 2000, Pezawas 2007, Pierre 2008, Seidl 2000).

The frequency of TLoC and time to recurrence, where reported, were as follows:

- 24-hour Holter monitor: Lacroix (1981) - estimated to be 3 per year; not stated for the other studies.
- 48-hour Holter monitor: Rockx (2005) – 2 per year
- EER: Linzer (1990) - 10 per year and mean duration of monitoring before diagnosis was 7 days; Rockx (2005) – 2 per year and mean time to diagnosis 17 days; Schuchert (2003) – 6 per year; the other studies did not state the frequency or time to recurrence.
- IER: Boersma (2004) – median 2.7 per year; Donateo (2003) – median 1.5 / year and median time to activate the device 9 months; Farwell (2006) – mean 1.5 / year; Krahn (1998) – mean 7.2 / year and time to event mean 5.1 months; Krahn (2001) – 2.6 / year; Krahn (2002) – not stated and mean 93 days; Krahn (2004) – median 2 / year; Lombardi (2005) – 2 / year and mean time to recurrence 7.6 months; Moya (2001) – median 2 / year and median time to recurrence 105 days; Nierop (2000) – mean 5.2 / year; Pezewas (2007): recurrence rate 30% at 3 months and 91% at 24 months; Pierre (2008) – mean time to recurrence 5.4 months; Seidl (2000) – mean 6.3 / year.

Thus, for most studies, TLoC was infrequent, so devices other than IER were less likely to detect an event during the monitoring time. The exception was Linzer (1990), for which the patients had a TLoC frequency compatible with the EER monitoring period.

D1. No TLoC during recording period

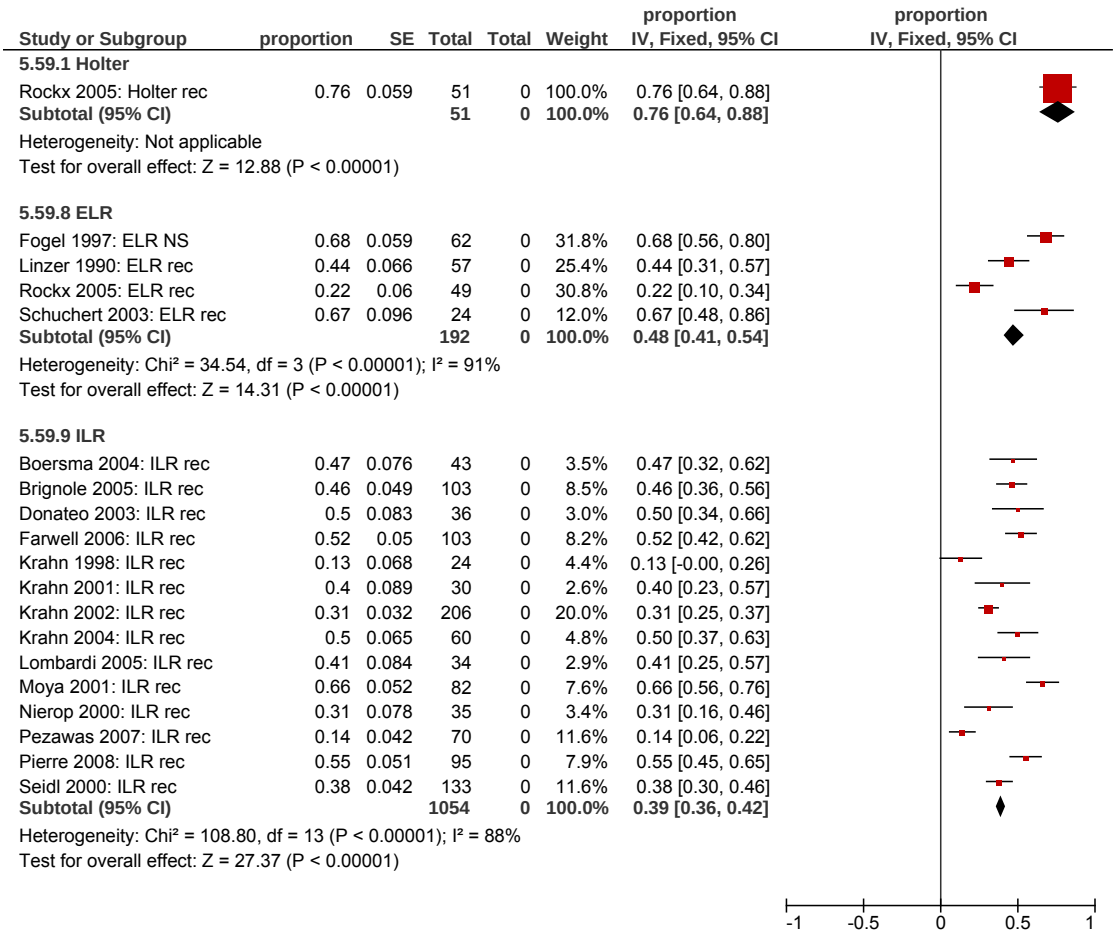
Eighteen studies reported the number of patients with no TLoC during the recording period (Boersma 2004, Brignole 2005, Donateo 2003, Farwell 2006,

Fogel 1997, Krahn 1998, Krahn 2001, Krahn 2002, Krahn 2004, Linzer 1990, Lombardi 2005, Moya 2001, Nierop 2000, Pezawas 2007, Pierre 2008, Rockx 2005, Schuchert 2003, Seidl 2000).

Four of these studies did not record all outcomes: Boersma 2004, Nierop 2000; Pezawas 2007, Pierre 2008). A sensitivity analysis without these studies (not shown) did not significantly change the heterogeneity.

We carried out a subgroup analysis, splitting the studies by whether patients were included or excluded following secondary tests (Appendix D4). This did not account for the heterogeneity.

Figure 5-21. No TLoC during recording period (unexplained after secondary tests); subgroup by type of device; recurrent only.

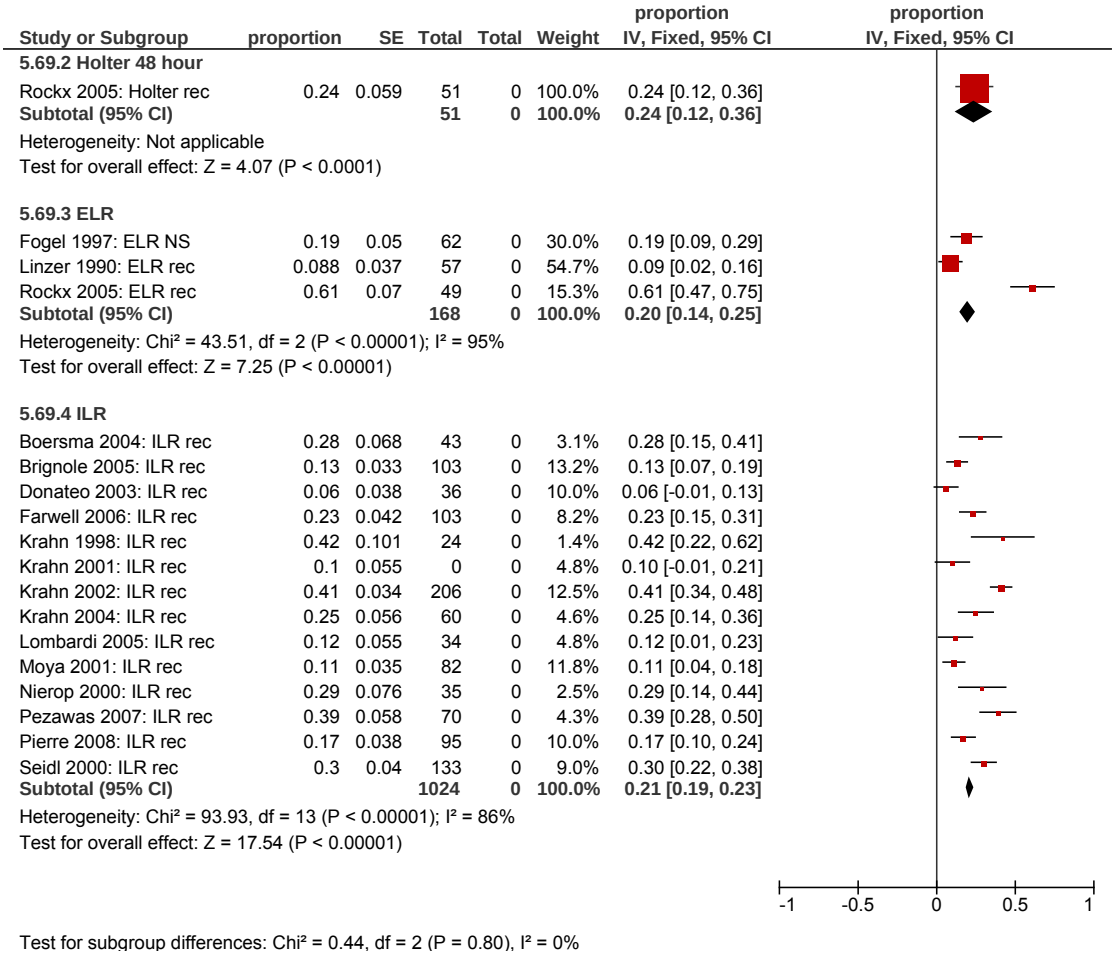


Test for subgroup differences: Chi² = 40.01, df = 2 (P < 0.00001), I² = 95.0%

D2 Normal rhythm during TLoC

There was significant heterogeneity for the EER device, with Rockx (2005) showing a very high proportion with normal rhythm. The study referred to 'symptoms' which we assumed meant syncope or pre-syncope. The IER device also had significant heterogeneity and subgroup analysis of patients excluded or included after secondary tests did not explain this (Figure 5-22).

Figure 5-22. Normal rhythm during TLoC (unexplained after secondary tests); subgroup by type of device

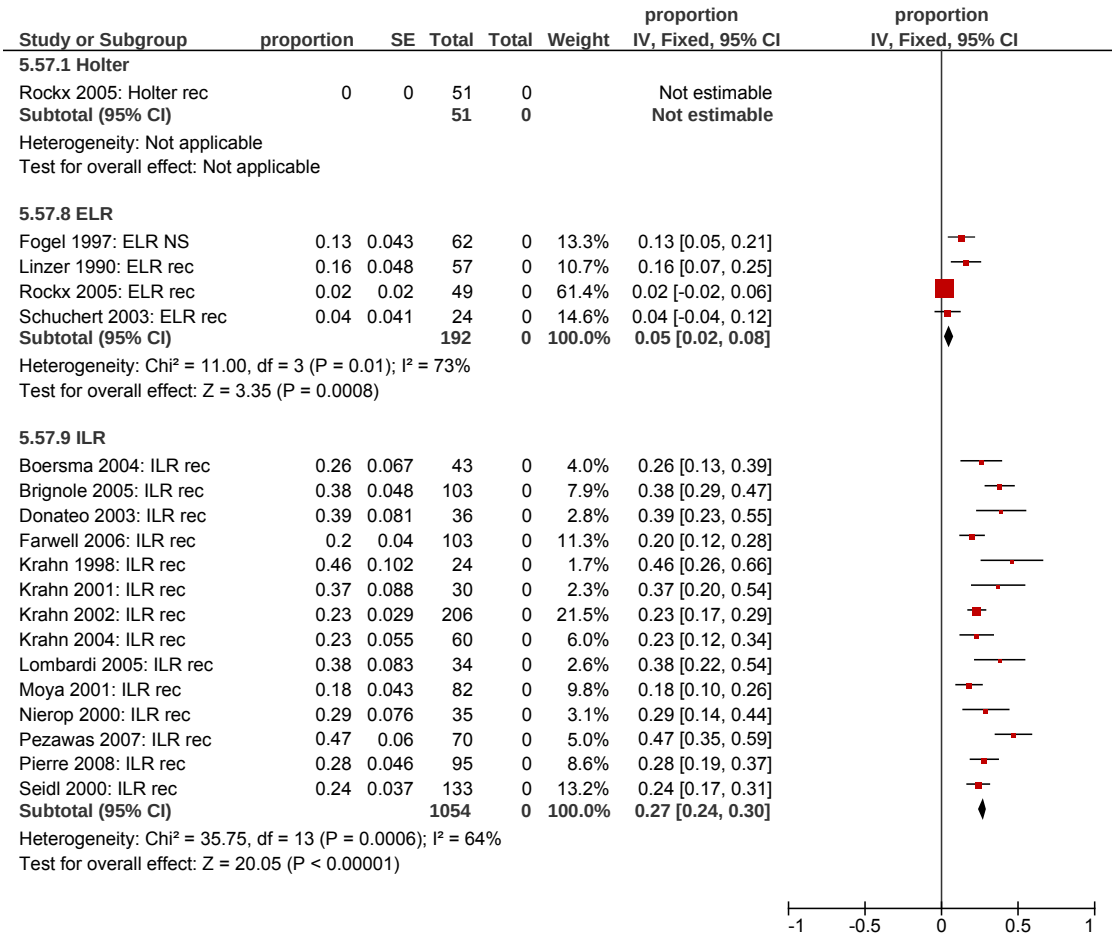


Test for subgroup differences: Chi² = 0.44, df = 2 (P = 0.80), I² = 0%

D3 Arrhythmia during TLoC

Again heterogeneity was found for the IER and EER devices. This did not appear to be explained by the subgroup analysis of excluded or included following initial tests.

Figure 5-23. Arrhythmia during TLoC (unexplained after secondary tests); subgroup by type of device; recurrent TLoC only

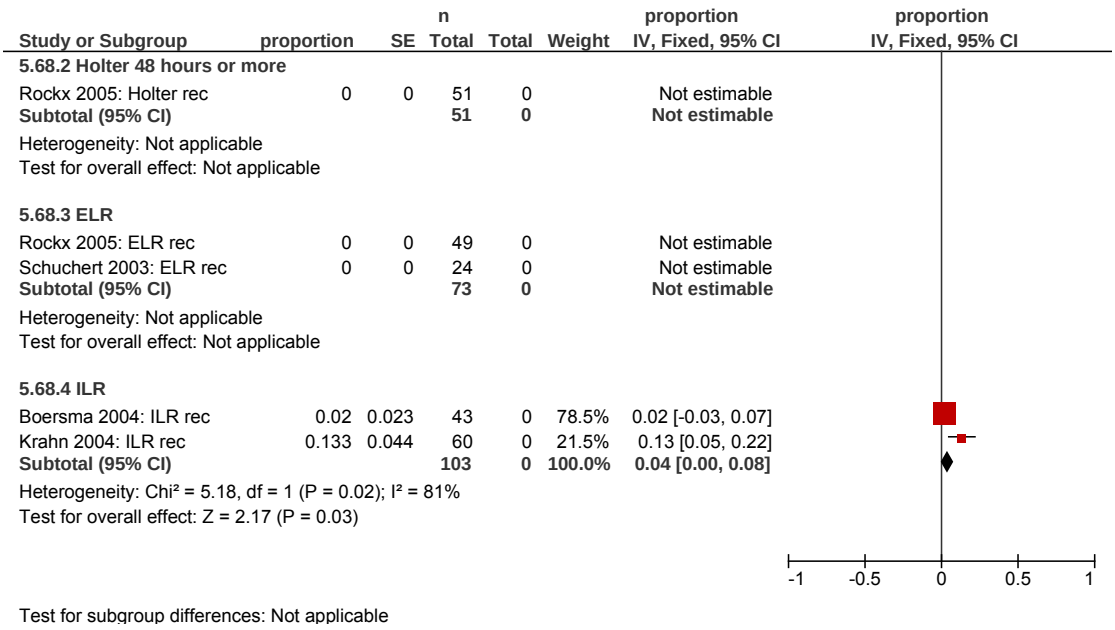


Test for subgroup differences: Chi² = 110.76, df = 1 (P < 0.00001), I² = 99.1%

D4 Arrhythmia not during TLoC

Few studies identified arrhythmias during TLoC for this population.

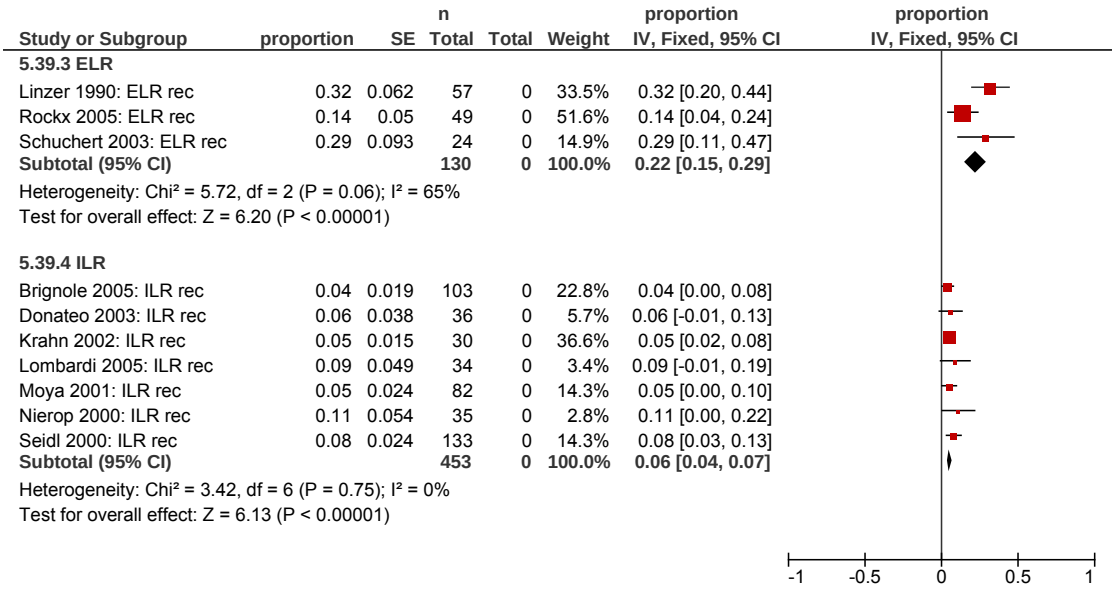
Figure 5-24. Arrhythmia not during TLoC (unexplained after secondary tests); subgroup by type of device



D5 No ECG during TLoC

The studies included for this outcome all had self consistent results. There was no heterogeneity for the IER group and the proportion for this outcome ranged from 4 to 11%.

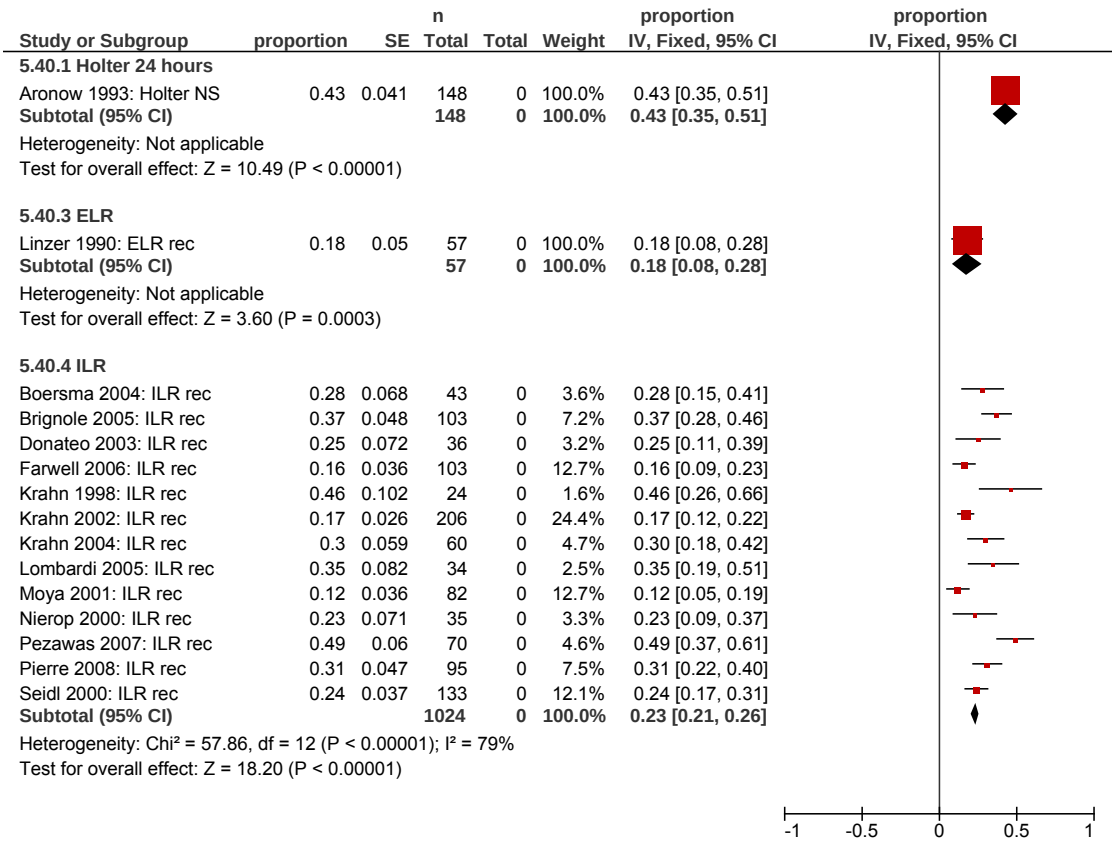
Figure 5-25. No ECG during TLoC (unexplained after secondary tests); subgroup by type of device



Test for subgroup differences: Chi² = 20.35, df = 1 (P < 0.00001), I² = 95.1%

D6 Number of patients started on therapy

Figure 5-26. Number of patients started on therapy (unexplained after secondary testing); subgroup by type of device



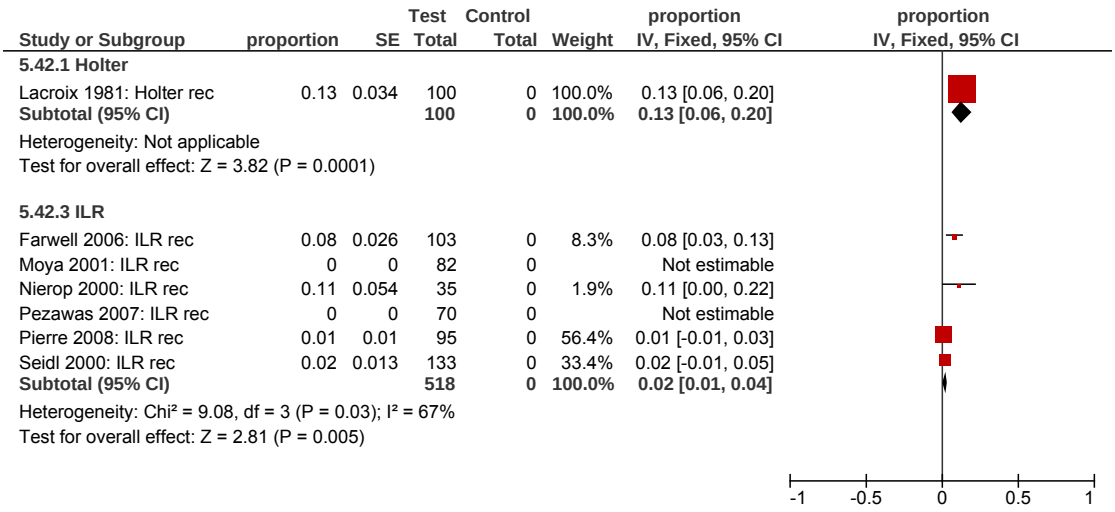
Test for subgroup differences: Chi² = 22.76, df = 2 (P < 0.0001), I² = 91.2%

D7 Adverse events

Seidl (2000) reported that 12 patients out of 130 had an adverse event.

D8 Number of patients who died

Figure 5-27. Number of patients who died (unexplained after secondary tests).



Test for subgroup differences: Chi² = 9.78, df = 1 (P = 0.002), I² = 89.8%

1 Summary

2 The results from these tests are summarised in Table 22. A high level of
3 heterogeneity is indicated by blue shading.

Table 22: Summary of results: reported as the weighted mean for the proportion (range) and inconsistency (I^2)

	Holter 24h	Holter 48h	External ER	Implantable ER
No TLoC during recording				
Suspected arrhythmia (>50% single episode)	84%; n=1	none	none	none
Suspected arrhythmia	none	87%; n=1	31%; n=1	47% (32 to 60); n=4; I^2 = 81%
Suspected NM syncope	80%; n=1	none	none	64% (52 to 66); n=3; I^2=0%
Unexplained after initial	99% (85-99); n=2; I^2=93%	72h Holter 79% n=1	none	88%; n=1
Unexplained after secondary tests	none	76%; n=1	48% (22 to 68); n=4; I^2=91%	39% (13 to 66); n=14; I^2=88%
Normal rhythm during TLoC				
Suspected arrhythmia (>50% single episode)	9%; n=1	none	none	none
Suspected arrhythmia	none	6%; n=1	28%; n=1	6% (2 to 34); n=4; I^2 = 92%
Suspected NM syncope	12% ; n=1	none	none	8% (7 to 20); n=3; I^2=18%
Unexplained after initial	0% (0 to 14); n=2; 93%	72h Holter: 20% n=1	none	4%; n=1
Unexplained after secondary tests	none	24%; n=1	20% (9 to 61%); n=3; I^2=95%	21% (6 to 42); n=14; I^2=86%
Arrythmia during TLoC				
Suspected arrhythmia (>50% single episode)	6%; n=1	none	none	none
Suspected arrhythmia	none	7% (6 – 8); n=2; 0%	41%; n=1	30% (25 to 38); n=4; I^2 = 0%
Suspected NM syncope	8%; n=1	none	none	20% (20 to 28); n=3; I^2=0%
Unexplained after initial	1% (1-1); n=2; I2=0%	72h Holter: 1% n=1	none	8% ; n=1
Unexplained after secondary tests	none	0% n=1	5% (2 to 16); n=4; I^2=73%	27% (18 to 47); n=14; I^2=64%
Arrhythmia recorded, not during TLoC				
Suspected arrhythmia (>50% single episode)	none			
Suspected arrhythmia	none	13% (8-35); n=2; I2=92%	0%; n=1	8%; n=1
Suspected NM syncope	none	0% n=1	none	3%; n=1
Unexplained after initial tests	16% (10-19); n=2; I2=80%	48h Holter 18% n=1; 72 hour Holter 21%; n=1	none	26%; n=1
Unexplained after	none	0%; n=1	0% n=2 (both	4% (2 to 13);

Table 22: Summary of results: reported as the weighted mean for the proportion (range) and inconsistency (I^2)

	Holter 24h	Holter 48h	External ER	Implantable ER
secondary tests			0%)	n=2; I^2=81%
No ECG recorded				
Suspected arrhythmia (>50% single episode)	none	none	none	none
Suspected arrhythmia	none	none	none	8% (6 to 9); n=2; I^2=0%
Suspected NM syncope	none	none	none	9% (7 to 9); n=2; I^2= 0%
Unexplained after initial	0%; n=1	none	none	none
Unexplained after secondary tests	none	none	22% (14 to 32%); n=3; I^2=65%	6% (4 to 11%); n=7; I^2=0%
Number of patients started on therapy				
Suspected arrhythmia (>50% single episode)	none	none	none	none
Suspected arrhythmia	none	13%; n=1	none	28% (22 to 44); n=3; I^2=72%
Suspected NM syncope	none	3%; n=1	none	15% (14 to 28); n=3; I^2 = 14%
Unexplained after initial	none	none	none	32%; n=1
Unexplained after secondary tests	43%; n=1	none	18%; n=1	23% (12 to 49%); n=13; I^2=79%
Number of patients who died				
Suspected arrhythmia (>50% single episode)	none	none	none	none
Suspected arrhythmia	20% (16 to 29); n=3; I^2=59%	none	none	2% (2 to 2); n=3; I^2=0%
Suspected NM syncope	none	none	none	0%; n=1
Unexplained after initial	none	none	none	6%; n=1
Unexplained after secondary tests	13%; n=1	none	none	2% (1 to 11); n=4; I^2=67%

Some general trends can be identified:

For each population, there is a general increase in the proportion of people with a TLoC during monitoring in the order Holter 24-hour, Holter 48-hour, EER and IER, although the EER for the suspected arrhythmia group is anomalously high, possibly due to a good match between frequency of TLoC and the event recorder duration of monitoring. For example, for the suspected arrhythmia group, the Holter 48-hour monitor had a 13% with no TLoC, the EER was 69% and the IER was 53%.

The same trends are found for arrhythmia during TLoC, with the yield for this outcome, ranging from 7 (Holter 48h) to 30% (IER) for the suspected

arrhythmia group and 1 to 8% for the group with unexplained syncope after the initial assessment

The proportion with normal rhythm during TLoC appears to be independent of device, and a similar trend is found for arrhythmia recorded not during TLoC

Only the IER reported a failure to record an ECG during TLoC, giving a fairly constant value of 4 to 11%. Three studies in EERs for patients with unexplained syncope after secondary tests reported a range of 14 to 32% for this outcome. It is unclear why this should be.

The IER had a higher proportion of people started on therapy as directed by the monitoring device. A single study reported 43% of patients received Holter 24-hour directed therapy for TLoC unexplained after secondary tests.

5.3.5.6 Results by test – subgroup comparisons of populations

Appendix D4 shows forest plots for each test (Holter 24-hours, Holter 48-hours or more, EER, IER), with subgroups by population, for each outcome. In addition, subgroup analyses were carried out for the IER device, separating the population groups into patient activated and patient plus automatic activated devices (Appendix D4). The following trends can be observed:

1) Holter 24-hour monitoring

- There appears to be a significantly higher incidence of TLoC during monitoring for people with suspected arrhythmic syncope (16%) than for those with unexplained syncope following initial tests (1-15%), although the latter had heterogeneity.
- The same trend was observed for the proportions of patients with arrhythmia during TLoC, and for those with arrhythmia not during TLoC.

2) 48-hour monitoring

- There appeared to be no significant difference between population groups for the incidence of TLoC during a 48-hour period of monitoring.
- There was a trend for increased proportions of patients with normal arrhythmia during TLoC across the groups: suspected arrhythmia (6%), suspected neurally mediated syncope (12%), unexplained after initial tests (20%) and unexplained after secondary tests (24%); all results were for single studies.
- There were low proportions of patients with arrhythmias detected during TLoC, and this appeared to be lower for the two groups with unexplained TLoC.

3) External event recorder

- There was too much heterogeneity to determine if there was a difference between the population groups suspected arrhythmia versus unexplained syncope after secondary tests, for the incidence of TLoC and for normal rhythm during TLoC.
- There was a significantly higher incidence of arrhythmia during TLoC for the suspected arrhythmia group (41%) than for the people with unexplained syncope after secondary tests (2-16%). We note that the single study in the arrhythmia group was in people who had frequent TLoC.
- All the studies (one in people with suspected arrhythmia and two with unexplained syncope after secondary tests) reported no patients with arrhythmia not during TLoC.

4) Implantable event recorder

Studies of the IER generally showed heterogeneity for most outcomes, for each population group.

- For the proportion of patients with a TLoC during monitoring; there appeared to be a lower incidence in the group with suspected neurally mediated syncope (36%) versus suspected arrhythmia (40-68%) and

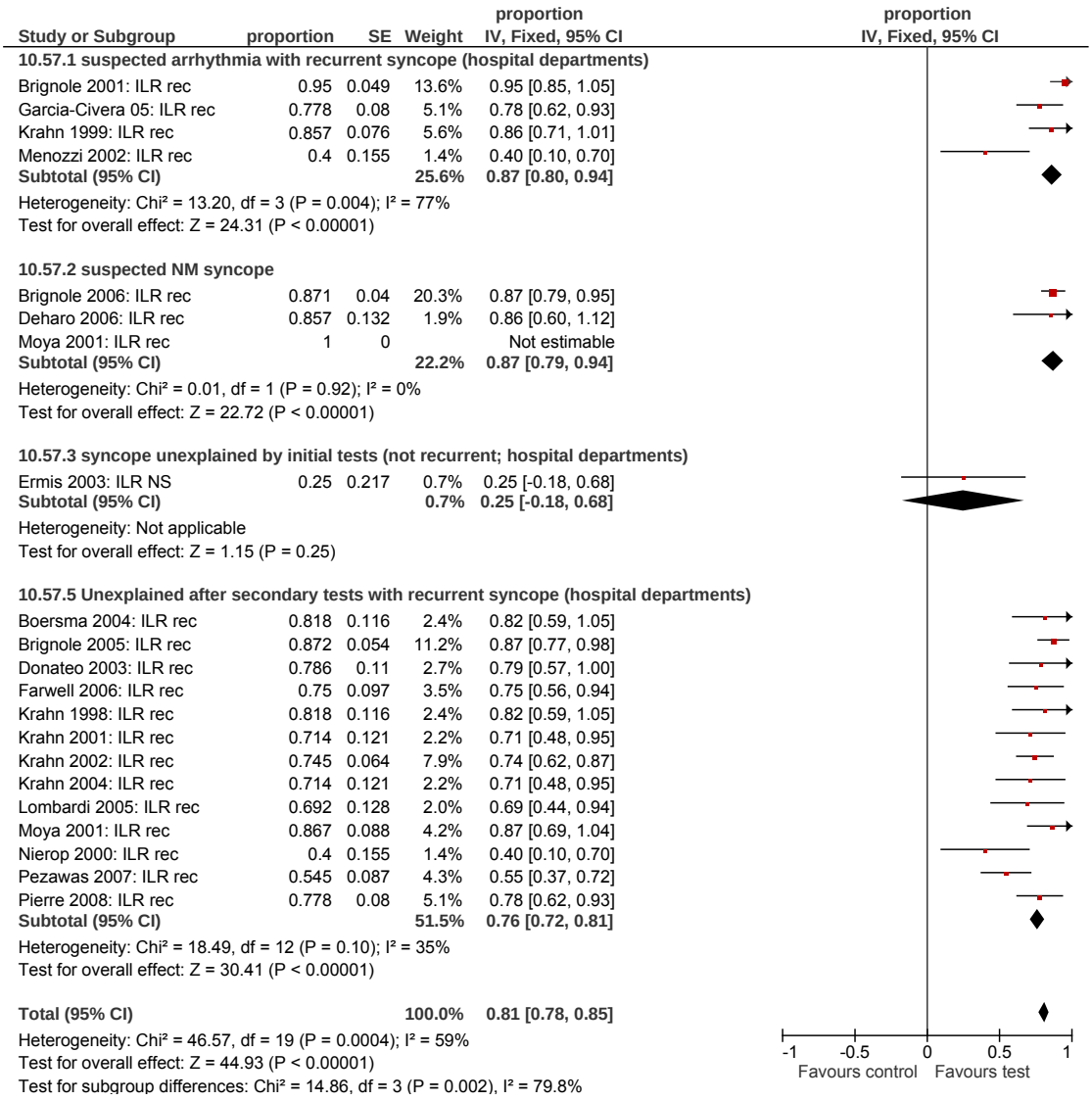
versus unexplained syncope following secondary tests (34-87%). There was only one study for unexplained syncope following initial tests and this may have been an outlier.

- There appeared to be a significantly higher proportion of people with a normal rhythm during TLoC for the group, unexplained syncope following secondary tests (6-41%) versus the other populations (around 6%). There was not a significant effect of patient activated versus patient plus automatically activated devices.
- For the proportion with arrhythmia during TLoC: this appeared to be higher for the groups with unexplained syncope after secondary tests (18-47%) and the suspected arrhythmia group (25-38%), compared with the suspected neurally mediated syncope group (20-28%) and the study reporting unexplained syncope after initial tests (one study; 8%). There was not a significant effect of patient activated versus patient plus automatically activated devices.
- For the proportion with arrhythmia not during TLoC: this generally was low (3-6%) but the single study in the group, unexplained after initial tests had a much higher proportion (26%). There was not a significant effect of patient activated versus patient plus automatically activated devices.
- There was no significant difference between any of the population groups for the outcome no ECG during TLoC (6-9%).

5.3.5.7 Results: proportion of bradyarythmias for IERs

For the number of bradyarrhythmias as a proportion of all arrhythmias the following results were obtained for the IERs (Figure 5-28). With a few exceptions, there was an approximately constant proportion of bradycardia arrhythmias of around 80-90%, which appeared to be independent of the population group.

Figure 5-28 Proportion of bradycardias (of all arrhythmias)



5.3.5.8 Results: subgroup analyses to investigate heterogeneity in IER studies

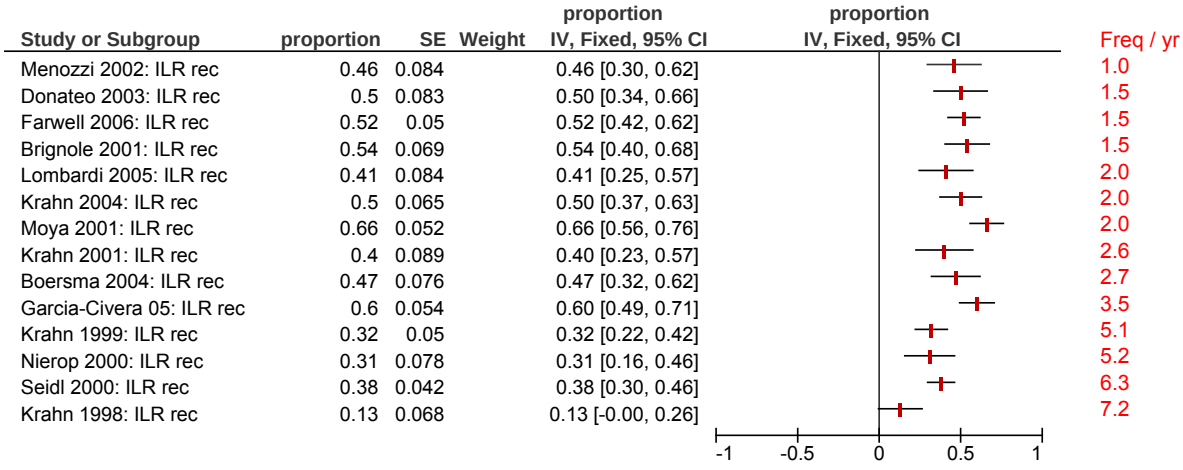
We carried out three subgroup analyses for the IER studies: by duration of monitoring; by frequency of previous TLoC and according to the product, duration of monitoring x frequency of TLoC. These analyses were peformed for the outcome, no TLoC during monitoring. Since there was little difference in the incidence of TLoC for the suspected arrhythmia and unexplained TLoC groups, we decided to combine the results for these two populations (the

suspected NM syncope population was excluded from these analyses). Forest plots are shown in Appendix D4.

Subgroup analysis was carried out for the pre-specified durations (less than 6 months, 6-12 months and more than 12 months), but this did not explain the heterogeneity.

For frequency of TLoC, the GDG had pre-specified separating the studies into highly frequent, frequent and infrequent, but all the studies for this device fell into the infrequent category. Figure 5-29 shows the studies in order of increasing frequency of previous TLoC. As might be expected, the proportion with no TLoC during monitoring decreases as the frequency increases, suggesting that this may be an important factor; the post-hoc subgroup analysis showed some reduction in heterogeneity. There is some indication that the product of frequency and duration of monitoring had an effect too, but there was still heterogeneity.

Figure 5-29: No TLoC during monitoring, IER, studies ordered by frequency



We also conducted a sensitivity analysis in which studies were included only if they had a frequency of TLoC of more than 5 per year. Six studies fell into this category. For the IER device there was very little heterogeneity for all outcomes (Appendix D4).

There was a trend towards a smaller proportion with TLoC for the suspected neurally mediated group, and no difference between population groups for the outcome, arrhythmia during TLoC – this was recorded in 25% of patients.

5.3.5.9 Results: Implantable event recorders – patient activation versus patient plus automatic activation

Implantable event recorders can capture events by patient activation or by automatic activation. Earlier devices (e.g. Reveal) were patient-activation only; later ones (e.g. Reveal Plus) can be activated either automatically or by the patient.

One study (Ermis 2003) reported that 5 of 6 patients had syncope recorded by automatic activation, but only 1 of 6 was detected by patient activation. For all arrhythmias, including those not during syncope, 30 patients had recordings, 24 of which were automatically activated alone, 3 were activated only by the patient and 3 by both.

In a second study (Farwell 2006), 37% of patients failed to capture their first TLoC event. This was due either to a failure to activate the IER or to a delay between the TLoC and subsequent device interrogation, resulting in overwriting of the event data by subsequently captured data. The study noted that, after longer term follow up, this figure reduced to 5%. The Farwell (2006) study noted that automatic activation considerably enhanced the diagnostic yield: this gave 19% of all diagnoses.

The authors of the Farwell (2006) study recommended that patients with an IER should be regularly followed up, in order to:

- Interrogate the device
- Fine-tune the sensitivity for auto-activation
- Re-educate patients about the technique of manual activation
- Encourage early presentation after any TLoC event to prevent overwriting of the auto-holters and the loss of diagnostic data.

As mentioned above, we also looked at subgroup analyses that subdivided studies into those that used patient-activated devices versus those using patient plus automatic activation (Appendix D4). There appeared to be no significant differences between subgroups, but we note that this is an indirect comparison.

5.3.6 Results: comparative studies

5.3.6.1 Ambulatory ECG versus 'conventional' testing

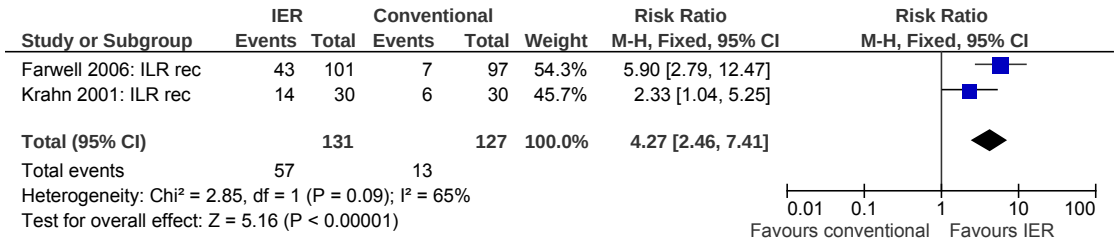
IER versus conventional testing – diagnostic yield

Two RCTs compared an IER with 'conventional' testing (Farwell 2006, Krahn 2001). Both studies were in people with unexplained TLoC after secondary tests, but the Krahn (2001) study specifically excluded people with a presentation typical of neurally mediated syncope on initial assessment. The studies differed in the comparator arm, with all patients in the Krahn (2001) study being given an EER, followed by tilt and electrophysiology tests, but only some of those in the Farwell (2006) study received a 24-hour Holter monitor or an EER. We note that Farwell (2006) is a UK-based study, i.e. the conventional investigation and management is appropriate for the guideline's population. We also note that the Farwell (2006) study was part funded by Medtronic Inc and three of the Krahn (2001) authors are consultants to Medtronic Inc.

The overall diagnostic yield (diagnoses achieved) is shown in Figure 5-30. Meta-analysis shows a significantly larger diagnostic yield (4 times larger) for the IER compared with the conventional testing arm. There is some heterogeneity (I^2=65%), but both studies had the same effect direction, and the heterogeneity is probably attributable to the differences in the conventional testing arm.

The Krahn (2001) study reported that the six diagnoses in the conventional arm were made using the EER (1 patient), tilt test (2 patients) and electrophysiology (3 patients), i.e. both EER and tilt test had a low yield.

Figure 5-30: diagnostic yield for IER versus conventional testing



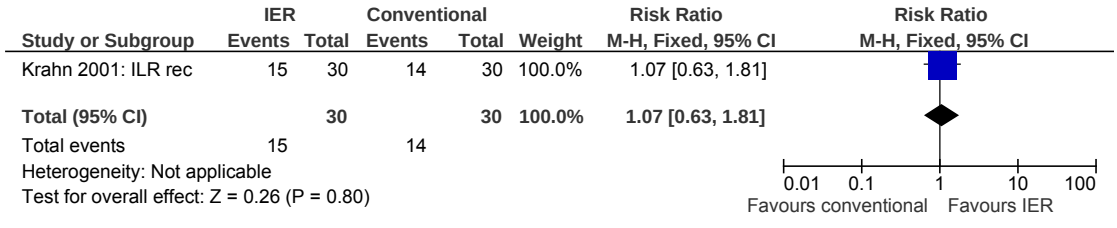
The Farwell (2006) study also reported time-to-ECG-diagnosis data, which gave a hazard ratio of 6.53 (95%CI 3.73 to 11.4) for IER versus conventional testing. This compares with the time to first syncope, which gave a hazard ratio of 1.03 (95%CI 0.67 to 1.58), i.e. not significantly different between the two groups.

IER then conventional testing versus conventional testing then IER

The Krahn (2001) study also considered two strategies such that patients randomised to one test could choose to receive the other test if they were undiagnosed after the first stage. Thirteen patients undiagnosed after IER were offered crossover to conventional monitoring, of whom 6 consented to crossover; only one of these patients was then diagnosed. Twenty-four patients undiagnosed after initial conventional testing consented to crossover to IER, of whom 8 were diagnosed; 5 undiagnosed, and 8 still in follow up at the time the paper was written.

The diagnostic yield for the full strategy shows no significant difference between strategies (Figure 5-31).

Figure 5-31: diagnostic yield for the full diagnostic strategy in Krahn (2001)



Test and treat strategies

The Farwell (2006) study reported the time to second syncope recurrence (i.e. recurrence following test, diagnosis and treatment). Their Kaplan Meier plot showed no significant differences between the curves for the two groups over the first 300 days from randomisation, but the curves diverged after that, with a smaller recurrence rate for the IER group. The time to second syncope recurrence gave a non-significant hazard ratio of 0.88 (95%CI 0.43 to 1.80) (Farwell 2004).

The Farwell (2006) study also reported patient outcomes following the different tests and treatment as a consequence of these test results. There was no significant difference in the number of deaths at censorship, but the time to recurrence of syncope was significantly longer for the IER group (p=0.04).

Quality of life: There was a significant improvement in the general wellbeing score for the IER group (p=0.03) but there was no significant difference in the SF-12 scores.

5.3.6.2 Comparison of different types of ambulatory ECG

External event recorders versus Holter monitoring

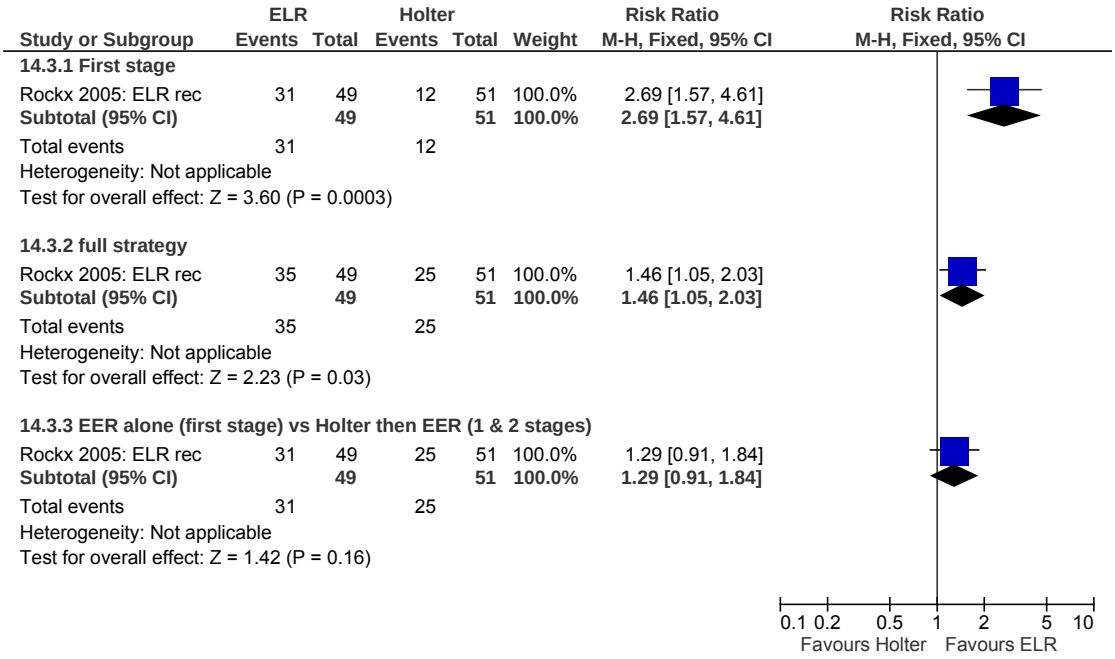
One RCT (Rockx 2005) in 100 patients with unexplained, recurrent syncope after secondary testing, compared an EER with 48-hour Holter monitoring. There was also another study (Krahn 2000) which contained a non-randomised comparison of these types of ambulatory ECG, but this study was not included because it was retrospective and there was alternative data from an RCT.

The Rockx (2005) study interventions were given in two stages: patients were randomised to the EER or Holter monitoring and then, if there was no recurrence of symptoms (or the EER was not activated), patients were offered

crossover to the other intervention. The results for the end of the first stage are reported in Figure 5-32, but the study also compared the two strategies, which can be considered a pragmatic representation of the clinical situation.

Thus, the results at the end of the second stage are concerned with the diagnostic yields if Holter 48-hour monitoring followed by EER in Holter negative patients is compared with EER followed by Holter monitoring in EER negative or EER failed activation patients. Crossover was accepted by 29/39 patients who were Holter negative and 4/18 of those who were EER negative/failed activation. The diagnostic yield (defined as arrhythmia or normal rhythm during TLoC) for the two strategies is shown in Figure 5-32, together with the comparison of EER alone versus EER then Holter.

Figure 5-32: diagnostic yield for EER versus Holter monitoring – after first stage, then after full strategy

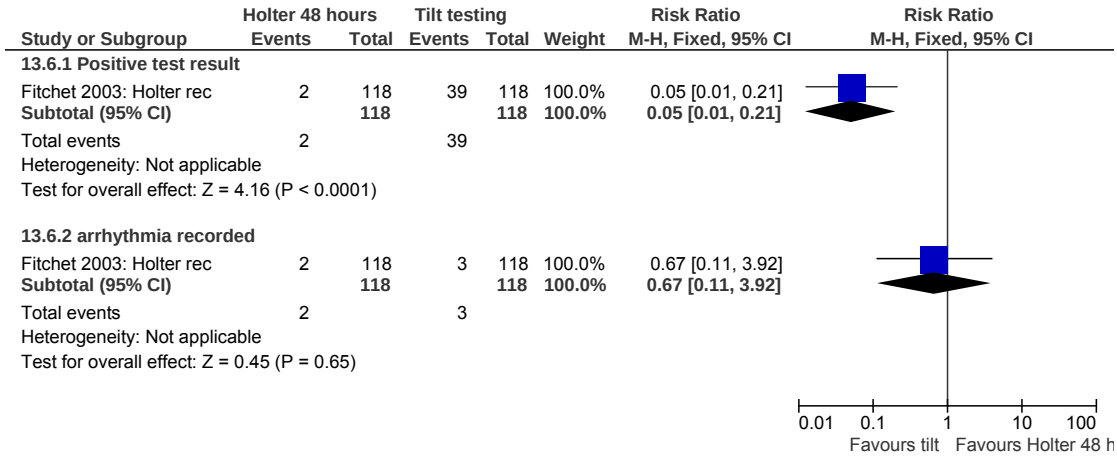


5.3.6.3 Comparison of ambulatory ECG device with other tests in the same patients

Two studies compared ambulatory ECG with other tests in the same patients: The Brignole (2006) study is reported in chapter 6 and one additional study (Fitchet 2003) is reported here.

The Fitchet (2003) study compared 48-hour Holter monitoring with a tilt test. This was a prospective study in which the 118 patients with suspected vasovagal syncope received both a 48-hour Holter monitor and a tilt test, within 3 months of each other. The tilt test (head up tilt (HUT) then glyceryl trinitrate (GTN) or isoprenaline) was positive in 39 (33%) patients and the yield for a cardioinhibitory response was 3/118 (2.5%). TLoC occurred in 2 (2%) patients during Holter monitoring (both of whom had a sinus tachycardia rhythm) and pre-syncope in 22 (19%). One patient had syncope during both tests, which was attributed to a sinus tachycardia rhythm. The diagnostic yield is shown in Figure 5-33 for both a positive response (on either test) and for an arrhythmia response on both tests. There is no significant difference in the latter (although the outcome is imprecise).

Figure 5-33. Tilt test versus Holter monitoring in the same patients with suspected NM syncope



5.4 *Clinical Evidence Review: people with exercise-induced syncope - accuracy of exercise testing*

5.4.1 Methods of the review: selection criteria

5.4.1.1 Population

Adults in secondary care with TLoC on exercise, in whom arrhythmic syncope is suspected after the initial assessment (patient history and eye witness

accounts, physical examination including upright and supine BP and 12-lead ECG). No clear alternative diagnosis based on patient history or physical examination. Subgroups (1) above 65 years (2) below 65 years.

5.4.1.2 Prior tests

12-lead ECG normal or any identified abnormality not likely to be the cause of TLoC.

5.4.1.3 The target condition

Arrhythmia provoked by exercise

5.4.1.4 The index test

Exercise testing

5.4.1.5 The reference standard

Expert clinician

5.4.2 Characteristics of included studies (Appendix D1)

We identified 107 studies as being potentially relevant to the review. Of these, three were included (Boudoulas 1979, Colivicchi 2002, Doi 2002) and 104 studies were excluded. The excluded studies are listed in Appendix F, along with reasons for exclusion.

One of the included studies was a case control study of diagnostic test accuracy (i.e. comparing patients with controls who had no evidence of syncope) (Doi 2002). The other studies were case series (Boudoulas 1979, Colivicchi 2002) in which patients who had had a TLoC underwent both exercise testing and another test (Holter 24-hour in Boudoulas 1979; tilt test in Colivicchi 2002), thus giving comparative diagnostic yields and diagnostic test accuracy statistics; the order of the tests was not randomised in either study.

5.4.2.1 Population

The inclusion and exclusion criteria for each of the studies are shown in the Appendix D1.

- The case control study (Doi 2002) included 64 people (mean age 46 years; 59% male) with unexplained syncope, in whom cardiovascular and cerebrovascular disease had been excluded by a 12-lead ECG, echo and CT scan; 18 of the patients had exercise-induced syncope, 26 had exercise-unrelated syncope (mostly vasovagal and situational) and there were 20 controls.
- Boudoulas (1979) included patients (mean around 51 years; 53% male) with syncope or presyncope (dizziness or lightheadedness), and in whom 64% had a suspected arrhythmic cause of syncope.
- Colivicchi (2002) included patients (mean age 21.4 years; 61% female) who were highly trained athletes with at least two witnessed episodes of syncope during or immediately after exercise in the last 6 months.

5.4.2.2 Index test

The index test was exercise testing, using the multistage treadmill exercise test Bruce protocol (Boudoulas 1979, Colivicchi 2002) or a modified rapid protocol (Doi 2002).

5.4.2.3 Reference standard

The Doi (2002) study compared the outcome of exercise testing between 'cases', with or without a medical history of exercise-induced syncope, and 'controls' who had no evidence of syncope. This constituted the reference standard for this study.

The Boudoulas (1979) study used the exercise test as the index test versus 24-hour Holter monitoring as the reference standard. The Colivicchi (2002) study used the exercise test as the index test versus a tilt test using isosorbide dinitrate as the reference standard.

5.4.2.4 Outcome

We constructed 2 x 2 tables for all the studies that reported diagnostic test accuracy. Other outcomes reported were diagnostic yield.

5.4.3 Methodological quality of included studies (Appendix D2

The reference standard for this review is expert clinician, however, no study reported this. The diagnostic test accuracy data for the Doi (2002) study are derived from results for patients versus controls who did not have syncope. Therefore, the spectrum of patients is biased. The selection of patients and controls may also introduce a bias, as the selection process was not defined in the studies. Selection of patients appeared to be 'all eligible patients selected', but these patients were those who had been referred to a syncope unit, for example, and the process of defining them as patients is not documented. Also, the control group was defined as people without syncope. Thus the representativeness of the sample was defined as inadequate. The comparison between people with exercise-induced TLoC and exercise-unrelated TLoC still constitutes a case-control study, with some selection bias, but the degree of spectrum bias is reduced.

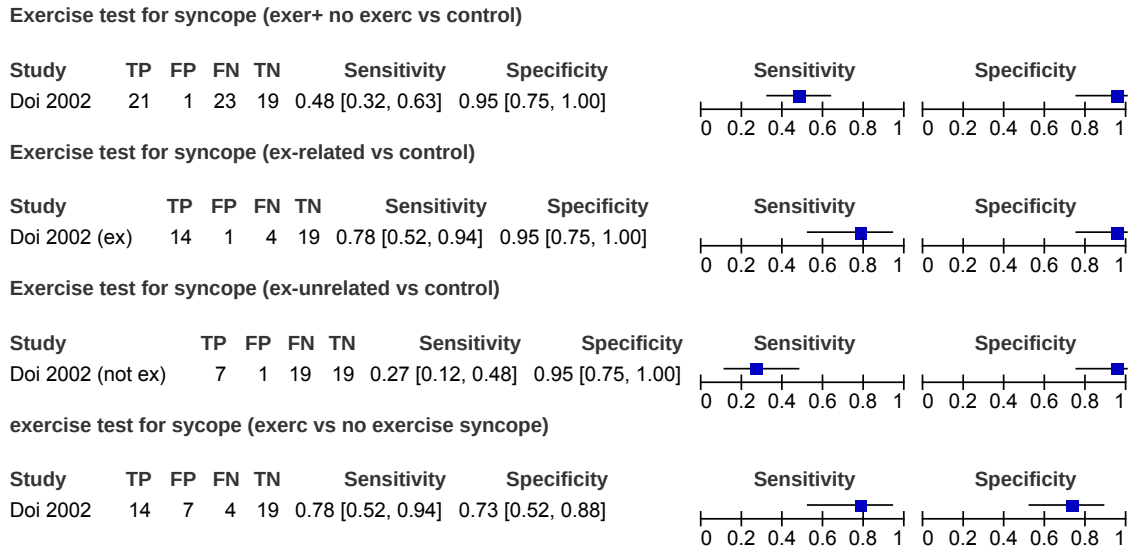
The other two studies (Boudoulas 1979; Colivicchi 2002) used another test as the reference standard: 24-hour Holter monitoring and tilt testing respectively. These are also unrepresentative reference standards. Overall, the studies were given a "-" rating on QUADAS.

5.4.4 Results

5.4.4.1 Exercise testing in patients with a history of exercise-induced TLoC versus no history – case control study

One case control study (Doi 2002) in patients with unexplained syncope reported diagnostic test accuracy statistics for exercise testing. The study used as its reference standard the definitions of cases and controls for two populations, those with exercise-induced syncope and those with exercise unrelated syncope. Figure 5-34 shows the sensitivity and specificity for syncope versus controls; exercise-induced syncope versus controls; exercise-unrelated syncope versus controls; and exercise-induced versus exercise-unrelated syncope.

Figure 5-34: Sensitivity and specificity of exercise testing



This study showed moderate sensitivity (78%) for the group with a history of exercise-induced syncope, with high specificity for the non-syncope controls (95%); the pre- and post-test probabilities were 47 and 93% respectively, and the likelihood ratio was 15.6. The corresponding sensitivity for the exercise-unrelated group was only 27% and the pre- and post-test probabilities were 57 and 88% respectively; the likelihood ratio was 5.4.

Comparing people with a history of exercise-induced syncope with those with other forms of syncope, the sensitivity and specificity were 78% and 73% respectively, with pre- and post-test probabilities of 41 and 67%, and a likelihood ratio of 2.9.

Exercise testing can be considered to distinguish moderately well between patients with exercise-induced syncope and those with other types of syncope. The test had high specificity for ruling out exercise-induced syncope in controls without a history of TLoC, but this is not especially useful for the TLoC population.

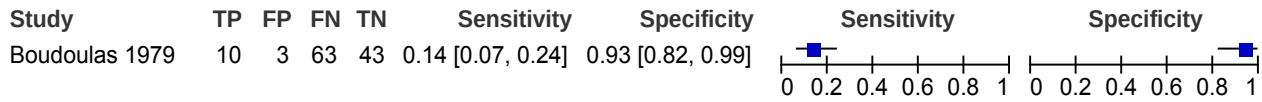
5.4.4.2 Exercise testing versus ambulatory ECG in people with a suspected arrhythmic cause of syncope

One study (Boudoulas 1979) compared exercise testing with 24-hour Holter monitoring in 119 people with a suspected arrhythmic cause of syncope. Previous history of exercise-induced syncope was not mentioned.

The study reported that 73/119 (61%) of patients had arrhythmias on Holter monitoring and there were 13 patients with arrhythmias on exercise testing. There were respectively 31 and 5 arrhythmias associated with 'symptoms' but it was unclear what these symptoms were, and within-patient correlations were not reported for the symptom-related arrhythmias. Diagnostic test accuracy statistics could be calculated for all arrhythmias and are shown in Figure 5-35 but this study should be treated with caution because we are unclear what was being reported for Holter monitoring.

The exercise test had low sensitivity (14%) in this population, although the specificity was high (Figure 5-35); the pre- and post-test probabilities were 61 and 77% respectively and the likelihood ratio was 2.1.

Figure 5-35 Exercise test versus 24-hour Holter monitoring.

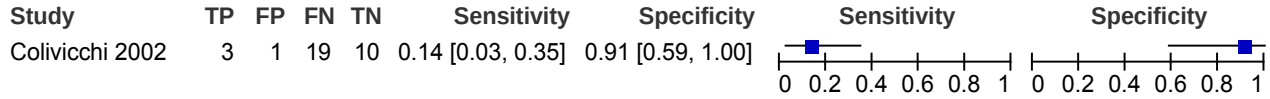


5.4.4.3 Exercise testing versus tilt test in young athletes without evidence of structural heart disease

One study (Colivicchi 2002) in 33 young athletes (mean age 21.4 years), with recurrent unexplained exercise-induced syncope, investigated various tests including exercise testing, a tilt test and 24-hour Holter monitoring and other tests. The study reported that 4 people had hypotension associated with pre-syncope on exercise testing; there were no episodes of syncope. Taking into consideration both syncope and pre-syncope, and comparing exercise testing versus the tilt test, with the latter as the reference standard, the sensitivity was 14%, with a specificity of 91%. Exercise testing showed the presence of sinus

tachycardia, whilst the tilt test revealed 45.4% of patients had an asystolic pause of more than 3 seconds on tilting. The tilt test is unlikely to be reliable as a reference standard and these results should be treated with caution.

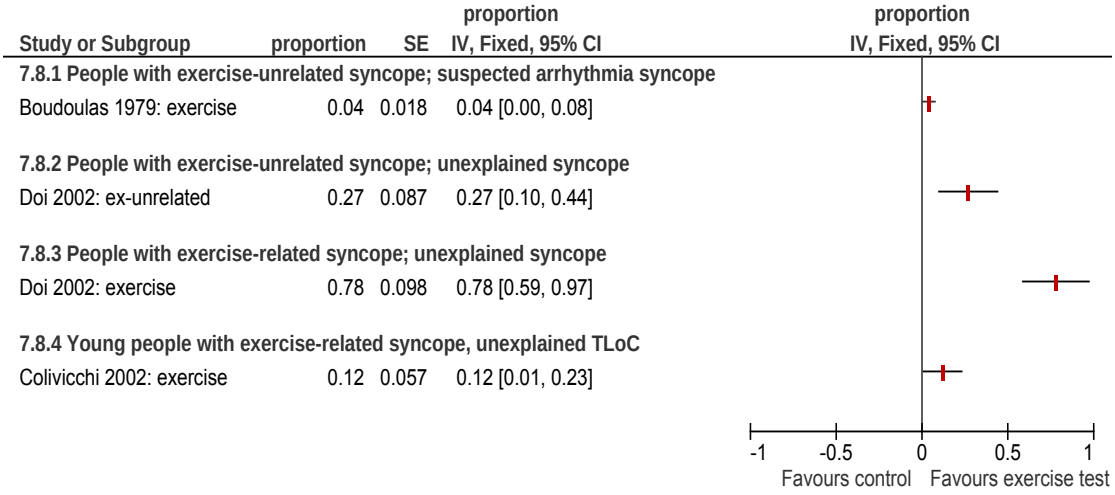
Figure 5-36: Exercise test versus HUT-ISDN



5.4.4.4 Diagnostic yields

All three studies reported the diagnostic yield for exercise testing in the various patient groups; for the case control study (Doi 2002), results were given for the 'cases' only. In the Boudoulas (1979) study the number of patients with symptoms was reported and the number with syncope and pre-syncope for the other studies (Figure 5-37).

Figure 5-37: Exercise testing diagnostic yield



5.5 Clinical Evidence Review: people with suspected neurally mediated syncope after initial assessment - accuracy of tilt-testing

5.5.1 Methods of the review: selection criteria

5.5.1.1 Population

Adults in secondary care with TLoC, in whom neurally mediated syncope is suspected after the initial assessment (patient history and eye witness accounts, physical examination including upright and supine BP and 12-lead ECG). No clear alternative diagnosis based on patient history or physical examination.

5.5.1.2 Prior tests

12-lead ECG normal or any identified abnormality not likely to be the cause of TLoC.

5.5.1.3 The target condition

Neurally mediated syncope.

5.5.1.4 The index test

Tilt Table test (all types)

5.5.1.5 The reference standard

Expert clinician

5.5.1.6 Sensitivity analyses

Sensitivity analyses were to be carried out to address the following:

- Poor quality on QUADAS
- Differences in the definition of what constituted an 'event':
  - Vasodepressor = TLoC plus isolated hypotension (decrease in systolic blood pressure more than 60%) [VASIS classification type 3 (Brignole 2000b)]

- Mixed = TLoC plus mild bradycardia (> 40 bpm) or brief asystole (< 3s) [VASIS type 1]
- Cardioinhibitory = TLoC plus marked bradycardia (less than 40 bpm) or prolonged asystole (more than 3 seconds) [VASIS types 2A and 2B respectively]
- TLoC alone with no other symptoms

5.5.1.7 Subgroup analyses

For this review, we stratified the data according to the presence or absence of drug infusion and by different drugs, and considered the following subgroups in order to investigate heterogeneity

- Age above 65 years and 65 years and below
- Age above 35 years and 35 years and below
- Prior tests (extensive and basic)
- Type of control group patients in case control studies: other types of TLoC and healthy volunteers (no TLoC) and patients in hospital for another reason (no TLoC)
- Duration of tilt (with a cut off at 60 minutes, the median point)
- Angle of tilt (with a cut off at 60 degrees, the median point)

5.5.2 Characteristics of included studies

We identified 272 studies as being potentially relevant; 151 studies were excluded. The excluded studies are listed in the Appendix F, along with reasons for exclusion. We included 121 tilt test studies, of which 41 were studies of diagnostic test accuracy, and are reported in this review. The test accuracy studies differed in their design:

- 37 were prospective case control studies, in which the cases were people considered to have neurally mediated syncope on the basis of prior tests, history and examination, and the controls were those who did not (Aerts 1997, Aerts 1999, Aerts 2005, Aerts 2005b, Almquist 1989, Aslan 2002, Athanasos 2003, Benchimol 2008, Brignole 1991, Brignole 1991b, Carlioz 1997, Del Rosso 1998, Del Rosso 2002, Dhala 1995, Doi 2002, Englund

1997, Fitzpatrick 1991, Fouad 1993, Gielerak 2002, Gilligan 1992, Graham 2001, Grubb 1991b, Grubb 1992b, Herrmosillo 2000, Lagi 1992, Lazzeri 2000, Micieli 1999, Mittal 2004, Morillo 1995, Mussi 2001, Oribe 1997, Podoleanu 2004, Prakash 2004, Shen 1999, Theodorakis 2000).

- Two were non-randomised studies: in one (Theodorakis 2000), the patients received two tests sequentially (all in the same order), and in the other (Carlioz 1997), two groups of patients received different index tests. Each of these studies also included cases and control participants.
- Six were crossover RCTs in which two or more tests were given in random order (Bartoletti 1999, Graham 2001b, Oraii 1999, Parry 2008, Theodorakis 2003, Zeng 2001). Each of these included cases and control participants.

Two studies (Del Rosso 2000, Dhala 1995) included only control participants in order to assess the specificity of tilt table tests.

5.5.2.1 Population

The inclusion and exclusion criteria for each of the studies are shown in the Appendix D1.

Where reported, the mean age of the participants in the studies was mostly below 65 years but varied as follows:

- mean age above 65 years (Del Rosso 2002 over 65's group, Fitzpatrick 1991, Mussi 2001)
- mean age between 35 and 65 years (Aerts 1997, Aerts 1999, Aerts 2005, Aerts 2005b, Almquist 1989, Aslan 2002, Athanasos 2003, Benchimol 2008, Brignole 1991, Brignole 1991b, Del Rosso 1998, Del Rosso 2002 under 65's group, Dhala 1995, Doi 2002, Englund 1997, Gilligan 1992, Graham 2001, Grubb 1991b, Grubb 1992b, Lagi 1992, Mittal 2004, Morillo 1995, Oribe 1997, Podoleanu 2004, Shen 1999, Theodorakis 2000)
- mean age 35 or less (Carlioz 1997, Fouad 1993, Gielerak 2002, Hermosillo 2000, Lazzeri 2000, Micieli 1999, Prakash 2004)

Cases

Studies differed in the prior tests that patients could have had, and therefore in the type of population of patients who were defined as 'suspected neurally mediated syncope' (NMS). Often, the classification of patients was not well described in the publications. Extrapolating from the prior tests reported, in some studies, patients were classified as follows:

- 'probable' NMS (i.e. in which extensive prior tests had excluded other causes: Aerts 1997, Aerts 2005, Aslan 2002, Brignole 1991, Brignole 1991b, Carlioz 1997, Del Rosso 1998, Del Rosso 2002, Fitzpatrick 1991, Gielerak 2002, Graham 2001, Graham 2001b, Grubb 1991b, Grubb 1992b, Morillo 1995, Mussi 2001, Oraii 1999, Oribe 1997, Podoleanu 2004, Theodorakis 2000, Theodorakis 2003, Zeng 2001).
  - In the Micieli (1999) study of bromocriptine tilt tests, patients were included only if they had had a negative passive tilt test
  - The Parry (2008) study excluded patients with a history strongly suggestive of vasovagal syncope who did not require a tilt test to confirm the diagnosis
- 'possible' NMS defined as the patients having:
  - a typical history of NMS (Aerts 1999, Aerts 2005b, Doi 2002, Herrmosillo 2000, Lagi 1992)
  - syncope described as 'unexplained' but other diagnoses had not been excluded by extensive testing, i.e. the patients had only had basic tests (Almquist 1989, Athanasos 2003, Bartoletti 1999, Fouad 1993, Lazzeri 2000, Mittal 2004, Prakash 2004, Shen 1999).
  - The Benchimol (2008) study was concerned with an investigation of unexplained fainting or falls.

However, in many studies, various tests were listed as having been performed in 'some of the patients', so it was not clear whether patients had had all of the tests.

The frequency of TLOC was described in various ways (e.g. frequency in the last year or last 6 months; lifetime total number of episodes) and varied

between studies (e.g. the lifetime number of episodes ranged from 1 to 100); in some studies it was not described at all.

Three studies were excluded from the analysis because participants were not typical of those with NMS: one in which patients had hypertrophic cardiomyopathy (Gilligan 1992); one in which patients had bifascicular block (Englund 1997) and one subgroup of a study in which patients had exercise-induced syncope (the patients with non-exercise-induced syncope in this study were included in the review) (Doi 2002).

Controls

Studies also differed in the type of control group participants. Most studies reported that these were healthy people with no evidence of TLoC. One study (Grubb 1992b) compared patients with suspected NMS versus patients with syncope of another origin. Four studies (Almquist 1989, Theodorakis 2000, Theodorakis 2003, Zeng 2001) included control group participants who were neither healthy nor with TLoC, but who were in hospital for another reason.

5.5.2.2 Index tests

The index tests (tilt tests) differed between studies. Some used no pharmacological agents (known as passive tilt test, head-up tilt test or HUT). Others used a variety of drugs: adenosine, clomipramine, dopamine, glyceryl trinitrate (GTN), isoprenaline / isoproterenol (IPN), or isosorbide dinitrate (ISDN). These drug-stimulated tests could have been done in one of three ways: with the drug administered at the start of the test; only if a passive HUT had been negative; or the dose of the drug could have been titrated upwards during the testing protocol.

Tests also varied in duration, from 26 to 150 minutes, and angle of tilt, from 60 to 80 degrees (see Appendix D1).

The following tests were carried out:

- Passive tilt test
  Aerts 1997, Aerts 2005, Almquist 1989, Aslan 2002, Athanasos 2003,

Brignole 1991, Carlioz 1997, Del Rosso 1998, Del Rosso 2002, Del Rosso 2002, Englund 1997, Fitzpatrick 1991, Fouad 1993, Gielerak 2002, Gilligan 1992, Graham 2001, Grubb 1991b, Grubb 1992b, Herrmosillo 2000, Lagi 1992, Lazzeri 2000, Morillo 1995, Mussi 2001, Oraii 1999, Oribe 1997, Oribe 1997, Oribe 1997, Parry 2008, Prakash 2004, Shen 1999, Theodorakis 2000, Theodorakis 2003

- HUT-GTN:
  - drug administered at the start of the test (Aerts 2005b; Graham 2001; Parry 2008)
  - accelerated protocol: drug administered then supine for 5 minutes then HUT for 20 min (Bartoletti 1999; Zeng 2001)
  - drug administered as an additional stage if a passive HUT had been negative (Athanasos 2003, Bartoletti 1999, Del Rosso 1998, Del Rosso 2002, Mussi 2001, Podoleanu 2004)
  - the dose of the drug was titrated upwards during the testing protocol (Oraii 1999, Zeng 2001).
- HUT-IPN:
  - drug administered at the start of the test (Aerts 2005b, Graham 2001)
  - as an additional stage if a passive HUT had been negative (Carlioz 1997, Herrmosillo 2000, Shen 1999, Theodorakis 2000, Theodorakis 2003)
  - the dose of the drug was titrated upwards during the testing protocol (Almquist 1989, Brignole 1991, Doi 2002, Grubb 1991b, Grubb 1992b, Morillo 1995, Oraii 1999)
- HUT-ISDN:
  - drug administered at the start of the test (Benchimol 2008)
  - as an additional stage if a passive HUT had been negative (Aerts 1997, Aerts 2005, Aslan 2002)
  - the dose of the drug was titrated upwards during the testing protocol (Aerts 1999)
- HUT-clomipramine:
  - as an additional stage if a passive HUT had been negative (Theodorakis 2000, Theodorakis 2003)

- HUT-adenosine
  - the dose of the drug was titrated upwards during the testing protocol (Mittal 2004)
- HUT-bromocriptine:
  - as an additional stage if a passive HUT had been negative (Micieli 1999)
- HUT-IPN-ISDN:
  - as an additional stage if a passive HUT had been negative then isoproterenol then ISDN (Hermosillo 2000)

5.5.2.3 Reference standard

All the studies compared the outcome of one or more types of tilt test between patients (cases of suspected NMS) and controls and this separation into cases and controls constituted the reference standard. We note that, apart from one study (Grubb 1992b), all the controls were people excluded from the guideline, i.e. they did not have a TLoC. Therefore, the studies do not discriminate between people with different types of TLoC, which will distort the test accuracy results.

5.5.2.4 Comparisons

Eight studies also compared two types of tilt test (Bartoletti 1999; Carlioz 1997; Graham 2001; Oraii 1999; Parry 2008; Theodorakis 2000; Theodorakis 2003; Zeng 2001): six of these were randomised trials (RCTs), in which the patients underwent the two tests in random order (Bartoletti 1999; Graham 2001; Oraii 1999; Parry 2008; Theodorakis 2003; Zeng 2001). In one non-randomised study (Theodorakis 2000), the patients received the two tests sequentially (all in the same order), and in the other non-randomised study (Carlioz 1997), two groups of patients received different index tests.

- GTN-HUT versus passive HUT – 1 RCT (Parry 2008: 1 week between tests); non-RCT, (Carlioz 1997: 2 groups of patients),
- accelerated GTN-HUT versus classic GTN-HUT – 2 RCTs (Bartoletti 1999: 24-72 hour interval between tests, not compared independently with

reference standard of expert clinician; Zeng 2001: 1 to 14 days between tests)

- HUT-IPN versus HUT-GTN – 2 RCTs (Graham 2001: one week between tests; Oraii 1999: tests on two successive days)
- HUT-IPN versus HUT-clomipramine – 1 RCT (Theodorakis 2003: 24-hours between tests); 1 sequential non-randomised comparison (Theodorakis 2000: HUT-IPN first and HUT-clomipramine 24-hours later)

All the washout periods between the tests were therefore at least 24-hours.

5.5.2.5 Outcomes

All the studies except one (Bartoletti 1999) reported raw data to enable calculation of diagnostic test accuracy, and 2 x 2 tables were constructed for the numbers of patients and controls with positive and negative tests. The definition of a positive test also varied between studies. One study (Fitzpatrick 1991) only required syncope; all the other studies required syncope or pre-syncope plus hypotension, bradycardia or both. However, definitions varied of the 'both' (or 'mixed') category, in which patients had both hypotension and bradycardia. Some studies followed the VASIS definition in section 5.5.1.6, for which patients in the mixed group did not have bradycardia or asystole. In other studies, 'mixed' meant both bradycardia/asystole and hypotension. The definition of cardioinhibitory was similar.

5.5.3 Methodological quality of included studies (Appendix D2)

The methodological quality was assessed separately for the RCTs and the non-randomised studies.

5.5.3.1 RCTs

For RCTs, the general methods for assessment of risk of bias were used.

The method of sequence generation was adequate in one study (table of random numbers: Parry 2008) and was unclear in the remaining studies (Bartoletti 1999, Graham 2001, Oraii 1999, Theodorakis 2003, Zeng 2001).

The method of allocation concealment was partially adequate in two studies (sealed envelopes: Graham 2001, Parry 2008) and was unclear in the remaining studies.

Blinding was reported in none of the studies.

Baseline comparability between randomised groups was not applicable for many patient-inherent characteristics because of the crossover design. Baseline data that could have varied between tests (e.g. blood pressure) was not stated for the other studies at the start of the two tests, but with a washout period of at least 24-hours in all studies, the baseline characteristics of the samples at the two starting times may be assumed to be similar.

In randomised trials, each test is still compared with the reference standard and we did not report head-to-head comparisons. However, we note that the comparison between tests has some properties of paired data.

One study carried out a power calculation (Parry 2008): 140 patients were calculated as needed to estimate a difference in yield (35% positive on passive tilt and 47% positive GTN tilt) with a standard error of 2.5% (power level not stated).

Study size ranged from 48 patients (Graham 2001) to 232 patients (Parry 2008).

Overall, the RCTs did not give enough details to determine that they were free from bias and in the absence of blinding, there is a risk of bias in these studies.

5.5.3.2 Non-randomised studies

The methodology of the non-randomised studies was assessed using standard criteria. All the studies were prospective. Almost all studies included all eligible patients; in three studies (Athanasos 2003, Fouad 1993, Grubb 1992b) this was unclear. Full data were available for all participants with no attrition in any of the studies. In one study, which compared IPN and GTN tests (Graham 2001b), the authors noted that 47% of the patients screened were ineligible for the isoprenaline test arm of the study (the principal contraindication being cardiovascular comorbidity) and of those who did not have a contraindication, isoprenaline was poorly tolerated (75% of patients and 58% of controls did not complete the test protocol).

5.5.3.3 Diagnostic test accuracy

All studies recorded diagnostic test accuracy and their quality was assessed using QUADAS criteria (see Appendix D2).

The studies in this review have a case-control design, which gives rise to spectrum bias. Selection of patients appeared to be ’all eligible patients selected‘, but these patients are those who have been referred to a syncope unit, for example, and the process of defining them as patients is not documented. Also, the control groups were mainly defined as people without syncope, but the process of recruitment of controls was not discussed in any detail in the papers.

It was not clear if the index test was performed blinded to whether a person was a ’case‘ or a ’control‘; during the tilt test, if the person experienced symptoms, they might have been asked whether these reproduced their normal symptoms during syncope/pre-syncope (in some studies this was an outcome criterion), so it would have been hard to blind the test operators to the reference standard condition. The overall QUADAS assessment on all the studies was “-“ due to potentially non-representative patients. The exception to this was the Grub 1992 b study, but this had very few ‘other syncope’ controls.

5.5.3.4 Sensitivity analyses

We considered studies with fewer than 20 cases and/or fewer than 20 controls to have potential for bias and these studies were considered in sensitivity analyses (Aerts 2005, Almquist 1989, Aslan 2002, Athanasos 2003, Fouad 1993, Carlioz 1997, Graham 2001b, Grubb 1991b, Grubb 1992b, Podoleanu 2004, Prakash 2004).

The Graham (2001b) study reported that 47% of the patients screened were ineligible for the isoprenaline arm of the study (the principal contraindication being cardiovascular comorbidity) and of those who did not have a contraindication, isoprenaline was poorly tolerated (75% of patients and 58% of controls did not complete the test protocol). We considered that this study was likely to be confounded by the protocol violations in the IPN test arm, and so this study was also considered in sensitivity analyses.

The following studies had unusual patient populations which were considered in sensitivity analyses:

- Micieli (1999): patients were included in this study of bromocriptine tilt tests only if they had had a negative passive tilt test.
- The Parry (2008) study stated that they did not include patients with a history strongly suggestive of vasovagal syncope who did not require a tilt test to confirm the diagnosis (reducing the pool of potentially positive responses); this was considered in sensitivity analyses as it represented a different patient population.

5.5.4 Results

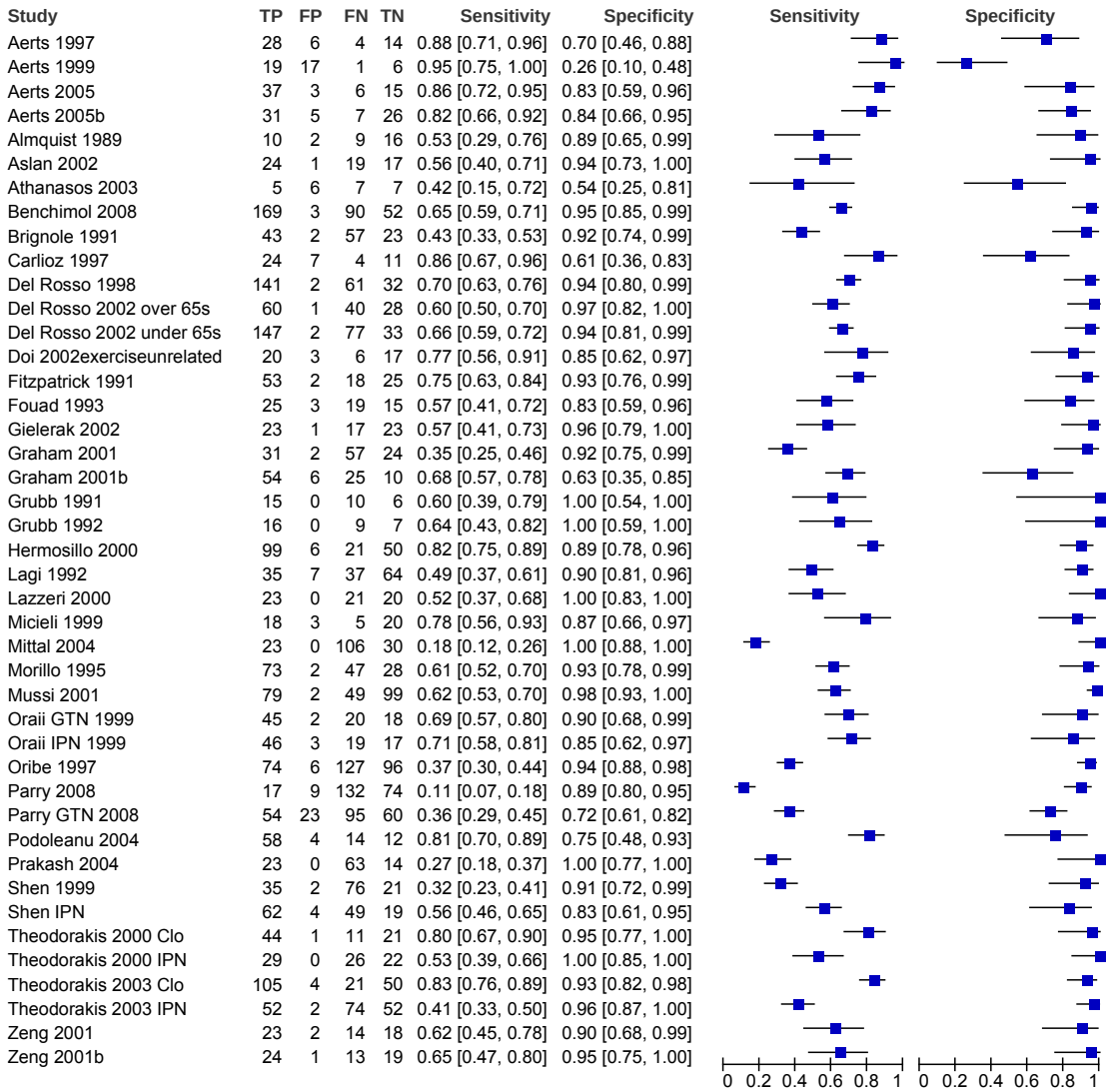
5.5.4.1 Diagnostic test accuracy (all studies, patients versus controls)

The first stage of the analysis of the results was to examine all studies on one plot initially, then to undertake sensitivity analyses, then to examine the different types of tilt test separately, with subgroup analyses where appropriate. Several studies carried out a 2-stage test: patients were initially given a passive tilt test and then if this was negative, drugs were used in a further approach to inducing TLoC. In this type of study, the results of the

passive test are recorded separately, and then the overall results of the entire tilt test strategy are given. For the initial plot, we used only the overall results to give the highest measure of sensitivity and to avoid double counting of studies, but in the subgroup analysis by tilt test type, both passive and overall results were used.

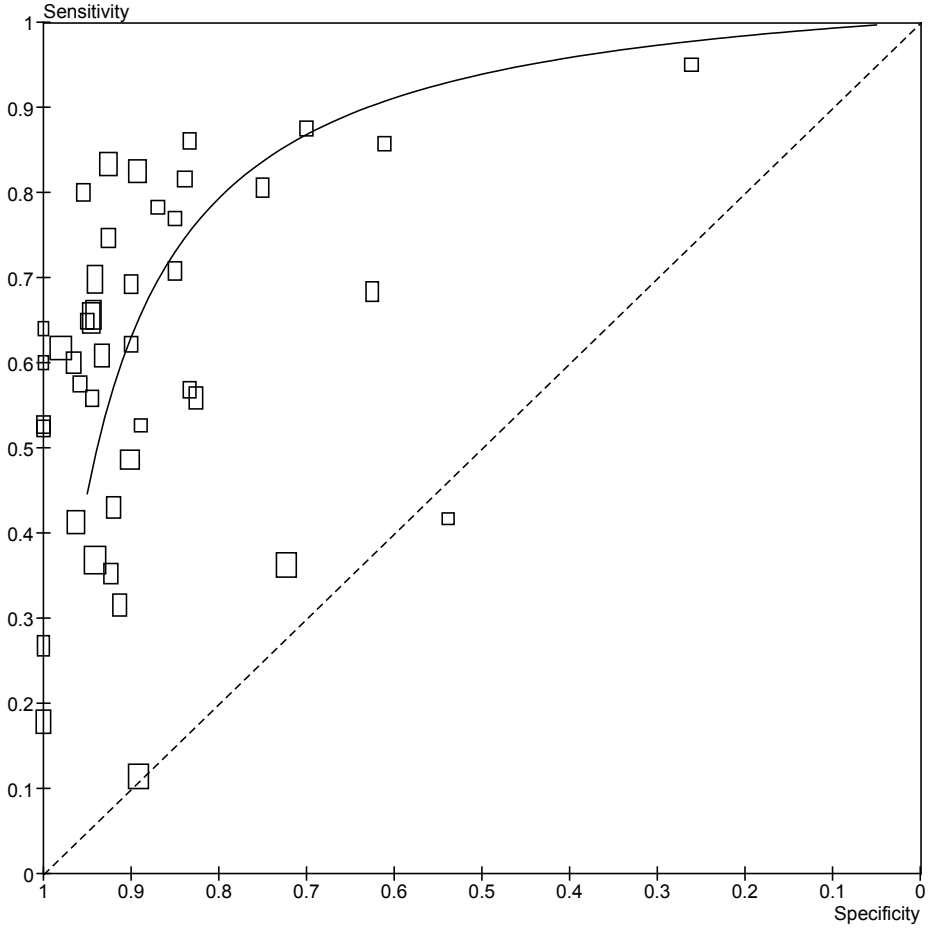
A forest plot of sensitivity and specificity is shown in Figure 5-38, and it can be seen that there is significant heterogeneity, particularly for sensitivity, and there is also some variation in specificity. Such heterogeneity could be due to variability in thresholds, disease spectrum, test methods, and study quality.

Figure 5-38a: Forest plot of all tilt test types.



The ROC curve is shown in Figure 5-38b. In this curve each point represents a single study, each of which has a different threshold because of different definitions of a positive event.

Figure 5-38b: ROC curve all tilt tests



5.5.4.2 Sensitivity analyses – all tests

Sensitivity analysis was carried out excluding the following studies: those with fewer than 20 cases and/or fewer than 20 controls (Aerts 2005, Almquist 1989, Aslan 2002, Athanasos 2003, Fouad 1993, Graham 2001b, Grubb 1991b, Grubb 1992b, Podoleanu 2004, Prakash 2004); those with large numbers of patients with a protocol violation (Graham 2001b); and those with unusual patient populations (Micieli 1999, Parry 2008).

Figure 5-39a. Forest plot of studies remaining after excluding studies in sensitivity analysis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Aerts 1997	28	6	4	14	0.88 [0.71, 0.96]	0.70 [0.46, 0.88]
Aerts 1999	19	17	1	6	0.95 [0.75, 1.00]	0.26 [0.10, 0.48]
Aerts 2005b	31	5	7	26	0.82 [0.66, 0.92]	0.84 [0.66, 0.95]
Benchimol 2008	169	3	90	52	0.65 [0.59, 0.71]	0.95 [0.85, 0.99]
Brignole 1991	43	2	57	23	0.43 [0.33, 0.53]	0.92 [0.74, 0.99]
Del Rosso 1998	141	2	61	32	0.70 [0.63, 0.76]	0.94 [0.80, 0.99]
Del Rosso 2002 over 65s	60	1	40	28	0.60 [0.50, 0.70]	0.97 [0.82, 1.00]
Del Rosso 2002 under 65s	147	2	77	33	0.66 [0.59, 0.72]	0.94 [0.81, 0.99]
Doi 2002exerciseunrelated	20	3	6	17	0.77 [0.56, 0.91]	0.85 [0.62, 0.97]
Fitzpatrick 1991	53	2	18	25	0.75 [0.63, 0.84]	0.93 [0.76, 0.99]
Fouad 1993	25	3	19	15	0.57 [0.41, 0.72]	0.83 [0.59, 0.96]
Gielerak 2002	23	1	17	23	0.57 [0.41, 0.73]	0.96 [0.79, 1.00]
Hermosillo 2000	99	6	21	50	0.82 [0.75, 0.89]	0.89 [0.78, 0.96]
Lagi 1992	35	7	37	64	0.49 [0.37, 0.61]	0.90 [0.81, 0.96]
Lazzeri 2000	23	0	21	20	0.52 [0.37, 0.68]	1.00 [0.83, 1.00]
Mittal 2004	23	0	106	30	0.18 [0.12, 0.26]	1.00 [0.88, 1.00]
Morillo 1995	73	2	47	28	0.61 [0.52, 0.70]	0.93 [0.78, 0.99]
Mussi 2001	79	2	49	99	0.62 [0.53, 0.70]	0.98 [0.93, 1.00]
Oraii GTN 1999	45	2	20	18	0.69 [0.57, 0.80]	0.90 [0.68, 0.99]
Oraii IPN 1999	46	3	19	17	0.71 [0.58, 0.81]	0.85 [0.62, 0.97]
Oribe 1997	74	6	127	96	0.37 [0.30, 0.44]	0.94 [0.88, 0.98]
Shen 1999	35	2	76	21	0.32 [0.23, 0.41]	0.91 [0.72, 0.99]
Shen IPN	62	4	49	19	0.56 [0.46, 0.65]	0.83 [0.61, 0.95]
Theodorakis 2000 Clo	44	1	11	21	0.80 [0.67, 0.90]	0.95 [0.77, 1.00]
Theodorakis 2000 IPN	29	0	26	22	0.53 [0.39, 0.66]	1.00 [0.85, 1.00]
Theodorakis 2003 Clo	105	4	21	50	0.83 [0.76, 0.89]	0.93 [0.82, 0.98]
Theodorakis 2003 IPN	52	2	74	52	0.41 [0.33, 0.50]	0.96 [0.87, 1.00]
Zeng 2001	23	2	14	18	0.62 [0.45, 0.78]	0.90 [0.68, 0.99]
Zeng 2001b	24	1	13	19	0.65 [0.47, 0.80]	0.95 [0.75, 1.00]

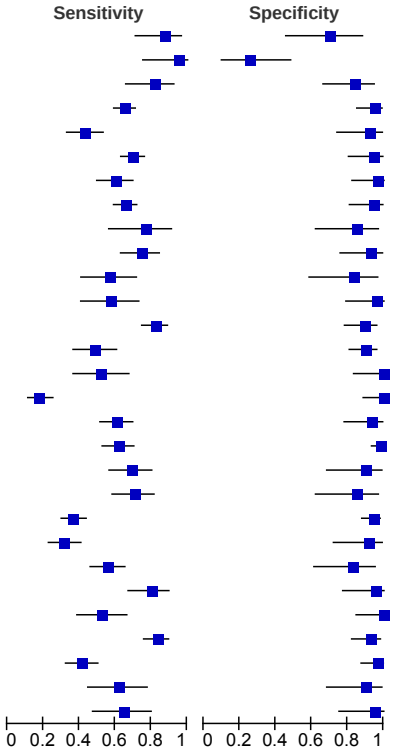
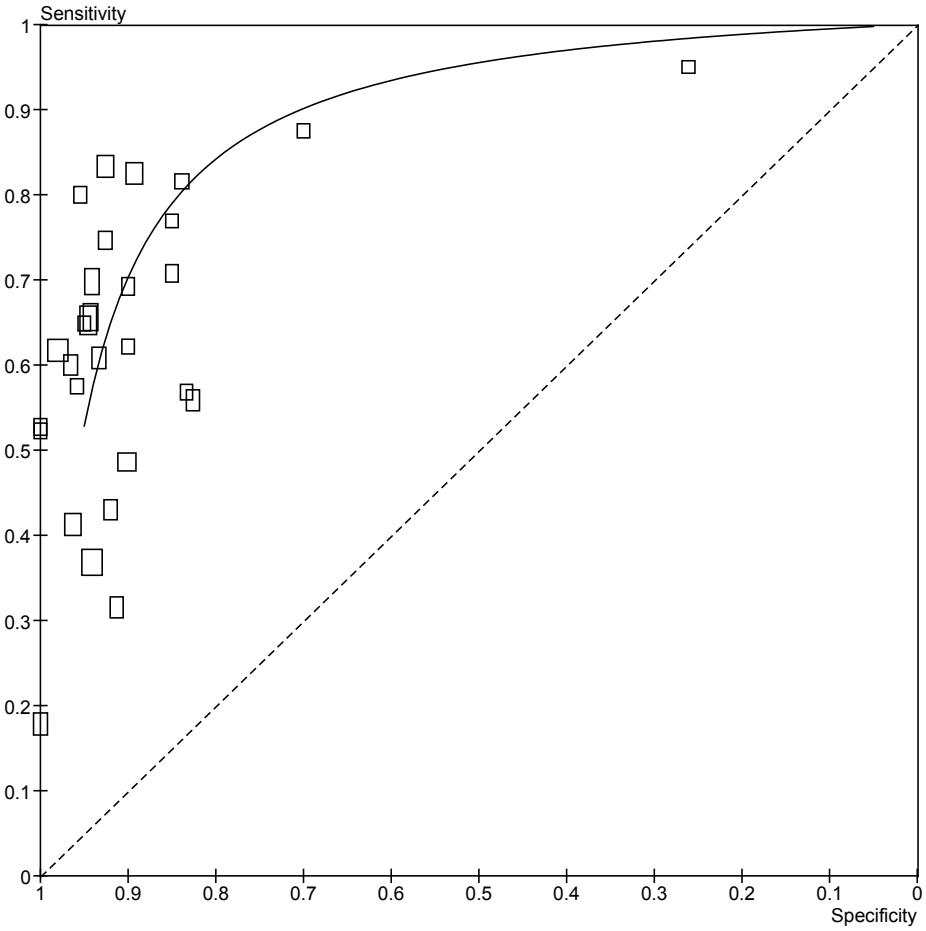


Figure 5-39b. ROC curve excluding studies in sensitivity analysis



We concluded that the remainder of the analyses should be carried out without the studies that were excluded in the sensitivity analysis.

5.5.4.3 Subgroup analyses by type of tilt test

The set of studies were split by type of tilt test, either passive tilt or using drug provocation and examined in Figures 5-40a to 5-40f (below and Appendix D4).

Figure 5-40a. Forest plot subgroup analysis by type of tilt test (passive or GTN or IPN)

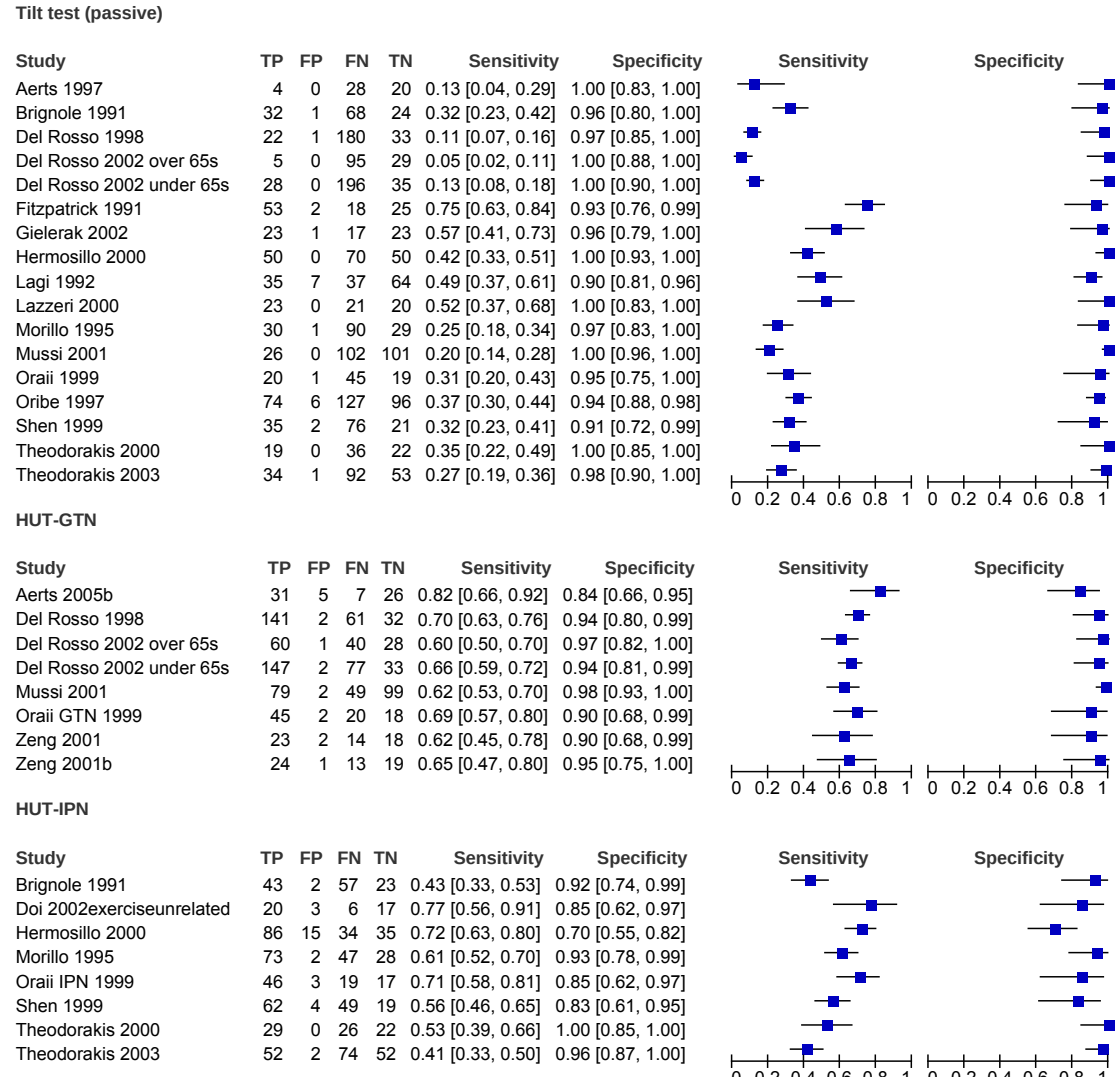
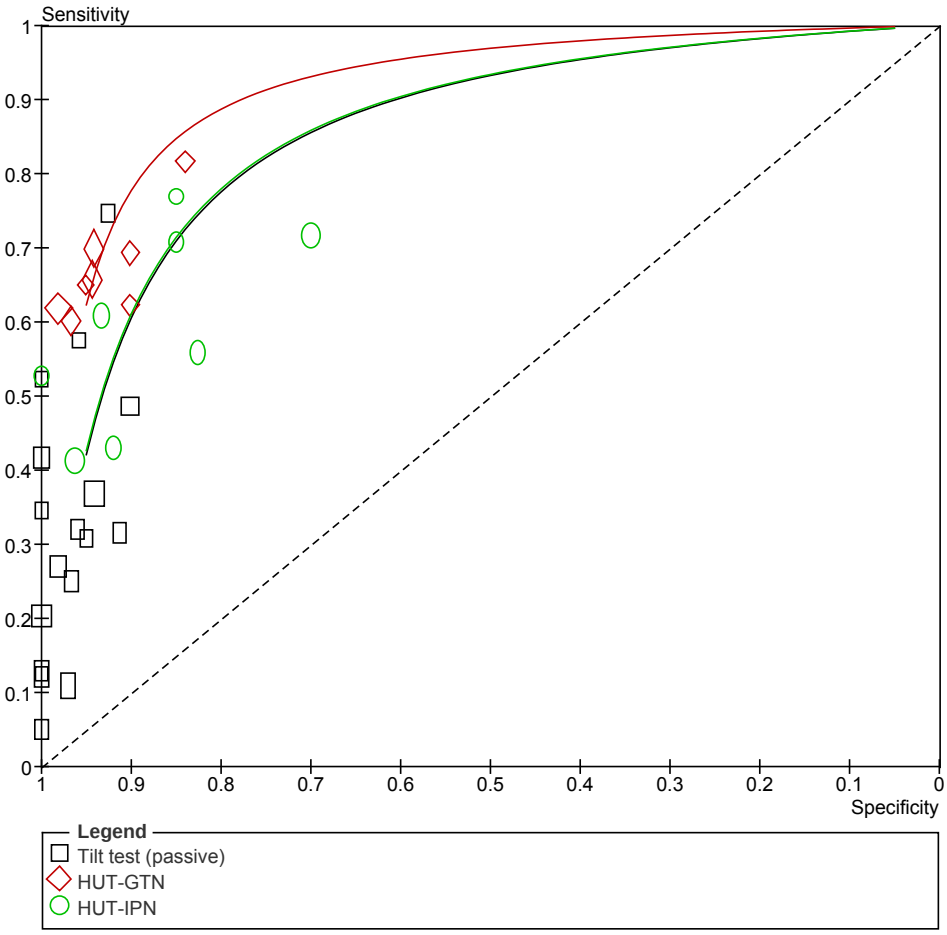


Figure 5-40b. ROC curves of passive tilt test, GTN and IPN



It is evident that there is little variation in specificity for the passive tilt test, but variation in sensitivity. The IPN test follows an identical SROC curve to the passive test and shows heterogeneity. The GTN test appears to be a stronger test than the passive test.

Figure 5-40c. ROC curve for passive test and ISDN test

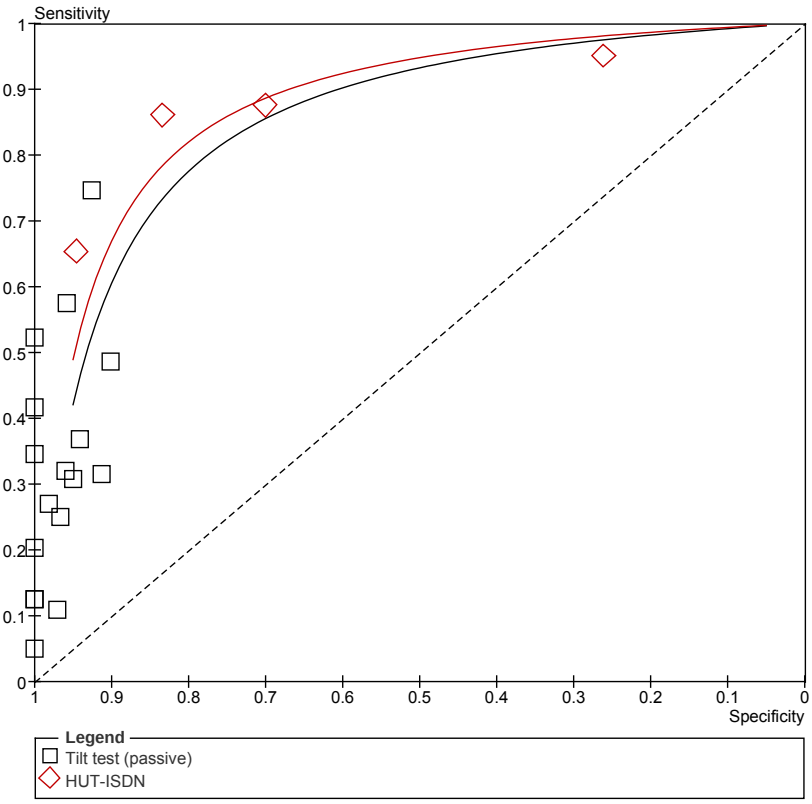


Figure 5-40d. Forest plot of IPN, ISDN and IPN followed by ISDN)

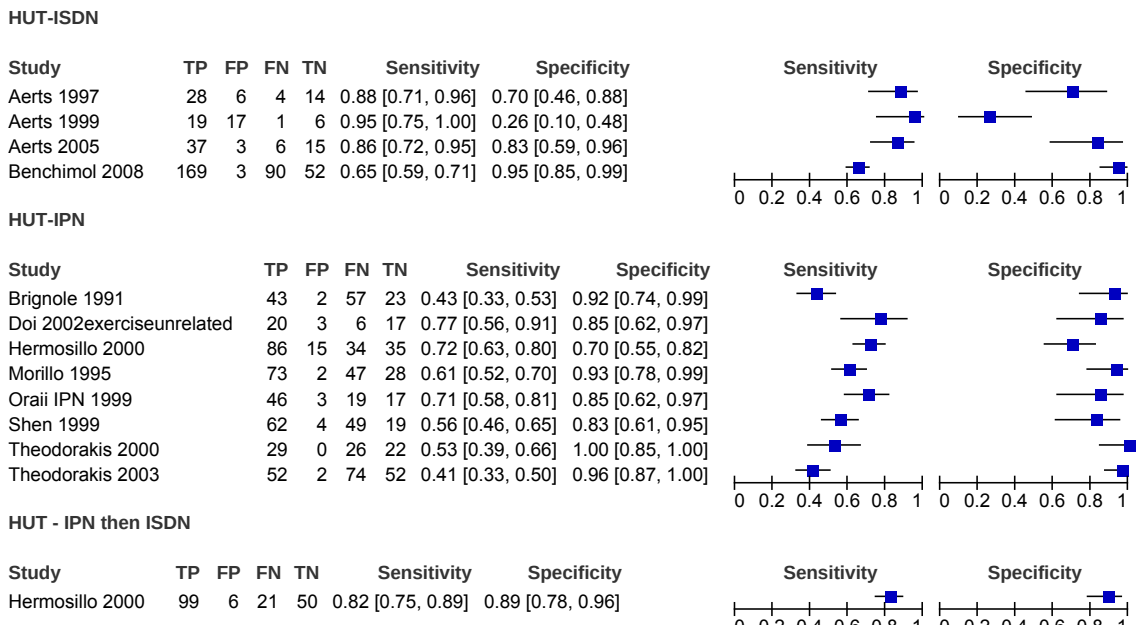


Figure 5-40e. Forest plot of adenosine, clomipramine, bromocriptine.

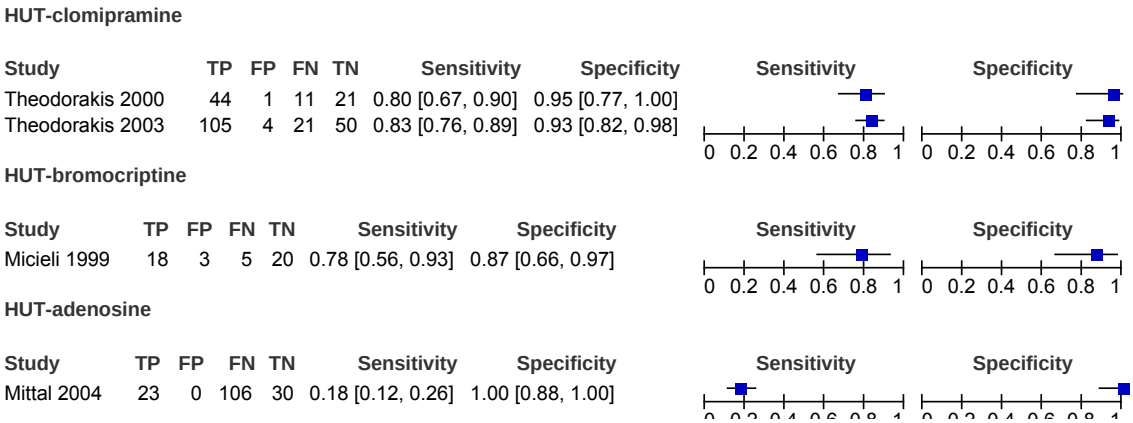
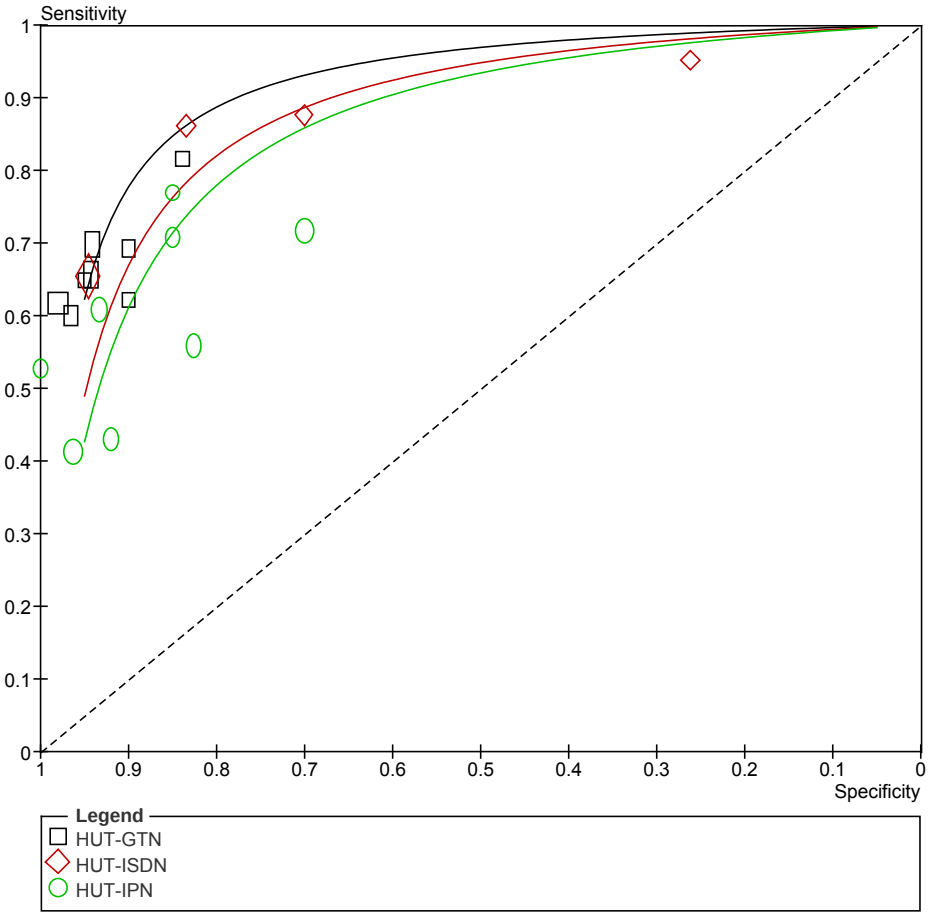


Figure 5-40f. ROC curves for main drug-stimulated tests (GTN, IPN, ISDN)

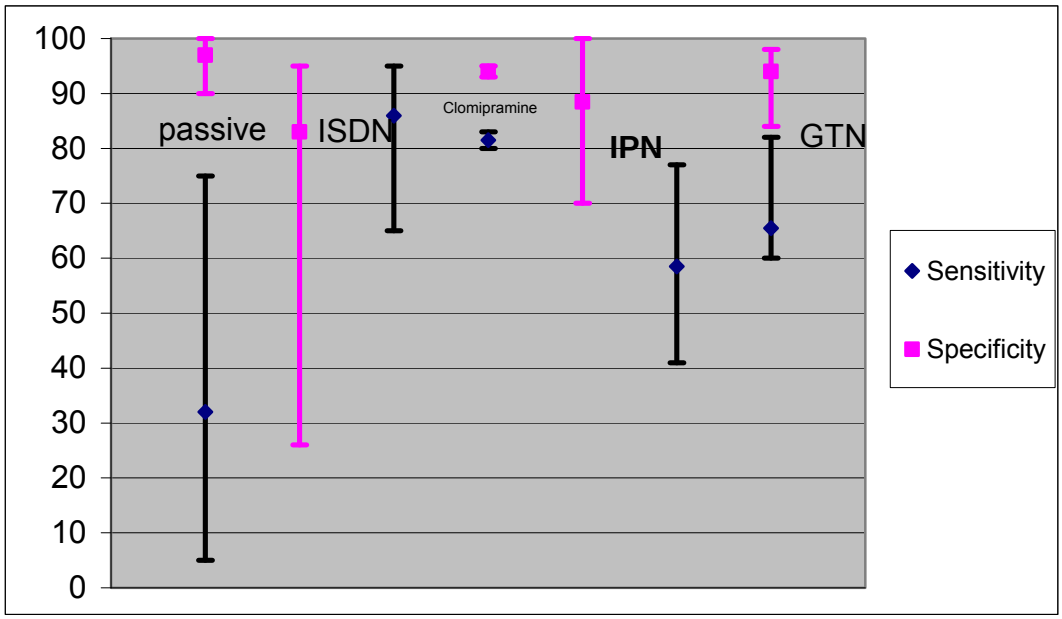


The median and interquartile range were calculated for the sensitivity and specificity for each test and are shown in Table 23, and the median and range are plotted in Figure5-40. There is clearly considerable variation in the sensitivity for both passive and IPN tests and also variation in specificity for ISDN. The GTN test appears to be better than a passive test and an isoprenaline stimulated test.

Table 23:

Drug	passive	ISDN	Clomipran	IPN	GTN
Sensitivity					
Sensitivity Median	32	86	81.5	58.5	65.5
Sensitivity 25% IQR	20	82	80.75	50.5	62
Sensitivity 75% IQR	42	88	82.25	71.25	69.25
min Sensitivity	5	65	80	41	60
max Sensitivity	75	95	83	77	82
Specificity					
Specificity Median	97	83	94	88.5	94
Specificity 25% IQR	95	70	93.5	84.5	90
Specificity 75% IQR	100	89	94.5	93.75	95.5
min Specificity	90	26	93	70	84
max Specificity	100	95	95	100	98

Figure 5-40g: Sensitivity and Specificity with their ranges for different tilt tests



5.5.4.4 Investigation of heterogeneity: HUT-passive

Seventeen studies used passive HUT. There was high specificity for each study, but the sensitivity was heterogeneous.

Figure 5-41a. Forest plot of all studies assessing HUT-passive (sorted by author)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Aerts 1997	4	0	28	20	0.13 [0.04, 0.29]	1.00 [0.83, 1.00]
Brignole 1991	32	1	68	24	0.32 [0.23, 0.42]	0.96 [0.80, 1.00]
Del Rosso 1998	22	1	180	33	0.11 [0.07, 0.16]	0.97 [0.85, 1.00]
Del Rosso 2002 over 65s	5	0	95	29	0.05 [0.02, 0.11]	1.00 [0.88, 1.00]
Del Rosso 2002 under 65s	28	0	196	35	0.13 [0.08, 0.18]	1.00 [0.90, 1.00]
Fitzpatrick 1991	53	2	18	25	0.75 [0.63, 0.84]	0.93 [0.76, 0.99]
Gielerak 2002	23	1	17	23	0.57 [0.41, 0.73]	0.96 [0.79, 1.00]
Hermosillo 2000	50	0	70	50	0.42 [0.33, 0.51]	1.00 [0.93, 1.00]
Lagi 1992	35	7	37	64	0.49 [0.37, 0.61]	0.90 [0.81, 0.96]
Lazzeri 2000	23	0	21	20	0.52 [0.37, 0.68]	1.00 [0.83, 1.00]
Morillo 1995	30	1	90	29	0.25 [0.18, 0.34]	0.97 [0.83, 1.00]
Mussi 2001	26	0	102	101	0.20 [0.14, 0.28]	1.00 [0.96, 1.00]
Oraii 1999	20	1	45	19	0.31 [0.20, 0.43]	0.95 [0.75, 1.00]
Oribe 1997	74	6	127	96	0.37 [0.30, 0.44]	0.94 [0.88, 0.98]
Shen 1999	35	2	76	21	0.32 [0.23, 0.41]	0.91 [0.72, 0.99]
Theodorakis 2000	19	0	36	22	0.35 [0.22, 0.49]	1.00 [0.85, 1.00]
Theodorakis 2003	34	1	92	53	0.27 [0.19, 0.36]	0.98 [0.90, 1.00]

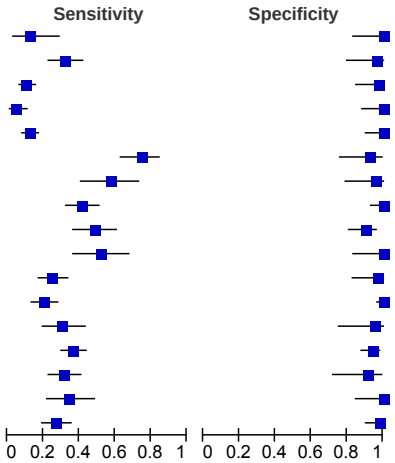
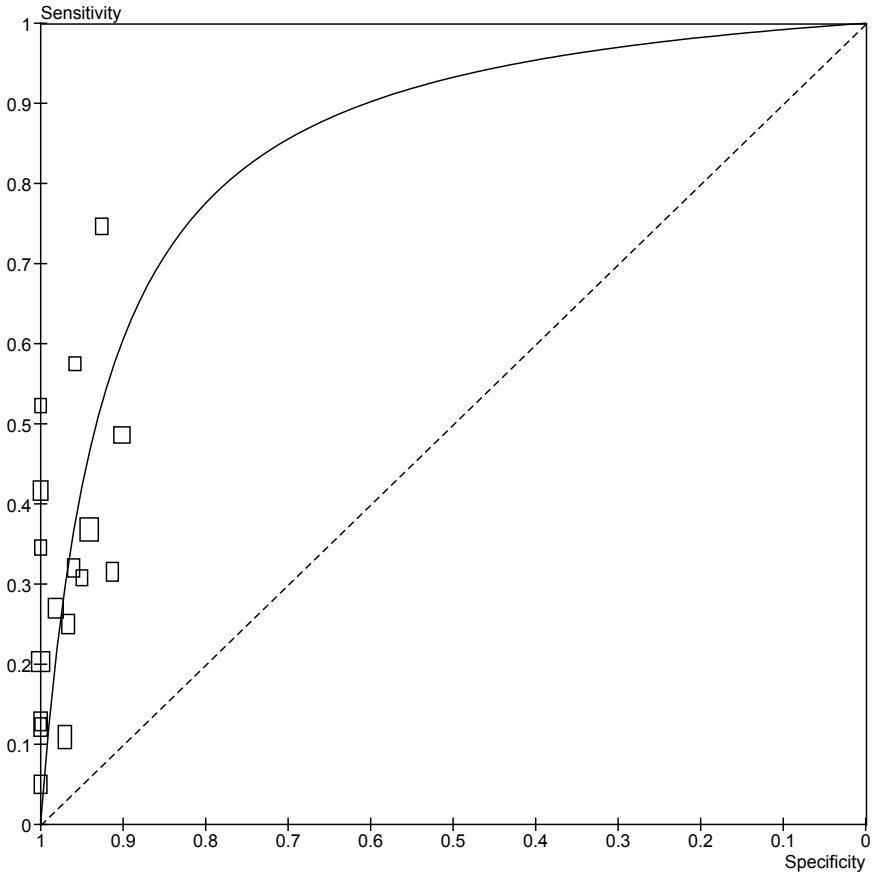


Figure 5-41b. ROC curve HUT passive



Subgroup analyses were carried out for the a priori defined parameters of age (over versus under 65 years; over versus under 35 years; and whether NMS was 'probable' or 'possible'). We also investigated angle of tilt and duration of tilt as possible sources of heterogeneity. Results are shown in Appendix D4.

There was some indication that the tilt test was better in people younger than 35 years; there was no significant dependence on the definition of NM syncope, age over 65 years, or on the angle of tilting; there may have been some increases in sensitivity if the studies used a longer duration of tilting. Other sensitivity analyses are shown in Appendix D4.

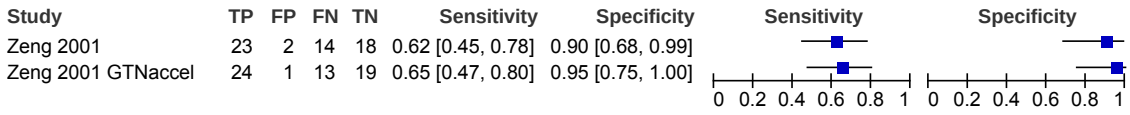
5.5.4.5 Comparisons from RCTs (one type of tilt test versus another type)

Of the six RCTs, two compared an accelerated GTN-HUT with a classic GTN-HUT (Bartoletti 1999, Zeng 2001); two compared HUT-IPN with HUT-GTN (Graham 2001 although this was excluded at the sensitivity analysis stage due to protocol violations, Oraii 1999); one compared HUT-IPN with HUT-clomipramine (Theodorakis 2003) and one compared a GTN-HUT with a passive HUT (Parry 2008 although this study was excluded at the sensitivity analysis stage). The patients underwent the two tests in a random order.

a) Accelerated HUT-GTN versus standard HUT-GTN.

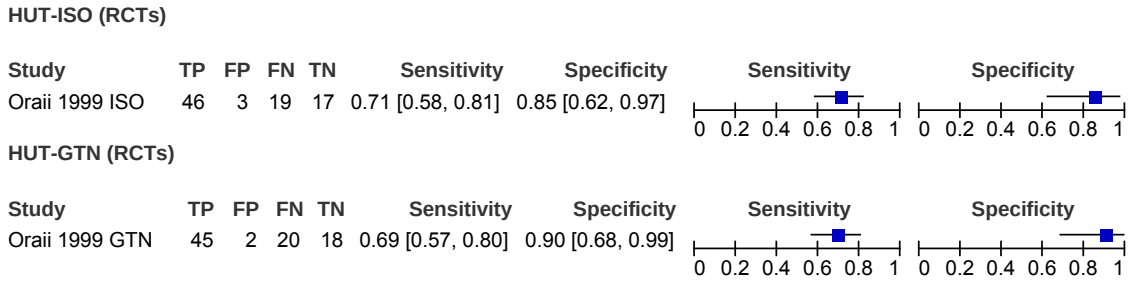
Bartoletti (1999) did not compare the results of HUT-GTN or HUT-GTN accelerated with the reference standard of expert clinician (patients versus controls).

Figure 5-42a. Forest plot of standard HUT-GTN versus accelerated HUT-GTN



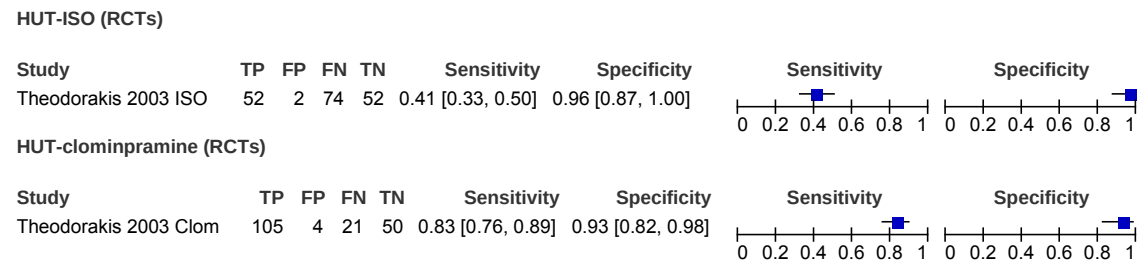
b) HUT-IPN versus HUT-GTN

Figure 5-42b. Forest plot of HUT-IPN versus HUT-GTN



c) HUT-IPN versus HUT-clomipramine

Figure 5-42c. Forest plot of HUT-IPN versus HUT-clomipramine



5.5.4.6 Tilt test in a population that excluded patients with a history strongly suggestive of vasovagal syncope

The Parry (2008) study stated that they did not include patients with a history strongly suggestive of vasovagal syncope who did not require a tilt test to confirm the diagnosis (reducing the pool of potentially positive responses). We note from Figures 5.38a and 5.38b and the diagnostic test accuracy statistics (Table 5.3) that the tilt test seems to be particularly poor for this study, even in comparison to non-TLoC controls; two other studies are included for comparison.

Table 5.3: Diagnostic test accuracy for tilt tests in 3 studies of GTN HUT

Test	Sensitivity	Specificity	LR	Pre-test prob	Post test prob
HUT (Parry 2008)	11	89	1.05	64.2	65.3
GTN HUT (Parry 2008)	36	72	1.31	64.2	70.1
Cf GTN HUT Oraii 1999	69	90	6.92	76.4	95.7
GTN HUT Zeng 2001	62	90	6.22	64.9	92.0

5.5.4.7 Incidence of cardioinhibitory vasovagal syncope

Some studies broke down the positive tilt test results into different responses: cardioinhibitory, vasodepressor and mixed. Details are given in Appendix D1.

The studies varied in their definitions of mixed response (e.g. some used the VASIS description (Brignole 2000b), which did not include a cardioinhibitory response, and others used other definitions). Taking this into account, across the studies there was a cardioinhibitory response of between 0 and 56% as a proportion of all 'cases' in the study, although many of the studies had proportions less than 20%, with the Parry (2008) study reporting 4%. The few studies reporting separately the number of patients with asystole longer than 3 seconds, had a positive asystolic response that varied between 0 and 19%, with the Parry (2008) study reporting 1%. Thus, in these studies of people with suspected vasovagal syncope, the yield of an asystolic response is low and this becomes very low in people who do not have a diagnosis of NM syncope after the initial stage.

5.6 Clinical Evidence Review: people with suspected neurally mediated syncope after initial assessment - accuracy of carotid sinus massage

5.6.1 Introduction

Carotid sinus syndrome (CSS) is a condition of older people. It is the occurrence of syncope or pre-syncope that is precipitated by any manoeuvre which causes mechanical stimulation of the carotid sinus - such as turning the head, looking up, or wearing tight collars.

It is rare before the age of 40 years and increases with age (Strasberg 1989). Carotid sinus hypersensitivity (CSH) is diagnosed when abnormal findings occur during carotid sinus massage (CSM) – that is, 5–10 seconds of longitudinal massage over the carotid sinus, at the point of maximal impulse two fingerbreadths below the angle of the mandible at the level of the cricoid cartilage. CSH is characterised by an asystolic pause of 3 seconds or more

(cardioinhibitory CSS), a reduction in systolic blood pressure by 50 mmHg or more (vasodepressor CSS), or both (mixed CSS).

CSM should be first performed on the right side, because 70% of positive responses occur with right-sided massage (McIntosh 1993). If a negative response is obtained on the right, then left-sided CSM should be performed after 1–2 minutes. CSM is usually performed in supine and upright positions on a standard tilt-table, but this is merely to support the patient and should not be confused with tilt testing.

5.6.2 Methods of the review: selection criteria

5.6.2.1 Population

Adults in secondary care with TLoC, in whom neurally mediated syncope is suspected after the initial assessment (patient history and eye witness accounts, physical examination including upright and supine blood pressure measurements and 12-lead ECG). No clear alternative diagnosis based on patient history or physical examination.

Subgroups: (1) above 65 years (2) below 65 years

5.6.2.2 Prior tests

12-lead ECG normal or any identified abnormality not likely to be the cause of TLoC.

5.6.2.3 The target condition

Neurally mediated syncope (carotid sinus syndrome).

5.6.2.4 The index test

Carotid sinus massage

5.6.2.5 The reference standard

Expert clinician

5.6.3 Characteristics of included studies (see Appendix D1)

We identified 129 studies to be potentially relevant to the review. Of these, 123 were excluded. The excluded studies are listed in the Appendix F, along with reasons for exclusion. Six studies of the diagnostic test accuracy of CSM were included (Benchimol 2008, Brignole 1991, Freitas 2004, Kumar 2003, Morillo 1999, Parry 2000). All were diagnostic case control studies, and one was retrospective (Kumar 2003).

Two studies were carried out in the UK (Kumar 2003, Parry 2000); and one each in Italy (Brignole 1991), Portugal (Freitas 2004), USA (Morillo 1999) and Brazil (Benchimol 2008).

The study size ranged from 125 (Brignole 1991) to 1174 (Parry 2000). None of the studies reported funding by commercial companies, although three did not say anything about funding (Brignole 1991, Freitas 2004, Kumar 2003).

5.6.3.1 Population

The inclusion and exclusion criteria for each of the studies are shown in the tables in the Appendix D1.

The mean age across studies ranged from 50 to 79 years, and the proportion of males ranged from 34 to 63%.

'Cases'

Of the six studies of diagnostic test accuracy, five investigated patients with unexplained syncope (Brignole 1991, Freitas 2004, Kumar 2003, Morillo 1999, Parry 2000) and one (Benchimol 2008) included patients referred for investigation of 'non-convulsive faints or unexplained falls'; ECG and echo were normal or showed no association with symptoms in this study. Two studies included some patients with heart disease: Morillo (1999) had 29% with coronary artery disease and Brignole (1991) had 39% with structural heart disease. Therefore, the population for this review in people with suspected NM syncope was indirect.

Studies differed in the prior tests that patients could have had, and therefore in the type of population:

- The patients in the Brignole (1991), Freitas (2004) Kumar (2003) and Morillo (1999) studies had unexplained syncope following initial tests and 24-hour Holter monitoring (patients in the Brignole (1991), Freitas (2004) and Kumar (2003) studies were excluded if they had positive results on any of these tests. The Morillo (1999) study did not appear to exclude patients on this basis)
- The Benchimol (2008), Brignole (1991) and Morillo (1999) studies also had echocardiograms
- Brignole (1991) also reported chest x-ray and, where indicated, a stress test, EEG, Doppler, CT, cardiac catheter, EPS, and arteriography
- The Parry (2000) study was conducted in patients in the emergency department or syncope unit – so that extensive tests may not have been carried out

Controls

All studies included healthy controls (i.e. they had not had a TLoC). One study (Morillo 1999) also included a second control group, in which the patients had syncope of another cause: 12 had ventricular tachycardia/ventricular fibrillation [VT/VF]; two had complete AV block, and two severe sinus node dysfunction (Morillo 1999). In addition, ten of these patients had documented Chagas cardiomyopathy and the other six had ischaemic cardiomyopathy.

The number of control participants ranged from 25 (Parry 2000 and Brignole 1991) to 108 (Freitas 2004), with 16 other syncope controls in the Morillo (1999) study. Mostly these numbers comprised between 18 and 27% of the total number of participants; the Parry (2000) study only had 2% of controls.

5.6.3.2 Index test

The index test (CSM) differed between studies in that it could be performed at different degrees of tilt:

- supine followed by standing (no details) (Brignole 1991)
- supine followed by 60 degrees of tilt (Benchimol 2008; Morillo 1999)
- supine followed by 70 degrees of tilt (Freitas 2004, Kumar 2003, Parry 2000).

In all cases CSM consisted of 5 seconds of massage of the carotid sinus.

In the Parry (2000) study, patients only received CSM in the tilted position if they had a negative result on the supine test. In three studies (Benchimol 2008, Morillo 1999) the patients had both supine and tilted CSM. In Freitas (2004) it was unclear if all the patients had supine then tilted CSM, or if only the supine-negative group did.

The requirements for a positive test result were described as follows:

- In four studies (Brignole 19991, Freitas 2004, Kumar 2003, Morillo 1999), this was defined as cardioinhibitory (when CSM resulted in asystole of 3 seconds or longer); vasodepressor (when CSM resulted in a fall in systolic blood pressure of at least 50 mm Hg) or mixed, each with syncope
- The Parry (2000) study defined a positive response as cardioinhibitory or mixed only; this outcome was also reported by the other four studies
- The Benchimol (2008) study did not report separately the number of participants with asystole

5.6.3.3 Reference standard

All six studies compared the outcome of CSM between patients and controls who had no evidence of syncope, and this separation into cases and controls constituted the reference standard. We note that, apart from one study (Morillo 1999), all the controls were people excluded from the guideline, i.e. they had not had a TLoC. Therefore, these studies do not discriminate between people with different types of TLoC, and this distorts the test accuracy results.

5.6.3.4 Outcomes

All the studies that reported diagnostic test accuracy had 2 x 2 tables constructed for the numbers of patients and controls with positive and negative tests. The sensitivity and specificity of the tests were then calculated based on the reference standard of expert opinion (i.e. cases versus controls).

5.6.4 Methodological quality of included studies

All the studies had a case control design. All were prospective except one (Kumar 2003), in which the cases were identified by retrospective record review while the controls were studied prospectively. All eligible patients were selected in each study.

In one study, cases and controls were matched on age and gender (Brignole 1991); in two studies they were matched on age only (Morillo 1999, Parry 2000); in one study the ages of the cases and controls were similar but there was a disparity in the gender distribution (cases 64% female; controls 36% female; Kumar 2003); and the remaining two studies did not give information on potential confounders between cases and controls. In most studies, outcome assessment was not blinded; in one study (Freitas 2004) it was unclear. All participants were followed up and there was no attrition in any of the studies.

Studies were also assessed using the QUADAS criteria for diagnostic test accuracy. The selection process was not defined in any of the studies. Selection of patients appeared to be 'all eligible patients selected', but these patients were those who had been referred to a syncope unit, for example, and the process of defining them as patients was not documented. Also, the control groups were defined as people without syncope, but the process of recruitment of controls was not discussed in any detail in the papers. The restriction to specific groups of cases and healthy controls meant that the spectrum of patients was defined as not representative, with the exception of the Morillo (1999) study.

The reference standard was expert opinion (patients versus controls) in all studies, and this was independent of the index test. The index test was adequately described in all studies, but the operator of the test was not blinded to patient or control status. The same clinical data were available as would be when the test would be used in practice in all studies. There were no uninterpretable tests or withdrawals from the studies. All studies were given a "-" QUADAS rating.

The data for diagnostic test accuracy were examined in sensitivity analyses excluding a) the retrospective study (Kumar 2003) and b) the study for which the patients (cases) were not stated to have syncope (Benchimol 2008).

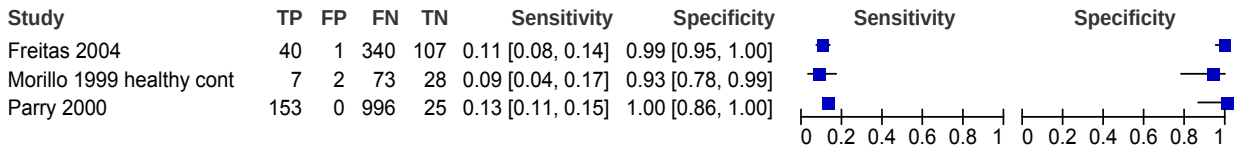
5.6.5 Results

Six studies reported diagnostic test accuracy statistics for diagnosis of CSM between patients with syncope and controls who had no evidence of syncope.

5.6.5.1 Results following the initial supine phase

Three studies reported the incidence of a positive response following both the supine and tilted phases (Freitas 2004, Morillo 1999, Parry 2000); the Benchimol (2008) study reported results only after both phases for the control group, but reported a sensitivity of 3/259 (1%) after the supine phase. The forest plot for the studies reporting the first stage is shown in Figure 5-43. There is consistency in both sensitivity and specificity, with the former ranging from 9 to 13% and the latter ranging from 93 to 100%. We note that the Benchimol (2008) study is not consistent with this range for sensitivity.

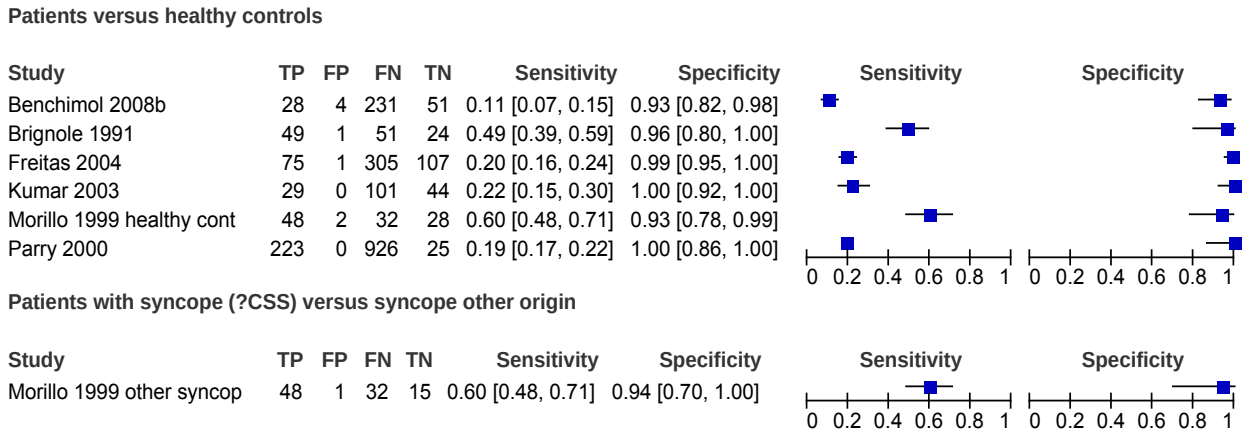
Figure 5-43. Forest plot of diagnostic test accuracy after supine CSM



5.6.5.2 *Results following the full protocol*

The studies also reported the number of positive responses following the full CSM protocol, which included the supine phase and a tilt with CSM (Figure 5-44).

Figure 5-44. Forest plot of diagnostic test accuracy following full protocol: CSM in patients versus controls

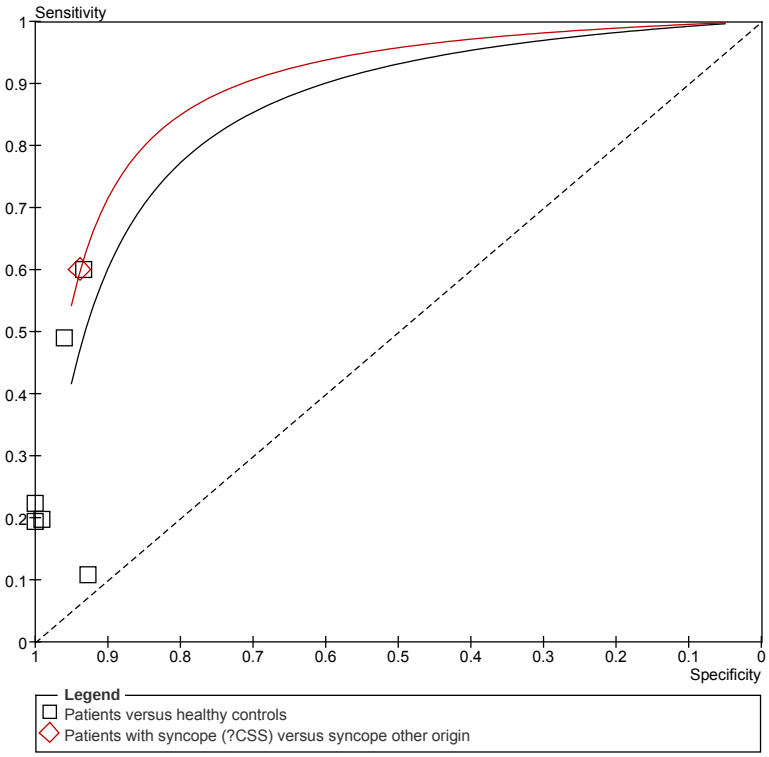


There was little variation in specificity and the two Morillo (1999) control groups had almost identical specificities, although there were very few other-syncope controls (n=16). However, across the studies, there was a wide variation in sensitivity. This may be due to the use of different thresholds for the index test or may be differences in the definition of cases.

The sensitivity represented the proportion of patients with suspected neurally mediated syncope, who had a positive result on CSM: this ranged from 10 to 60%. This is the diagnostic yield for this patient group.

Figure 5-45 shows the ROC curve for all studies – the Morillo (2001) 'other controls' is shown in red (diamond), even though there is only one data point. Although we have plotted the ROC curve, most of it represents variation in the sensitivity only.

Figure 5-45. ROC curve of DTA studies of CSM



5.6.5.3 Sensitivity analyses

Two sensitivity analyses were carried out to investigate heterogeneity, separately excluding (a) the retrospective study (Kumar 2003) and (b) the Benchimol (2008) study, in which there was some doubt whether the patients had TLoC. Results are shown in Figures 5-46 to 5-49.

a) Excluding the retrospective study (Kumar 2003)

Figure 5-46. Forest plot excluding the retrospective study (Kumar 2003)

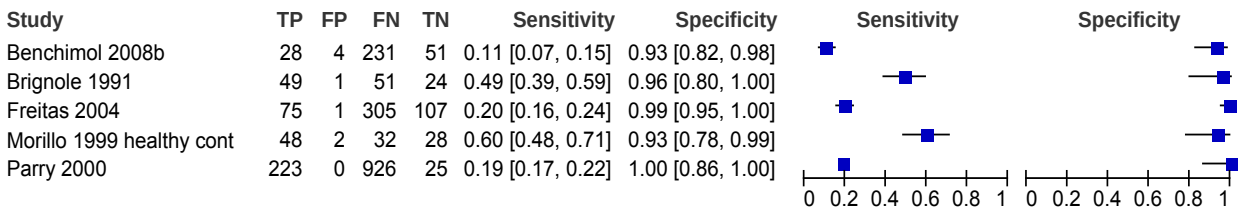
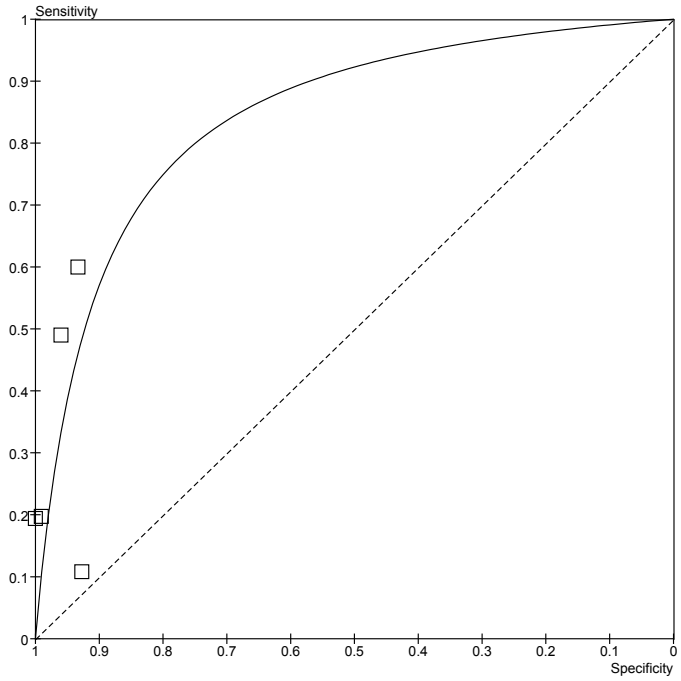
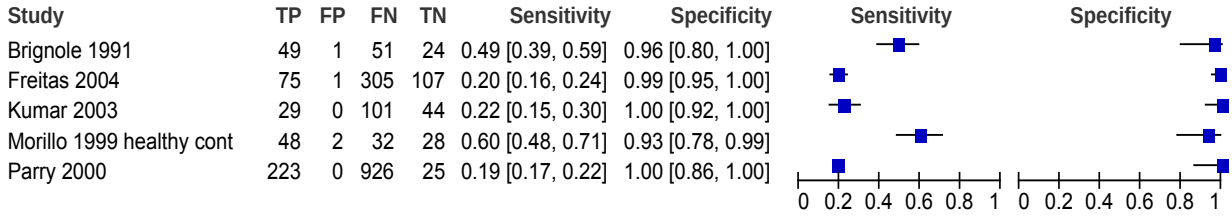


Figure 5-47. ROC curve excluding the retrospective study (Kumar 2003)



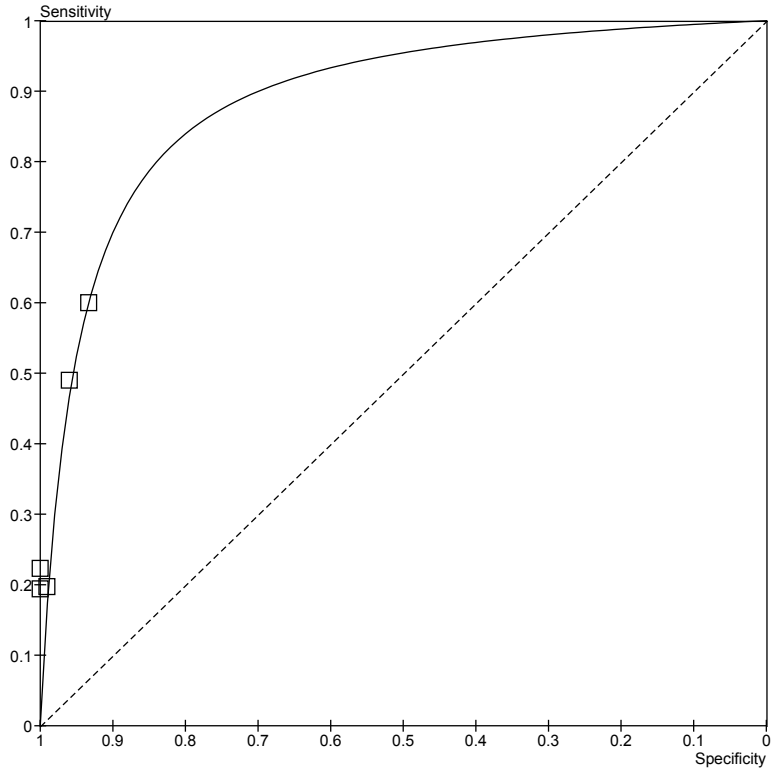
b) Excluding the study in which the patients were not stated to have syncope (Benchimol 2008).

Figure 5-48. Forest plot excluding the study in which patients were not stated to have syncope (Benchimol 2008).



Thus, for these studies the sensitivity ranged from 19 to 60% and the specificity from 93 to 100%.

Figure 5-49. ROC curve excluding the study in which patients were not stated to have syncope (Benchimol 2008).



5.6.5.4 Results for cardioinhibitory and mixed NM syncope

All studies except Benchimol (2008) reported the number of patients with a positive response following asystole or bradycardia (cardioinhibitory plus mixed).

The following results were obtained:

Figure 5-50. Forest plot for a positive response with a cardioinhibitory or mixed component

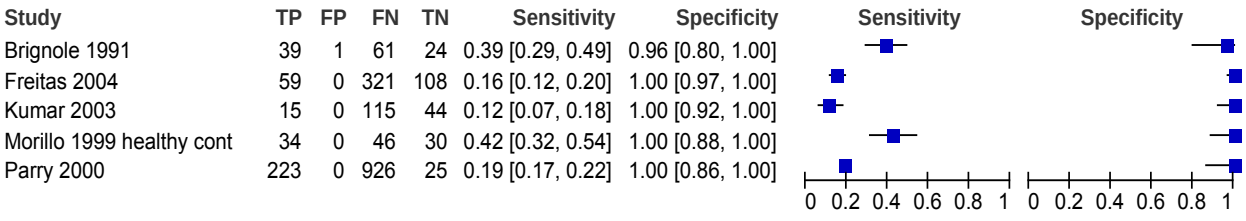
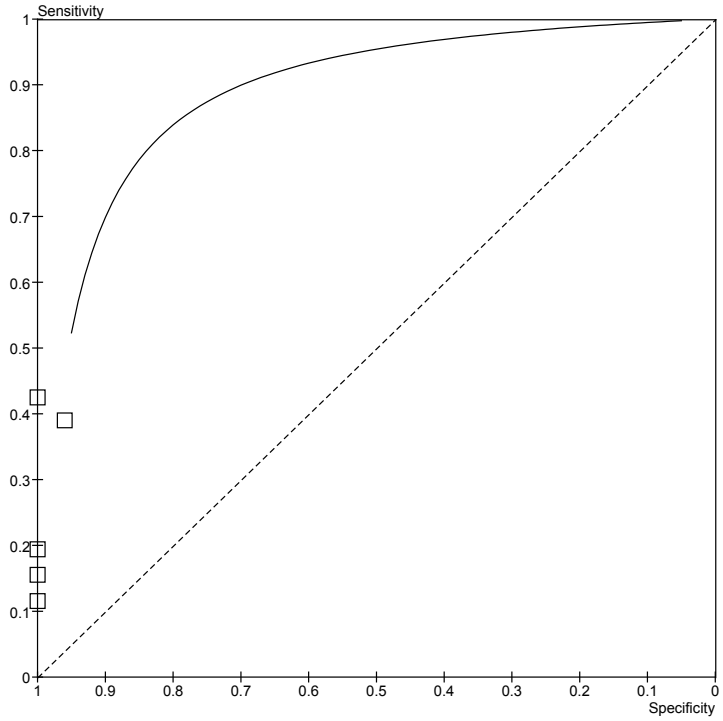


Figure 5-51. ROC curve for a cardioinhibitory or mixed positive response



In the absence of the Kumar (2003) study, the sensitivity for this type of response varies from 16 to 42%, with some heterogeneity. All of the specificity results were either 100% or 96% (Brignole 1991).

5.7 Economic review of second stage diagnostic tests

Eight papers where identified which compared alternative diagnostic testing strategies. Three of the publications report model based economic evaluations (Krahn 1999, Simpson 1999 and MSAC 2003) with the two of these reporting the same economic model in different settings (Krahn 1999 and Simpson 1999). The remaining studies are trial based economic evaluations based on RCTs (Krahn 2003, Rockx 2005, Farwell 2004&2006), with two papers reporting outcomes from the same trial at different durations of follow-up (Farwell 2004&2006). An additional methodological paper was identified (Hoch 2006) which reports further statistical analysis using data from one of the trials (Rockx 2005).

Two trials and one model based evaluation compared IER monitoring to conventional testing or standard care (MSAC 2003, Krahn 2003, Farwell 2004&2006). Rockx 2005 compared one month of external event recording (EER) with Holter monitoring (48hours). In two of the RCTs (Krahn 2003 and Rockx 2005) cross-over was allowed but not mandated if the allocated testing was completed without a diagnosis being obtained. The model based evaluation described in Krahn 1999 and Simpson 1999 considers alternative diagnostic pathways to determine the optimum sequencing of diagnostic tests.

Only one study considered the impact of diagnosis on patient outcomes in terms of successful treatment and prevention of further syncope recurrence and used this to estimate the cost per QALY gained (MSAC 2003). The majority of studies estimated the cost per diagnosis for each strategy and some presented the incremental cost per additional diagnosis of one strategy compared to another. Farwell 2004 and 2006 did not estimate a cost-effectiveness ratio but simply reported costs and outcomes separately.

The quality of the model based economic evaluations, evaluated against an economic checklist can be found in Appendix E. The quality of the trial based economic evaluations has not been evaluated using the economic check list as it is better to asses the methodological quality using criteria that are more relevant to RCTs. The cost and cost-effectiveness ratios for the trial based economic evaluations are reported here, but study quality has been assessed within the diagnostic review alongside the clinical outcomes.

Only two papers reported the UK costs from an NHS perspective (Farwell 2004 and 2006). The remaining studies report cost from the perspective of a non-UK publicly funded healthcare service in Canada (Rockx 2005, Krahn 2003 and Simpson 1999), Australia (MSAC 2003) or the US (Krahn 1999).

5.7.1.1 Implantable event recorder compared to standard care

Two trials and one model based evaluation compared implantable event recorder (IER) monitoring to conventional testing or standard care (MSAC

2003, Krahn 2003, Farwell 2004&2006). MSAC 2003 considered the use of IER at the end of the diagnostic pathway. The comparator is standard care, which is assumed to consist of no further ECG monitoring for most patients. In Krahn 2003 patients were randomised to 1 year of IER or conventional testing which was is defined as 2-4 weeks of EER followed by tilt-table and EPS. Cross-over was offered after completion of the assigned testing strategy if diagnosis was not obtained. In Farwell 2004&6 patients were randomised to IER monitoring or conventional testing but no testing protocol is given for conventional testing and the tests used are not described. Due to the differences in the methodological approach and the comparators, each trial is reported separately.

MSAC 2003

MSAC 2003 is a health technology assessment report undertaken to inform reimbursement decisions of the Australian Government. The assessment report contains an economic evaluation submitted by the manufacturer of the IER which considered the cost-effectiveness of using the IER at two different points in the diagnostic pathway. The MSAC report also contains an adaptation of the manufacturer's model which addresses several of the weaknesses identified in the manufacturer's model. This second model is the one considered here as it has been developed following independent academic review of the manufacturer's model.

The model considers the cost-effectiveness of IER in patients with recurrent syncopal episodes occurring at intervals greater than 1 week and who are determined either to have no structural heart disease or to be at a low risk of sudden cardiac death. It considers the use of IER at the end of the diagnostic pathway when diagnosis has not been achieved through history, physical examination, monitoring of blood pressure and ECG, and when EER is inappropriate or has failed to elicit a diagnosis. Therefore the comparator to IER is standard care, which is assumed to consist of no further ECG monitoring in the majority of cases.

The outcomes considered by the model are diagnosis with successful treatment, diagnosis but treatment unsuccessful and no diagnosis. The model considers the outcomes associated with diagnosis of bradyarrhythmia separately from diagnosis of tachyarrhythmia. The model uses data from the cross-over arm of an RCT (Krahn 2003) to estimate the diagnostic yield of IER in patients in whom EER has failed to elicit a diagnosis (33%) and assumes that no further diagnoses are established in the standard care arm. The model assumes that patients who are successfully treated (74% of those diagnosed) experience no further syncopal episodes and estimates the associated QALY gain (0.132 per annum). It also estimates the avoidance of health care costs associated with treatment of injuries sustained during syncope (0.584 hospitalisations avoided per annum at a cost of $2,383). The incremental cost of IER is $4,419 per patient. The time horizon is 3 years and costs and QALYs are discounted at 5% per annum.

The cost per diagnosis is $12,560, the cost per patient successfully treated is $16,973 and the cost per QALY is $44,969. Univariate sensitivity analysis demonstrate that the cost per QALY value is sensitive to the time horizon, the incremental number of diagnoses achieved by IER, the proportion of patients successfully treated, and the QALY gain associated with successful treatment. The lowest and highest values from the univariate sensitivity analysis were $23,555 and $76,132 respectively. This evaluation was considered to have potentially serious limitations as it was not clear from the report how the proportion of patients successfully treated had been estimated and the model was sensitive to this outcome. We converted the cost per QALY directly from 2003 AUS$ to 2007 UK£ using Purchasing Power Parity rates (2003 PPP rates UK/AUS = 0.64/1.35, OECD 2008) and Hospital and Community Health Services Pay and Pricing Index (2008/2003 = 256.9/224.8 (PSSRU 2008) giving a cost per QALY of £24,360. This is a crude estimate which does not take into account differences in the health care systems of the United Kingdom and Australia, but it suggests that a more accurate estimation of the cost-effectiveness in a UK setting is warranted.

Krahn 2003

This study aimed to assess the cost-effectiveness of 1 year of IER monitoring compared with conventional testing in patients with recurrent unexplained syncope (or a single episode associated with injury) who had been referred for investigation of syncope. Prior to enrolment patients underwent clinical assessment including postural blood pressure, 24hour ambulatory monitoring (Holter) or in-patient telemetry and echocardiogram. Patients were excluded if their LV ejection fraction was <35% or if they were unlikely to survive for one year. Patients with symptoms typical of neurally mediated syncope were excluded. Conventional testing consisted of 2-4 weeks of EER followed by tilt-table and EPS. Cross-over was offered after completion of the assigned testing strategy if diagnosis was not obtained. Unit costs are reported for each test, but resource use following randomisation is not reported separately from overall costs.

In the primary IER strategy the mean cost was $2,731 and 14/30 were diagnosed whereas in the primary conventional strategy the mean cost was $1,683 and 6/30 were diagnosed. The incremental cost per additional diagnosis for IER vs conventional was $3,930. Five of the IER patients crossed over to conventional testing and one received a diagnosis. 21 of the patients randomised to conventional testing crossed over to IER monitoring and 8 were diagnosed. The strategy of offering IER followed by conventional testing if unsuccessful was less costly than offering conventional testing followed by IER if unsuccessful (2,937 vs 3,683). It was also marginally more effective with 50% being diagnosed vs 47% being diagnosed on an intention to treat basis. However, the costs of the strategy in which IER is offered first would be much higher if all patients without a diagnosis crossed over to conventional testing. Eighty eight percent of those offered IER after conventional testing crossed over but only 31% of those offered conventional testing after IER crossed over. It is stated that 27 of the 29 patients diagnosed did not experience a recurrence during 19.8+-8.9 mths of follow-up, but one patients from each arm did experience a recurrence but these were not similar to their episodes prior to enrolment. Therefore 47% and 43% were recurrence

free during follow up from the IER then conv and conv then IER arms respectively.

Farwell 2004 and Farwell 2006

This study is an RCT comparing IER monitoring with conventional testing in patients presenting acutely with recurrent syncope in whom syncope remains unexplained following initial clinical work-up including carotid sinus massage and tilt testing in all patients and Holter monitoring where a cardiac cause is suspected. No testing protocol is given for conventional testing but the tests used in both arms are summarised in Farwell 2004. Farwell 2006 reports costs of hospitalisation and investigations for syncope incurred between randomisation and final study census (median follow-up of 17mths). Farwell 2004 reports intermediate results for the point when a minimum of 6 months follow-up had been achieved for all patients. Mean total costs post randomisation are reported with subtotals for diagnostic costs and hospitalisation costs. A breakdown of diagnostic costs for individual tests is also reported but resource use is not reported separately. Costs of treating the diagnosed cause of syncope are not included in the analysis and the costs associated with IER monitoring are not included although an estimate is given separately for the cost of the device alone (£1,350). The cost of investigations and hospitalisations and the total costs were significantly reduced for IER compared to conventional investigation at the intermediate census point (mean difference of £62, £747, and £809 respectively). At final census the cost of investigations were significantly lower for IER compared to conventional testing with a mean difference of £70, but total costs were not significantly different (p=0.28). As the cost of IER monitoring has not been included in the analysis, it is not possible to calculate the overall incremental cost per additional diagnosis.

5.7.1.2 External event recording compared to Holter monitoring

One study (Rockx 2005) presents the cost-effectiveness of external event recording (1 month) compared to Holter monitoring (48hours) in patients who

have been referred for ambulatory ECG following syncope or presyncope. This is described by the authors as “community acquired syncope” to reflect the fact that it is unlikely to include high risk patients who would be admitted and investigated promptly. Patients were randomised to the initial diagnostic strategy but cross-over was allowed following completion of the initial strategy if no diagnosis had been achieved. External event recording was extended to 2 months if requested by the patient.

In the EER arm and Holter arm, 31/49 and 12/51 patients respectively had an arrhythmia diagnosed or excluded prior to cross-over. No additional arrhythmias were diagnosed or excluded following cross-over from EER to Holter monitoring but thirteen patients had an arrhythmia excluded following cross over from Holter monitoring to EER giving an overall diagnostic yield of 25/51 for Holter monitoring followed by offering EER. However, only 22% of those offered cross-over following EER and 74% of those offered cross-over following Holter monitoring took up the option of further monitoring. This may reflect the fact that 41 of the 100 patients enrolled had undergone Holter monitoring previously.

Costs were based on Canadian resource use and price data but were subsequently converted to US$. Unit costs are reported for each test, but resource use following randomisation is not reported separately from overall costs. Holter monitoring was estimated to cost $175 per patient and EER $534 per patient. The cross over strategy of Holter monitoring followed by offering EER to undiagnosed patients cost on average $481 per patient, whilst EER followed by offering Holter monitoring cost $551 on average.

The cost per additional diagnosis was US$902 for EER vs Holter monitoring. The cost per additional diagnosis for EER followed by Holter vs Holter followed by EER was $500, although this estimate should be treated with caution given the differential uptake of further monitoring. Uncertainty was estimated by using statistical bootstrapping to generate 1000 ICER estimates. For EER vs Holter monitoring (without cross-over) 21% of ICERs were below US$750 and 90% were below US$1250. In Hoch 2006, the data from the Rockx 2005 has been used to generate a CEAC. The mean ICER in Hoch is

given as US$1,096 for EER vs Holter and the CEAC shows that there is a 3% probability of the ICER being under $750 and a 3% probability of it being over $2000.

5.7.1.3 Sequencing of diagnostic tests

Two papers (Krahn 1999 and Simpson 1999) report the results of an economic model using costs from the US and Canada respectively. The model estimates the costs and diagnostic yield of 6 diagnostic strategies in patients who have experienced a first episode of unexplained syncope using published estimates of diagnostic yield and local cost estimates for diagnostic testing. The model assumes that the patient progresses to the next test only if the previous test was negative and that the diagnostic yield of each test is independent of the result of the previous test. This second assumption is likely to be false if the order of tests does not reflect the testing history of the study populations in which the diagnostic yield was measured. The model considers patients with structural heart disease separately from those without as some of the strategies restrict electrophysiological studies (EPS) to those patients with structural heart disease. The baseline strategy consists of Holter monitoring, followed by echocardiography, tilt-table testing, external event recorder, and finally EPS. The second strategy considers the addition of IER for those patients undiagnosed at the end of the baseline strategy. The remaining strategies are broadly similar to the second strategy but they attempt to increase the diagnostic efficiency by restricting echocardiography to those patients in whom the presence of SHD is uncertain (strategy 3), or restricting EPS to those with SHD (strategy 4) or applying both these restrictions (strategy 5). Finally in the Simpson 1999 paper an additional strategy in which the tests are ordered according to their cost per diagnosis is considered. The validity of this strategy seems questionable as it involves the use of EPS in patients with SHD prior to the use of echocardiogram which may be useful in determining whether SHD is present. It also includes Holter monitoring after external event recording has failed which does not seem clinically useful. The order of tests in this final model is likely to result in tests being used in populations that differ significantly from the trial populations used to estimate the data on diagnostic yield and it is therefore most likely to

be biased. No attempt has been made to estimate the impact of diagnosis on patient outcomes and no value is placed on the time to diagnosis which may by important if long-term ECG monitoring is used early in the diagnostic strategy and delays testing that might identify significant structural heart disease.

In Krahn 1999, strategy 5 in which the most expensive tests are restricted to those patients most likely to benefit, had the lowest cost of all 5 strategies including the baseline strategy in which IER was not used. Strategy 2 had a slightly higher yield than strategy 5 (99% compared to 98%) but it cost an additional US$813 per patient making it unlikely to be cost-effective given the marginal increase in diagnostic yield.

In Simpson 1999 the lowest cost strategy was strategy 1 but strategy 6 had a lower cost and higher yield than strategies 2 to 5 and therefore dominated these strategies. The incremental cost per additional diagnosis for strategy 6 vs 1 was CND$425 to CND$1,566. If strategy 6 is discounted then strategy 5 dominates strategies 2 to 4 and the incremental cost per diagnosis compared to strategy 1 is CND$1,279 – 2,338

This study demonstrates that the overall cost and diagnostic yield of a diagnostic pathway are dependent on the order in which tests are used and whether certain tests are restricted to groups with a higher pre-test likelihood. Further economic analysis is required to determine the optimal diagnostic testing strategy and this should take into account patient outcomes following diagnosis and the impact of diagnostic delay on diagnosis.

5.8 Economic evaluation of ambulatory ECG

This economic evaluation assesses the cost-effectiveness of ambulatory ECG in patients who have been referred for specialist cardiology assessment based on their initial assessment. The population was split into three subgroups based on the suspected cause of TLoC after the initial assessment

and any prior use of diagnostic tests. This was done as the GDG felt that the yield of these tests is likely to be dependent on these factors.

The three populations subgroups considered in the model were patients with;

- Suspected arrhythmia on the basis of the initial assessment
- Unexplained cause on the basis of the initial assessment
- Unexplained cause following secondary tests

The ambulatory ECG technologies considered in the model were;

- 24hr Holter monitoring
- 48hr Holter monitoring
- External event recorder monitoring (EER)
- Implantable event recorder monitoring (IER)

As the aim of ambulatory ECG in patients who have experienced a TLoC is to record an ECG during a spontaneous TLoC episode, the GDG felt that these different forms of ambulatory ECG would be used in different populations based on the frequency of TLoC episodes. We have therefore not compared these forms of ambulatory ECG against each other as they are unlikely to be relevant alternatives in the same patient.

The GDG noted that the Farwell 2006 RCT, provided evidence on the diagnostic yield of implantable event recorders compared to conventional monitoring (in a UK setting) in the absence of an implantable event recorder. The GDG wished to model this comparison using the evidence from the Farwell 2006 study as the conventional monitoring arm was felt to be reasonably representative of the testing strategy that might be used in the UK if implantable event recorders were not available. The GDG were also

interested in knowing the cost-effectiveness of implantable event recorders compared to a strategy of no further diagnostic testing.

The conventional monitoring strategy from the Farwell 2006 paper was not considered to be a suitable comparator for external event recorder monitoring or Holter monitoring as these were available as part of the conventional monitoring strategy. The GDG advised that in patients with frequent or very frequent TLoC episodes the relevant comparator for 24/48hr Holter monitoring or external event recorder monitoring was no further diagnostic testing.

5.8.1 Costs of ambulatory ECG testing

In order to determine the cost-effectiveness of ambulatory ECG, we needed to determine the costs of testing. Where possible we have based our estimates of cost on the 2007/08 NHS reference costs (NHS reference costs 2007/08).

5.8.1.1 Implantable event recorders

The GDG advised that Implantation of an event recorder is usually done as a day case procedure with a NHS reference cost of £1895 (IQR £1160 – 2564) [NHS reference cost 2007/08 for EA03Z]. It should be noted that this is an average over all procedures combined under this HRG which includes intravenous implantation of cardiac pacemaker systems. Removal is usually also carried out as a day case procedure, with an NHS reference cost of £526 (IQR £347 – 575) [NHS reference cost 07/08 for EA47Z]. This is an average over a variety procedures including Holter monitoring and exercise ECG, although these are not likely to be commonly done as day case procedures.

IER devices have been excluded from the 2010/11 payment by results tariff as they have been identified as high cost devices that may not have been in common use when the 07/08 HRG cost data was collected making it possible that the cost of these devices are not accurately captured in the HRG costs (Department of Health 2009). We have therefore assumed that the cost of the device is not included in the HRG cost and have estimate this separately. The 2004 Horizon scanning briefing on IERs states that 1,429 devices were

implanted in 2003 and the unit cost in 2004 was £1,400 for the device, excluding any day case implantation costs (National Horizon Scanning Centre 2004). Uplifting this unit cost from 2004 to 2008 using the Hospital and Community Services Pay and Prices Index (uplift = 256.9/ 224.8, PSSRU 2008) gives an estimated unit cost of £1,600 for the device alone. This cost has been added to the cost of implantation and removal to give a total costs of £4021 at 2007/08 prices.

5.8.1.2 Holter monitoring and external event recorders

The outpatient HRG for ambulatory ECG (HRG code EA47Z) covers a variety of procedures including 24/48hr ambulatory ECG, Holter extended ECG, Cardiomemo ECG, exercise ECG, tilt-table testing and IER removal. The NHS reference cost for outpatient ambulatory ECG monitoring is £117 (IQR £64 – 156). There is also a direct access HRG code (DA09) for 24hour ECG / BP monitoring which has an NHS reference cost of £54 (IQR 37 – 63), which is significantly less than the outpatient NHS reference cost. However, this may reflect the variety of procedures covered by the outpatient HRG. The GDG advised that the direct access cost is likely to be the most relevant cost for ambulatory ECG in the TLoC population. However they also requested that a sensitivity analysis was conducted using the outpatient cost.

5.8.1.3 Conventional testing

Table 24 below shows the resource use and cost of diagnostic testing and hospitalisations after randomisation to IER or conventional monitoring as reported in Farwell 2004 when all patients had been followed up for at least 6 months. The costs reported exclude the cost of IER. The IER group had significantly lower overall costs (-£809, 95%CI –£2766.22 to –£123.42) at the study census reported in Farwell 2004. This was mostly driven by a difference in hospitalisation costs. However, in the Farwell 2006 paper when the median follow-up time was 17 months, the cost difference between the two groups was no longer statistically significant. In our basecase analysis we used the data from the 6 months follow-up to reduce the cost of IER relative to conventional monitoring to reflect the reduced rate of diagnostic testing and lower cost of hospitalisations in the IER group during follow-up. A sensitivity

analysis was also conducted in which we assumed that there was no cost saving in terms of reduced hospitalisations and fewer diagnostic tests for the IER group.

Table 24

Diagnostic test	IER	Conventional monitoring	Difference in costs, Mean (95%CI)
Computed tomography head	4	8	–5.30 (–13.86 to 1.29)
Magnetic resonance imaging	1	1	–0.05 (–3.06 to 2.91)
Electroencephalogram	0	2	–2.04 (–4.80 to 0.72)
Carotid doppler	3	5	–2.19 (–8.14 to 2.89)
Echo	12	15	–8.54 (–25.31 to 6.54)
24-hr Holter	4	11	–7.34 (–15.08 to –0.37)
EER: `R Test'	5	28	–29.84 (–43.49 to –18.04)
Electrophysiologic study	0	1	–6.12 (–17.90 to 5.65)
Total investigation costs	£34.0	£95.4	–£61.43 (–£92.92 to –£35.16)
Hospitalisation costs	£379	£1090	–£747.30 (–£2728.48 to –£72.75)
Total costs	£406	£1210	–£808.72 (–£2766.22 to –£123.42)

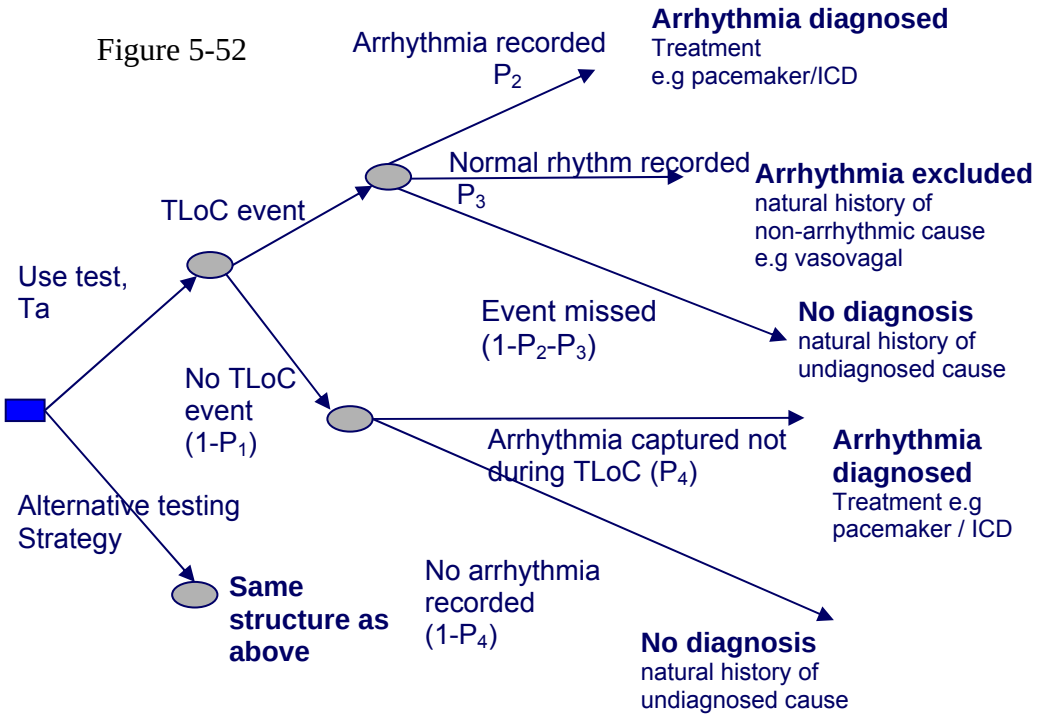
5.8.2 Diagnostic outcomes

The GDG advised that the reference standard for diagnosing or excluding an arrhythmic cause of TLoC is an ECG recording during a spontaneous TLoC event. Therefore we have assumed that there is a zero misdiagnosis rate for those patients who have an arrhythmic cause diagnosed or excluded after having an ECG recorded during TLoC. However, given that not every patient experiences a TLoC during monitoring and that an ECG is not always captured during the TLoC event, some patients will not gain any diagnostic information from ambulatory ECG but will still incur the cost of testing. In addition, some of the ambulatory ECG technologies can be programmed to record certain arrhythmias without the patient activating the device and it is therefore possible that arrhythmias may be recorded during a period when no

TLoC symptoms were experienced. We therefore structured the model to include the following outcomes, as shown in Figure 5-52;

- no TLoC during ambulatory ECG
- TLoC with ECG showing normal rhythm and rate during TLoC
- TLoC with ECG showing arrhythmia recorded during TLoC
- TLoC with no ECG recorded during TLoC
- arrhythmia recorded but not during TLoC

Figure 5-52



5.8.3 Effectiveness of ambulatory ECG

The data required to populate the model structure (probabilities P_1, P_2, P_3, P_4) for each form of ambulatory ECG were calculated using the event rates from all of the available studies within the relevant population for each ambulatory ECG technology. As our comparison of tests is not based on comparative studies, the raw data from the available studies have been summed for each outcome to give an overall probability across the population at risk. The studies reporting data for each population and outcome are described in the

ambulatory ECG diagnostic review (section 5.3). Table 25 summarises the data for each population for each of the ambulatory technologies.

For some populations there were no studies that provided suitable data from which to populate the model, for example there were no studies looking at external event recorders which were considered to be representative of people with an unexplained cause after the initial assessment. (The available studies for EER in people with an unexplained cause were all classified as representing people who had access to some second stage diagnostic tests such as Holter monitoring or tilt-testing). This was considered to be relevant indirect evidence for people with unexplained TLoC after the initial assessment. For the implantable event recorder there was only one study (Ermis 2003) which was classified in the clinical review as being potentially representative of people with unexplained TLoC after the initial assessment. However, the use of second stage tests in this study was unclear and the study was small (N=50). It was also noted that some studies classified to be in 'people with unexplained TLoC after secondary testing' did not exclude on the basis of the secondary tests. Therefore it was decided to combine the data from all studies in people with unexplained TLoC, with the results being considered as indirect evidence for the population, 'people with unexplained TLoC after the initial assessment'.

As there were no studies comparing ambulatory ECG with a strategy of no further testing, we had to make assumptions regarding the diagnostic outcomes in patients who did not receive any further ECG monitoring. We assumed that they had the same rate of TLoC during the monitoring period but that none of the recurrences resulted in a diagnosis. If there is in fact some rate of opportunistic diagnosis in patients who don't receive ambulatory ECG, our approach may have overestimated the cost-effectiveness of ambulatory ECG. However the GDG felt that opportunistic diagnosis would be unlikely in this population in the absence of access to ambulatory ECG, and therefore that this was not a significant cause of potential bias.

Table 25: Event rates used to populate model structure for indirect comparisons against no further testing

Population and technology	N Studies	Prob of TLoC, P_1	Prob of outcomes in patient having TLoC during monitoring			Prob of arrhythmia in a patient not having TLoC during monitoring, P_4
			Arrhythmia, P_2	Normal, P_3	No ECG, $(1-P_2-P_3)$	
Implantable event recorder						
Suspected arrhythmia	5[a]	153/277 =0.55	88/153 =0.58	49/153 =0.32	16/153 =0.10	4/48* (3 studies)[d] =0.08
Unexplained after secondary tests	14[b]	596/1078 =0.55	290/596 =0.49	266/596 =0.45	40/296 =0.07	23/171* (7 studies)[e] =0.13
External event recorder						
Suspected arrhythmia	1 (Rothman 2007)	35/51 =0.69	21/35 =0.60	14/35 =0.40	0/35 =0.00	0/16 =0.00
Unexplained after secondary tests	4[c]	98/192 =0.51	17/98 =0.17	49/98 =0.50	32/98 =0.33	8/16 (1 study)[f] =0.50
48 hr Holter						
Suspected arrhythmia	1 (Ringqvist 1989)	8/63 =0.13	4/8 =0.50	4/8 =0.50	0/8 =0.00	8/55 =0.15
Unexplained after initial tests	1 (Kapoor 1991)	20/95 =0.21	1/20 =0.05	19/20 =0.95	0/20 =0.00	25/75 =0.33
Unexplained after secondary tests	1 (Rockx 2005)	12/51 =0.24	0/12 =0.00	12/12 =1.00	0/12 =0.00	0/39 =0.00
24hr Holter						
Suspected arrhythmia	1 (Sarasin 2005)	22/140 =0.16	15/22 =0.68	7/22 =0.32	0/22 =0.00	0/118 =0.00
Unexplained after initial tests	1 (Comolli 1993)	3/287 =0.01	2/3 =0.67	1/3 =0.33	0/3 =0.00	55/284 =0.19

[a] Brignole 2001, Garcia-Civera 2005, Krahn 1999, Menozzi 2002, Krahn 1998
[b] Ermis 2003, Farwell 2006, Krahn 2001, Boersma 2004, Brignole 2005, Donateo 2003, Krahn 2002, Krahn 2004, Lombardi 2005, Moya 2001a, Nierop 2000, Pezawas 2007, Pierre 2008, Seidl 2000,
[c] Rockx 2005, Fogel 1997, Linzer 1990, Schuchert 2003
[d] Brignole 2001, Menozzi 2002, Krahn 1998
[e] Ermis 2003, Krahn 2001, Boersma 2004, Krahn 2004, Pezawas 2007, Pierre 2008
[f] Schuchert 2003

For the head-to-head comparison of IER against conventional monitoring we applied the event rates directly from the Farwell 2006 paper. These are summarised in Table 26. The study reports that 4 patients had an arrhythmia diagnosed and 3 patients had an arrhythmia excluded through conventional monitoring. This provides some information on the rate of opportunistic diagnosis when IER is not available. However, it is not clear how many of the diagnoses made in the conventional arm where achieved through other forms

of ambulatory ECG such as Holter or EER monitoring rather than through a repeat 12-lead ECG during the next TLoC episode. Therefore, it is not clear from this study what the rate of opportunistic diagnosis would be if ambulatory ECG monitoring were not available in any form.

Table 26: Event ratesfor direct comparison of IER against conventional monitoring in patients with an unexplained cause after secondary tests

Testing strategy	N Studies	Prob of TLoC, P_1	Prob of outcomes in patient having TLoC during monitoring			Prob of arrhythmia in patient not having TLoC during monitoring, P_4
			Arrhythmia, P_2	Normal, P_3	No ECG, $(1-P_2-P_3)$	
Implantable event recorder	1	48/101 =0.48	20/48 =0.42	23/48 =0.48	5/48 =0.10	0/53 =0.0
Conventional monitoring	1	37/97 =0.38	4/37 =0.11	3/37 =0.08	30/37 =0.81	0/60 =0.00

5.8.4 Modelling the distribution of arrhythmias diagnosed

In order to determine the cost-effectiveness of ambulatory ECG testing compared to no testing (or conventional monitoring), we needed to determine what would happen to patients who had an arrhythmia diagnosed or excluded and how this differed from what would happen to them if they did not receive a diagnosis. The economic model needed to capture the main costs and health outcomes that result from using ambulatory ECG testing in this population, but it cannot capture the exact prognosis for all of the possible diverse conditions which cause TLoC. The GDG advised that the arrhythmias identified during ambulatory ECG could be broadly categorised as follows;

- Bradyarrhythmia
  - Sick sinus syndrome
  - Atrioventricular (AV) block
  - Pacemaker malfunction
  - Drug-induced
- Tachyarrhythmia
  - Ventricular tachycardia (VT)

- Torsades de pointes
- Supraventricular tachycardia

The GDG also advised that the diagnoses that were most likely to result in significant treatment costs and / or significant health benefits were sick sinus syndrome, atrioventricular (AV) block and ventricular tachycardia VT. We therefore decided to focus on capturing the post testing outcomes for these diagnoses within the model. This approach may have underestimated the cost-effectiveness of diagnostic testing as it fails to capture benefits to patients who receive cost-effective treatment for one of the other arrhythmias, or who receive a beneficial change in their management as a result of having an arrhythmic cause excluded.

In order to calculate the proportion of arrhythmias that were due to sick sinus syndrome, AV block or VT, we combined data from all studies included in the ambulatory ECG diagnostic review (section 5.3) which reported information on the breakdown of arrhythmias. We therefore assumed that the distribution was constant across the all of the populations included in the ambulatory ECG review (section 5.3), and that none of the ambulatory ECG technologies were more likely than other ambulatory ECG technologies to diagnose or miss a particular arrhythmia.

We modelled post diagnostic outcomes for these three diagnoses when they were diagnosed by an arrhythmia being recorded during a TLoC event. However for arrhythmias recorded during an asymptomatic period we restricted the analysis to complete AV block, asystole >3 seconds (which we assumed to be caused by sick sinus syndrome) and sustained VT as these were felt to be clinically significant arrhythmias even when recorded in the absence of TLoC.

Table 27: Event rates used to parameterise the distribution of arrhythmias		
Parameter	Event rate	Number of studies
Proportion of arrhythmias during TLoC that are bradyarrhythmias	406/550 = 0.74	31[a]
Proportion of bradyarrhythmias during TLoC that are;		20[b]
AV block	106/279 = 0.38	
Sick sinus syndrome	157/279 = 0.56	
Other brady	16/279 = 0.06	
Proportion of tachyarrhtymias during TLoC that are;		27[c]
VT during syncope	38/141=0.27	
Other tachy	103/141 = 0.73	
Proportion of arrhythmias not during TLoC that are bradyarrhythmias	63/129 =0.49	8[d]
Proportion of bradyarrhythmias not during TLoC that are;		8[d]
Complete AV block	16/63 = 0.23	
Asystole >3s	44/63 = 0.64	
Other brady	9/63 = 0.13	
Proportion of tachyarrhythmias not during TLoC that are;		8[d]
Sustained VT	25/66 =0.38	
Other Tachy	41/66 = 0.62	

[a] The following studies reported data on this outcome: Aronow 1993, Arya 2005, Boersma 2004, Brignole 2001, Brignole 2005, Brignole 2006, Comolli 1993, Deharo 2006, Donateo 2003, Ermis 2003, Farwelll 2006, Fitchet 2003, Garcia-Civera 2005, Kapoor 1991, Krahn 1998, Krahn 1999, Krahn 2001, Krahn 2002, Krahn 2004, Linzer 1990, Lombardi 2005, Menozzi 2002, Moya 2001, Nierop 2000, Pezawas 2007, Pierre 2008, Ringqvist 1989, Rockx 2005, Sarasin 2005, Schuchert 2003, Seidl 2000,

[b] Of the 31 included above, the following studies didn't report any bradyarrhythmias or didn't report the type of bradyarrhythmias: Comolli 1993, Farwell 2006, Fitchet 2003, Kapoor 1991, Krahn 1999, Krahn 2001, Krahn 2002, Nierop 2000, Rockx 2005, Schuchert 2003, Seidl 2000.

[b] Of the 31 studies included above, the following studies didn't report any tachyarrhythmias or didn't report the type of tachyarrhythmias Kapoor 1991, Krahn 2001, Moya 2001, Rockx 2005.

[d] The following studies reported data on these outcomes: Boersma 2004, Brignole 2001, Brignole 2006, Comolli 1993, Fitchet 2003, Kapoor 1991, Krahn 2004,Ringqvist 1989,

5.8.5 Modelling prognosis in diagnosed and undiagnosed cases

In order to model the cost-effectiveness of diagnostic testing it is important to estimate the post testing costs and benefits that occur in diagnosed and undiagnosed cases. However, it was not feasible to construct a detailed disease model for several different conditions. Therefore a simplified approach was taken which tried to estimate post diagnostic costs and benefits for the three diagnoses which the GDG had advised that the model should focus on. Given that treatment after diagnosis was not within the scope of this guideline, it was not possible to conduct systematic reviews on the

effectiveness of treatments for AV block, sick sinus syndrome and VT. However, a narrative review (see Appendix D6) was conducted to gather evidence which could be used to model the prognosis of treated and untreated patients with sick sinus syndrome, AV block and VT. A review of quality of life evidence was also conducted to provide estimates of health utility for the economic model. This can be found in appendix H.

5.8.5.1 Costs of treatment for AV block and sick sinus syndrome

NICE's technology appraisal 88 recommends dual chamber pacing for patients with symptomatic bradycardia due to sick sinus syndrome or AV block (NICE TA88). The NHS reference cost for dual chamber pacemaker implantation as an elective day case is £2430 (NHS reference cost 2007/08 for EA05Z]. In the technology appraisal guidance for dual chamber pacing, it states that the average market price of dual-chamber pacemakers is between £1265 and £1713 excluding VAT, with leads costing £169 (NICE TA88). This is based on evidence submitted by the Association of British Healthcare Industries. The technology appraisal guidance states that the Institute believed that these market prices represented a substantial discount from the list price. We have applied a device cost (including leads) of £1,882 (£1713+£169) in the model which reflects the higher range of device costs from these market values. We have assumed that patients receive an annual follow-up appointment at a cost of £105 which is the NHS reference cost for a consultant led non-admitted face-to-face follow-up appointment in cardiology (2007/08 NHS reference cost).

5.8.5.2 Cost of recurrence

When modelling the recurrences after second stage diagnostic testing, we can assume that patients will have already had all of the tests indicated by the guideline. Therefore, if they present with a recurrence, their management is likely to focus on identifying any changes in presentation that would warrant a change in management. It is likely that they would therefore receive a repeat

initial stage assessment including 12-lead ECG, but they would be unlikely to undergo additional second stage testing unless new information had been gained during the initial stage assessment.

The NHS reference costs for A&E are categorised according to the dominant investigation and the dominant treatment. Patients presenting to A&E with minor injuries or no-significant injury are likely to receive treatment and / or investigations in categories 1 or 2. For example, an ECG, observation for head injury or wound cleaning would come under category 1, whilst an x-ray, wound closure or plaster would come under category 2. The GDG advised that it was reasonable to assume in the model that most patients presenting to A&E after experiencing a TLoC would incur the cost of a category 2 consultation which has a reference cost of £134 (IQR £111 to £161). The mostly likely HRG code for a paramedic call out to a patient who has experienced TLoC would be “PS31: Unconscious / fainting (near) / passing out (non-traumatic).” This has an NHS reference cost of £208 (IQR 3176 to £229) for a category A call out (256,856 units of activity) and £204 for a category b call out (137,109 units of activity). Category C call outs are much less common (23,622 units of activity) for this HRG code.

We have therefore assumed that each recurrence results in a category A ambulance call-out and a category 2 A&E consultation giving a total cost of £342 per recurrence. This assumes that no admission is needed to treat any injury and that there is no new information is obtained from the initial assessment which suggests that further second stage diagnostic tests are indicated.

However, some patients will be admitted to hospital either for further investigations or to treat injuries sustained during the TLoC episode. To determine how sensitive the model is to the costs associated with recurrence we have therefore conducted a sensitivity analysis assuming that all recurrences result in a non-elective short stay admission under the HRG code for “syncope or collapse without complications” which has a cost of £318 (IQR

237-365). In the sensitivity analysis this cost is applied in addition to the ambulance and A&E cost giving a total cost for recurrence of £660.

5.8.6 AV Block

5.8.6.1 Survival

Studies on the prognosis of treated and untreated AV block are summarised in a narrative review which can be found in Appendix D6. Untreated complete or 2nd degree AV block is associated with an increased risk of mortality (Johansson 1966, Shaw 2004, Shaw 1985). There is evidence from non-randomised studies to show that pacing improves survival in patients with 2nd degree or complete AV block (Shaw 1985, Johansson 1966). We have assumed in the model that patients experiencing TLoC due to AV block have 2nd degree AV block. We have used the data from the Devon Heart Block and Bradycardia Survey (Shaw 1985) to estimate the difference in survival between paced and unpaced patients.

The Devon Heart Block and Bradycardia Survey (Shaw 1985) recruited 214 patients with 2nd degree AV block. They had a mean age of 72 years and at least 50% were followed up for a minimum of 3 years. Thirty-nine percent (84/214) had syncope at baseline. Mortality for patients with 2nd degree AV block was similar for Mobitz Type I and Type II blocks. Pacing improved survival even when patients were matched for age. Survival in unpaced patients was worse when syncopal episodes (Stoke-Adams attacks) were present but most patients with syncope were paced so the impact of syncope on prognosis was underestimated in the cohort as a whole. Insufficient data is presented in Shaw 1985 to calculated paced and unpaced survival curves for the subgroup of patients with syncope. However, survival curves are presented for paced and unpaced patients from enrolment in the study (Figure b, Shaw 1985). Using these survival curves we have estimated that paced patients gained 4.85 LYs (life-years) over 6 years and the unpaced patients gained 3.92 LYs. Using the average mortality risk from the last 3 years of

follow-up from the paced arm (6.9% per annum) to extrapolate both curves to 10 years, we calculated expected LYs gained of 7.18 and 5.27 (undiscouted) for paced and unpaced patients respectively.

5.8.6.2 Recurrence

No useful data was identified in the narrative review (Appendix D6) on the rate of symptomatic recurrence in AV Block. The Framingham Study (Soteriades 2002) reported that the rate of recurrence in patients with cardiac syncope is 30 times higher (95% CI 14.9 to 60.3) than the rate of new onset syncope (cumulative incidence of 6% over 10 years when assuming a constant hazard). This rate is similar to the rate for unpaced patients with sick sinus syndrome (Alboni 1997). As there was no data for paced patients with AV block, the rates for paced and unpaced patients with sick sinus syndrome were applied to paced and unpaced patients with AV block.

5.8.6.3 Treatment costs

We have estimated treatment costs for paced and unpaced patients over 10 years. A longer time horizon was not considered appropriate given that the life-expectancy for the pacemaker generator is 5-12 years. (Castelnuovo 2005). A sensitivity analysis has been conducted using a 6 year horizon. The total undiscounted cost of treatment over 10 years was £4986 for AV block. The total discounted cost was £4,912 when discounting future costs at 3.5%.

5.8.6.4 HRQoL

Lopez-Jimenez 2002 provides the only preference based measure of HRQoL in this population identified by our search (see Appendix H). This study reports data from an RCT comparing dual and single chamber pacing in 407 patients aged over 65 with bradycardia as the indication for pacing. Time-trade off scores were obtained prior to pacing (in 398 patients) and at 3, 9 and 18 months follow-up (in 284, 291 and 250 patients respectively). Pre-implant utility was 0.76 (sd 0.06) There was no significant difference between the two pacing modes or between the different indications for pacing (57% AV block,

43% sinus-node dysfunction, 39% carotid sinus hypersensitivity). There was significant improvement of 0.165 (sd 0.4, p=0.001) from baseline to 3 mths when combining data from both arms. This utility improvement has been applied in the model to patients receiving pacing for either sinus node disease or AV block.

5.8.7 Sick sinus syndrome

5.8.7.1 Survival

The Devon Heart Block and Bradycardia survey (Shaw 1980) studied 381 patients with established or potential sinoatrial dysfunction (sick sinus syndrome). Patients with sinus arrest or extreme bradycardia on ambulatory ECG were included in the potential sinoatrial dysfunction group. Survival for both of the groups (established and potential sinoatrial disorder) was similar to population norms. Survival was worse in those with syncope but these patients tended to be older. Survival of paced and unpaced patients was similar even when age matching was applied. We have therefore used general population mortality rates for this group and assumed that pacing has no impact on survival.

We applied an annual mortality risk for this group of 8.7%. This was the mortality risk used in the economic model developed by the technology assessment group for NICE's appraisal of dual chamber pacing and it reflects the general population all cause mortality risk for patients aged 75 and older. (Castelnuovo 2005) Using this mortality risk we calculated expected LYs gained of 6.57 at 10 years (undiscounted). Using this approach the 5 year survival (63%) was similar to patients with sinoatrial disorder and syncope (61%) from the Shaw 1980 study.

5.8.7.2 Recurrence

Data on the recurrence of syncope in paced and unpaced patients is available from an RCT (Alboni 1997) comparing pacing to no treatment in patients with sick sinus syndrome. The duration of follow-up in this study was at least 12

months with a mean follow-up of 19 months. Based on the Kaplan-Meier curves presented, the risk of recurrence was 17% per annum in years 1 and 2 for unpaced patients. There was a 6% risk in year 1 for paced patients and there were no events in year 2. We applied this data to the sick sinus syndrome population and assumed no additional recurrences after the 2nd year. This is a conservative approach as it is likely that recurrences will continue in the untreated population, and this approach may therefore underestimate the cost-effectiveness of diagnostic testing.

5.8.7.3 Treatment costs

We have estimated treatment costs over 10 years. A longer time horizon was not considered appropriate given that the life-expectancy for the pacemaker generator is 5-12 years. (Castelnuovo 2005). A sensitivity analysis has been conducted using a 6 year horizon. Total cost of treatment over 10 years was £4928 for sick sinus syndrome. The total discounted costs was £4,866.

5.8.8 Ventricular Tachycardia

ICDs are recommended by NICE for the treatment of ventricular tachycardia causing syncope (NICE TA 95). The comparator used in the technology appraisal for ICDs was drug therapy with amiodarone. Amiodarone treatment aims to prevent arrhythmic events and therefore reduce the number of symptomatic episodes, but its overall impact on long-term mortality is uncertain (NICE TA95). ICDs on the other hand aim to reduce mortality by terminating arrhythmias once they develop, but TLoC often occurs before the arrhythmia is terminated. In order to estimate the benefits of diagnosing VT and treating with ICD therapy, we would need evidence comparing the outcomes for treated and untreated patients. Given that VT causing syncope is considered to be a life-threatening arrhythmia, the efficacy studies conducted for ICD therapy have focused on comparing ICDs to anti-arrhythmic drug therapy rather than no treatment or placebo. We have therefore had to use an indirect approach to estimate the costs and benefits of diagnosing and treating VT.

There is a published cost-effectiveness model comparing anti-arrhythmic drug therapy (amiodarone) to ICDs which was used to inform NICE's technology appraisal of ICDs for this patient population (Buxton 2006). Given that amiodarone is not thought to have a significant effect on mortality, the estimates of life-years gained for ICD treatment compared to amiodarone, are likely to approximate those gained for ICD treatment compared to no treatment. We have adapted the cost and QALY estimates from this published economic evaluation to estimate the costs and QALYs for untreated patients. Given that ICDs do not prevent arrhythmias from developing, we have assumed that the incidence of arrhythmias from the ICD arm is an approximate estimate of the incidence of arrhythmias in untreated patients. This may have underestimated the cost of arrhythmias in untreated patients as around half of those receiving ICDs also received amiodarone and therefore the rate of arrhythmic events may be lower than in untreated patients. This will possibly under estimate the cost-effectiveness of diagnostic testing. We have applied the rate of other cardiac and non-cardiac events from the amiodarone arm to the no treatment arm but we have removed any costs relating to ICD maintenance, ICD replacement and drug adverse events as these would not apply to undiagnosed and therefore untreated patients. We also removed the costs of ongoing follow-up care after initiation of amiodarone as this would not apply to undiagnosed patients.

In the published model (Buxton 2006) a constant utility of 0.75 was applied to patients receiving both ICD therapy and amiodarone. This approach was based on their review of the evidence which showed that there was conflicting evidence from RCTs on HRQoL for patients receiving ICD therapy compared to patients receiving amiodarone. However, we wanted to capture the quality of life impact of diagnosing and treating VT compared to VT remaining undiagnosed. Given that diagnosed patients may receive ICD therapy to reduce their mortality and amiodarone therapy to reduce the incidence of symptomatic episodes we felt that it was not reasonable to assume no improvement in quality of life following diagnosis. Our review of quality of life data (appendix H) didn't identify any studies reporting HRQOL before and after treatment with ICD thearpy. Groeneveld 2007 reported that HRQoL was

similar in patients receiving ICD therapy for primary and secondary prevention of sudden cardiac death and that HRQoL scores in these populations were similar to published estimates for non-ICD patients of a similar age. The reviewed HRQoL data shows that the improvement in HRQoL following treatment ranged from 0.069 to 0.165 across all populations with TLoC. Given that we don't know how successful amiodarone is at preventing TLoC recurrences, and we don't know the HRQoL gain associated with this improvement in symptoms, we decided to use the average of these two estimates (0.117) as the midpoint estimate of the improvement in QoL compared to untreated patients and the range of estimates as the 95% CI. We considered the impact of uncertainty in this figure using a sensitivity analysis in which we assumed no HRQoL gain due to ICD therapy. This assumption regarding HRQoL for untreated patients was used to adapt the QALY gain for ICD therapy compared to amiodarone treatment (1.03 QALYs) to reflect our comparison of ICD therapy compared to undiagnosed VT giving an adapted estimate of 1.68 QALYs gained.

The basecase cost for ICD implantation used it the Buxton model was £23,841 which included £1,566 of costs related to managing the presenting arrhythmia. The cost of managing the presenting arrhythmia was removed from both arms as this cost will already have been incurred in the population undergoing secondary tests to diagnose the cause of TLoC. In the technology appraisal, a lower cost for device acquisition and implantation (£16,250) was used to reflect current device costs. We applied this lower cost in our model also as this was the estimate which the technology appraisal committee considered to be most reflective of current practice (NICE TA95). Applying these changes to the model outputs gave an incremental cost over 20 years of £44,005 for diagnosed patients receiving ICD treatment compared to undiagnosed and untreated patients. This gives a cost per QALY of £26,141 and an incremental net monetary benefit of £6,500 (when assuming a willingness to pay of £30,000 per QALY).

5.8.9 Methods used to explore uncertainty in the model

We have used probabilistic sensitivity analysis to investigate the uncertainty in the cost-effectiveness estimates that arises from the fact that many of the parameters used in the model have been estimated from studies with a particular sample size which limits the precision to which the parameter can be determined. We have used beta functions and dirichlet distributions to estimate the uncertainty in the event rates shown in Table 25, Table 26 and Table 27. In some cases, particularly when the event rates were based on a single study, there were no events recorded for a particular outcome and the beta and dirichlet distributions are not defined in this case. However, it would be wrong to fix the value at zero in the model as there is still some uncertainty in the event rate associated with the finite size of the study. One way to deal with this is to add the observed event rates to uninformative prior distributions in which each outcome is equally likely. So for example, if a study recorded that no patients from 39 at risk had a particular event (beta [0,39]), the beta distribution for 1 event in 41 patients at risk (beta[1, 40]) would be used to describe the uncertainty. In the case of Holter monitoring, we allowed the event rate for “no ECG during TLoC” to be fixed at zero when no events were observed as Holter monitoring is a continuous form of monitoring in which one wouldn’t expect the device to fail to capture the event.

Beta distributions were also used to describe uncertainty in the annual rate of recurrence in paced and unpaced patients with sick sinus syndrome or AV block. Utility gains were described by fitted beta distributions to the confidence intervals reported. Costs were described by fitting gamma distributions to the confidence interval. For costs taken from the NHS reference costs database, the confidence interval was assumed to be equivalent to the interquartile range as this was the only measure of uncertainty available from the NHS reference costs data. The following parameters were not made probabilistic; the list price for IER devices and pacing equipment, the survival rates in AV block and sick sinus syndrome, the cost and QALY gains for ICD treatment compared to no treatment (except the utility difference) and the discounting rate for costs and benefits.

In addition to the probabilistic sensitivity analysis, several scenario analyses were used to determine whether the model results were sensitive to any of the key assumptions used to construct the model. These focused on the assumptions regarding recurrence rates and costs, the size of utility gain associated with pacemaker and ICD therapy, the time horizon for estimating the costs and benefits of pacing, and the choice of reference costs for Holter and EER monitoring.

5.8.10 Cost-effectiveness results for ambulatory ECG

Table 28 summarises the results from the cost-effectiveness model. It shows the additional diagnoses achieved for testing compared to no testing (or conventional monitoring for IER) per 1000 patients tested and the incremental costs and QALYs per patient tested. Each figure presented is the mean across 10,000 samples of the probabilistic model and the corresponding deterministic estimates are presented in brackets. The cost per QALY estimates from the probabilistic model were within 5% of the estimates from the probabilistic model with the exception of the results for 48hr Holter monitoring in patients with unexplained syncope after secondary tests. This comparison was informed by a single study in which none of the Holter tests resulted in an arrhythmia diagnosis. Therefore no benefit of testing was captured in our model using the deterministic estimates from the study. However, in the probabilistic model, there was a small rate of arrhythmia detection due to the addition of our prior distribution which added one patient to each outcome. This was sufficient to make the test cost-effective on average across the samples. This result should therefore be viewed with caution as it relies on there being 1 symptomatic arrhythmia detected in 14 patients having TLoC, and 1 asymptomatic arrhythmia being detected in 40 patients who had no TLoC. Whereas in the study no arrhythmias were detected in the 12 patients who had TLoC and no arrhythmias were detected in the 39 patients who had no TLoC during the study. This demonstrates that our use of prior distributions to generate probabilistic estimates may have caused the model to overestimate that cost-effectiveness of testing when diagnosis was a rare event within a small study

Table 28: Cost-effectiveness results for ambulatory ECG compared with no testing (or conventional monitoring for IER). Main results are averages across 10000 PSA samples and deterministic estimates are presented in brackets.

Comparison and population	Additional patients with arrhythmia diagnosed or excluded from 1000 patients tested					Incremental cost per patient tested	Incremental QALY gained per patient tested	Incremental cost per QALY	Likelihood of being cost-effective at threshold of	
	AV block diagnosed	SSS diagnosed	VT diagnosed	Other arrhythmia diagnosed	Arrhythmia excluded				£20K per QALY gained	£30K per QALY gained
IER monitoring vs no testing										
Suspected arrhythmia	94 (93)	145 (144)	31 (30)	91 (88)	177 (177)	£6,510 (£6,460)	0.403 (0.400)	£16,130 (£16,160)	95.4%	100.0%
Unexplained after secondary tests	82 (82)	131 (130)	31 (31)	86 (86)	247 (247)	£6,390 (£6,390)	0.364 (0.361)	£17,550 (£17,700)	86.2%	100.0%
IER monitoring vs conventional testing										
Unexplained after secondary tests	42 (44)	61 (65)	10 (11)	34 (37)	186 (197)	£4,150 (£4,220)	0.171 (0.181)	£24,310 (£23,360)	24.0%	72.0%
EER monitoring vs no testing										
Suspected arrhythmia	112 (115)	169 (171)	31 (29)	98 (96)	269 (275)	£2,770 (£2,700)	0.468 (0.471)	£5,910 (£5,730)	100.0%	100.0%
Unexplained after secondary tests	53 (53)	114 (113)	54 (54)	114 (114)	253 (255)	£3,220 (£3,207)	0.324 (0.361)	£9,930 (£10,140)	100.0%	100.0%
48hr Holter monitoring vs no testing										
Suspected arrhythmia	35 (32)	71 (66)	31 (29)	68 (63)	69 (63)	£1,940 (£1,800)	0.202 (0.184)	£9,590 (£9,790)	100.0%	100.0%

Unexplained after initial tests	35 (33)	90 (86)	52 (52)	106 (103)	197 (200)	£2,960 (£2,900)	0.260 (0.243)	£11,380 (£11,930)	100.0%	100.0%
Unexplained after secondary tests**	7** (0)	13** (0)	5** (0)	11** (0)	227** (235)	£361** (£50)	0.037** (0.000)	£9,850** (dominated)	96.7%**	99.0%**
24 Holter monitoring vs no testing										
Suspected arrhythmia	31 (30)	47 (45)	9 (8)	28 (25)	54 (50)	£823 (£743)	0.131 (0.123)	£6,270 (£6,019)	100.0%	100.0%
Unexplained after initial tests	24 (24)	64 (64)	38 (38)	76 (75)	6 (3)	£2,150 (£2,122)	0.184 (0.176)	£11,720 (£12,040)	100.0%	100.0%

** The probabilistic estimate for this comparison should be treated with caution. See text for further details

The scenario analyses presented in Table 29 show the mean results for the probabilistic model when applying alternative assumptions to those used in the basecase analysis. The results demonstrate that the model is most sensitive to using different assumptions regarding HRQoL gain after treatment and that it isn't particularly sensitive to different assumptions regarding the costs of ongoing recurrences in undiagnosed and therefore untreated AV block or sick sinus syndrome (SSS). For example, when comparing IER to no testing, applying the lower limit for HRQoL improvement after pacing and assuming no HRQoL improvement after ICD therapy increased the ICER from £17,550 to £22,680. Whilst assuming that every patient with undiagnosed SSS or AV block experiences one admission per annum only reduced the ICER to £16,130. Restricting the time-frame for estimating the post testing outcomes for diagnosed and undiagnosed AV block and SSS to 6 years had a marked effect on the ICER but didn't increase it to over £30,000 per QALY.

We investigated whether assuming lower HRQoL gain after treatment significantly affected the cost-effectiveness results for 24hr Holter compared to no testing in patients with suspected arrhythmias where the QALY gain was only 0.131 under basecase assumptions. When applying the lower limit for HRQoL improvement after pacing and assuming no HRQoL improvement after ICD therapy, the QALY gain reduced to 0.102, but the ICER was still well below £20,000 per QALY. We also found that the cost-effectiveness of 24hr/48hr Holter and EER was not significantly altered by applying the outpatient cost for ambulatory ECG rather than the direct access cost as the test cost was still low compared to the benefits of diagnosis.

IER was less cost-effective compared to conventional testing than compared to no further testing. This was due to there being some rate of rate of diagnosis through other forms of ambulatory ECG in the conventional testing arm. As discussed previously, the GDG felt that using Holter or EER monitoring was inappropriate in patients having very infrequent TLoC episodes as the likelihood of achieving symptom ECG correlation was low. They therefore felt that the appropriate comparator for IER was no further testing rather than Holter or EER monitoring. However, the results for IER vs

conventional testing based on the Farwell 2006 study, show that IER is still reasonably cost-effective (ICER <£30,000 per QALY) even when compared to a strategy in which some patients receive a diagnosis through the use of other forms of ambulatory ECG. This was true even when no cost was accrued for testing in the conventional arm.

Table 29: Scenario sensitivity anaylsis

Comparison and population	Incremental cost per patient tested	Incremental QALY gained per patient tested	Incremental cost per QALY
IER monitoring vs no testing in population with unexplained TLoC after secondary tests			
Basecase	£6,390	0.364	£17,550
Recurrences continue beyond 2 years in unpaced patients with AV block or SSS	£6,360	0.365	£17,410
Recurrences results in short stay admission in addition to ambulance call-out and A&E assessment	£6,380	0.365	£17,470
Continued recurrences beyond 2 years in unpaced patients and recurrences result in admission	£6,300	0.365	£17,250
Unpaced patients with AV block or SSS experience an average of one admission per annum	£5,880	0.365	£16,130
Lower limit for utility gain after pacing and no utility gain after ICD therapy	£6,402	0.282	£22,680
No uplift in IER device cost since 2004 (£1,400 instead of £1,600)	0.365	£6,200	£16,970
Costs and benefits of pacing estimated over 6 year horizon	0.260	£6,360	£24,420
IER monitoring vs conventional testing in population with unexplained TLoC after secondary tests			
Basecase	£4,150	0.171	£24,310
No cost saving (zero instead of -£809) from lower resource use after IER compared to conventional monitoring	£4,970	0.170	£29,130
24hr Holter monitoring vs no testing in population with unexplained TLoC after initial tests			
Basecase	£2,150	0.184	£11,720
Outpatient cost for ambulatory ECG (£117 instead of £54)	£2210	0.183	£12,050
24 Holter monitoring vs no testing in suspected arrhythmia			
Basecase	£823	0.131	£6,270
Lower limit for utility gain after pacing and no utility gain after ICD therapy	£825	0.102	£8,050

NB small changes in the estimates between rows may be due to the probabilistic sampling

5.8.11 Limitations of the analysis

By not including any benefits for patients who have an arrhythmia diagnosed other than SSS, AV block or VT and not including any benefits for patients

who have an arrhythmic cause excluded, the model probably underestimates the cost-effectiveness of testing. However, the estimates of post testing costs and benefits for SSS and AV block have been estimated using unadjusted estimates of survival from non-randomised trials and should therefore be treated with caution. The estimates of post testing costs and benefits for patients with VT have been generated by adjusting the outputs of another economic model which considered a different comparison and therefore should also be treated with caution. It should also be noted that apart from the comparison of IER with conventional monitoring, the cost-effectiveness results have been generated by combining diagnostic yield data from several non-randomised studies to determine diagnostic outcomes for ambulatory ECG and by making assumptions regarding the diagnostic outcomes in patients who receive no further testing.

5.8.12 Conclusions

The cost-effectiveness model results show that ambulatory ECG is cost-effective compared to no further testing in patients with suspected arrhythmic TLoC or unexplained TLoC and these results are robust under the sensitivity analyses conducted. However, it should be noted that many assumptions have been used to populate the model and the GDG took these into account when interpreting the cost-effectiveness evidence and forming their recommendations.

5.9 Evidence Statements

The evidence is summarised as follows:

5.9.1 Ambulatory ECG for suspected cardiac arrhythmic syncope

There is low-quality evidence from prospective case series studies to show the following:

- TLoC occurred during the monitoring period for 13-16% of patients with a Holter monitor, 69% with an EER (single study in patients with fairly frequent TLoC) and 40-68% with an IER (heterogeneity amongst 4 studies).
- Arrhythmias during TLoC were reported in 6% patients given a Holter monitor (3 studies), 41% for an EER (1 small study) and 25-38% for an IER (4 studies, no heterogeneity).
- Between 0 and 7% of patients did not have an IER recording during TLoC (4 studies)

5.9.2 Ambulatory ECG for suspected NM syncope

There is low-quality evidence from prospective case series studies to show the following:

- TLoC occurred during the monitoring period for 20% of patients with a 48-hour Holter monitor (1 study) and 34-48% with an IER (no heterogeneity amongst 3 studies). The IER studies were dominated by a study in people with a severe NM presentation (high number of previous TLoCs that had affected the patient's quality of life or put them at high risk of physical injury due to unpredictable recurrence)
- Arrhythmias during TLoC were reported in 8% patients given a Holter monitor (1 study) and 20-28% for an IER (3 studies, no heterogeneity).
- Between 7 and 9% of patients did not have an IER recording during syncope (2 studies)

5.9.3 Ambulatory ECG for unexplained recurrent syncope after initial tests

There is low-quality evidence from prospective case series studies to show the following:

- TLoC occurred during the monitoring period for 1-15% of patients with a 24-hour Holter monitor (2 studies) and 21% with a 72-hour Holter monitor; there were 12% with TLoC during IER monitoring (1 study)
- Arrhythmias during TLoC were reported in 1% patients given a Holter monitor (2 studies) and 8% for an IER (1 study).

5.9.4 Ambulatory ECG for unexplained recurrent TLoC after secondary tests

There is low-quality evidence from a large volume of prospective case series studies to show the following:

- TLoC occurred during the monitoring period for 24% of patients with a 48-hour Holter monitor (1 study); 32-78% with an EER (4 studies, high heterogeneity); and 34-87% with an IER (14 studies, high heterogeneity)
- Arrhythmias during TLoC were reported in 0% patients given a Holter monitor (1 small study); 2-16% for an EER (3 studies, heterogeneity) and 18-46% for an IER (14 studies, heterogeneity).
- Between 14 and 32% of patients did not have an EER recording during TLoC (3 studies, heterogeneity) and 4-11% of patients did not have an IER recording during TLoC (7 studies, no heterogeneity)

5.9.4.1 Holter 24-hour versus 48-hour versus 72-hour

- There is low-quality evidence from a single study in people with suspected cardiac arrhythmic syncope to show a significantly higher diagnostic yield of all arrhythmias detected, for a 48 hour monitoring period compared with a 24 hour period.
- There is low quality evidence from a single study in people with unexplained TLoC after initial assessment to show a significant increase in

the number of patients with arrhythmias detected (with or without TLoC), when the monitoring period of a Holter device is extended from 24 to 48 hours; no further significant improvement was found when the time was extended to 72 hours.

5.9.5 General trends across population groups for ambulatory ECG devices

There is a large volume of evidence for the IER, which showed heterogeneity within population groups, but the following differences between populations can be identified:

- A lower incidence of TLoC during monitoring for the group with suspected NM syncope (34-48%) compared with suspected arrhythmic cause (40-68%) and unexplained TLoC following secondary tests (34-87%; heterogeneity). The suspected NM syncope group is dominated by the large study in patients with more severe presentations.
- A lower incidence of arrhythmias during TLoC for the suspected NM syncope group (20-28%) compared with the suspected arrhythmia group (25-38%) and the unexplained TLoC after secondary tests group (18-47%).
- No significant difference between population groups for the proportion of patients in whom no ECG was recorded during TLoC (0-9%).
- No significant difference in the distribution of bradycardia-tachycardia arrhythmias across population groups (bradycardia proportion was 80-90%), although there was some heterogeneity within each population group.

5.9.5.1 Causes of heterogeneity for IERs

- There is low quality evidence from several studies to show that heterogeneity amongst studies for the outcome, no TLoC during monitoring, had an inverse dependence of the diagnostic yield for this outcome on the frequency of prior TLoC. Heterogeneity was not explained

by duration of monitoring alone or whether the patients were excluded or included on the basis of initial tests.

- A sensitivity analysis including only studies in patients with a frequency of TLoC of more than 5 per year showed little heterogeneity, either within or across groups. There were 25% people with an arrhythmia during TLoC.

5.9.5.2 Adverse events IERs

There is low quality evidence from several studies to show that between 0 and 4% people had infections with their IERs and one study reported adverse events in 9%.

5.9.5.3 Automatic versus patient and automatic activation

There is low-quality evidence from one small study to suggest that automatic activation of IERs detected significantly more arrhythmias than patient activation in the same patients. A second study showed that automatic activation gave 19% of diagnoses. Authors recommended that patients should be regularly followed up.

5.9.5.4 Ambulatory ECG versus conventional testing

There is moderate quality evidence from two RCTs (one from the UK) in patients with unexplained TLoC to show significantly more diagnoses were achieved for those given an IER compared to those given conventional testing, including tilt testing. One study reported time to diagnosis data for this comparison and quoted a hazard ratio of 6.5, significantly favouring the IER.

There is moderate quality evidence from one RCT in people with unexplained TLoC, to show a significant reduction in the recurrence of TLoC for people given an IER with test-directed appropriate treatment compared with a test-and-treat approach based on conventional testing.

There is moderate quality evidence from one RCT in people with unexplained TLoC, to show no significant difference between a strategy of IER followed by conventional monitoring (in patients without a diagnosis with IER and

choosing further testing) compared with conventional monitoring followed by IER.

5.9.5.5 Direct comparison of different ambulatory ECG tests

There is moderate quality evidence from one RCT in people with unexplained TLoC after secondary tests to show a significantly higher diagnostic yield for EER versus 48-hour Holter monitoring, but no significant difference between EER alone versus Holter followed by EER (in people who had not had a diagnosis).

5.9.5.6 Direct comparison between ambulatory ECG and tilt test

There is low-quality evidence in one study in people with suspected vasovagal syncope to show a significantly higher diagnostic yield for a tilt test compared with a 48-hour Holter monitor in the same patients. However, there was no significant difference between tests for arrhythmias recorded during TloC.

5.9.6 Exercise testing

There is very low quality evidence from one small study to show that the sensitivity of exercise testing in people with exercise-induced syncope is moderately high (78%), but in people with exercise-unrelated syncope it is low (27%); the specificity of the test in controls who did not have TLoC is high (95%), but the test has only moderately high specificity (73%) for ruling out people with exercise-unrelated TLoC.

There is very low quality evidence for one study in people with a suspected arrhythmic cause of TLoC, to show a low sensitivity (14%) and high specificity (93%) for exercise testing versus 24-hour Holter monitoring as a reference standard in the same patients

There is very low quality evidence in one small study in young people with exercise-induced TLoC to show a low sensitivity (14%) and fairly high specificity (91%) for an exercise test compared with an ISDN tilt test in the same patients. This is an unreliable reference standard.

5.9.7 Tilt testing

There is a large volume of low-quality evidence to show that a tilt test is useful in diagnosing neurally mediated syncope in people who have suspected NM syncope, compared with people who have not had a TLoC, although there is some heterogeneity.

There is a large volume of low-quality indirect evidence to suggest that a significantly higher sensitivity can be achieved when a head up tilt (HUT) protocol including Glycerine trinitrate is employed compared to HUT alone.

There is low quality evidence from a small study to show that there is no significant difference in sensitivity and specificity between HUT protocols using GTN or IPN.

There is low quality evidence to show that a tilt test gives a cardioinhibitory response in 5-29% of people with suspected neurally mediated syncope and the corresponding proportions for asystolic response are 5-21%.

There is low quality evidence from one large study to show a GTN HUT tilt test is ineffective as a diagnostic test in a population from which people were excluded if they had a history strongly suggestive of vasovagal syncope and did not require a tilt test to confirm diagnosis. The pre- and post-test probabilities were 64 and 70%, even in comparison with non-TLoC controls. The diagnostic yield of a tilt test in people with asystole in this group is 1%.

5.9.8 Carotid sinus massage

There is low-quality evidence from four large case-control studies in people with unexplained TLoC compared to non-TLoC controls to show that carotid sinus massage has low sensitivity (9-13%) and high specificity (93-100%) for the supine CSM test and 20-60% sensitivity for a full protocol including supine then upright CSM if the former did not give a positive response. The specificity for controls who had other types of syncope was also high (93%), although there was much uncertainty around this estimate (95%CI was 70 to100%).

There is low quality evidence for from three large case-control studies in people with unexplained TLoC compared to non-TLoC controls to show that

carotid sinus massage has low sensitivity (16-42%) and high specificity (96-100%) for a cardioinhibitory response.

5.10 Evidence to Recommendations

The evidence to recommendations section for this chapter is combined with that for chapter 6 in Section 6.9 because the recommendations draw on evidence from both chapters.

5.11 Recommendations

Hyperlink to recommendations Section 1.2.1 - Assessment and assignment to type of syncope

6 Diagnostic tests to direct pacing therapy

6.1 Clinical Questions

In people who have experienced a TLoC, which diagnostic tests should be performed, both in an unselected population and in specified subgroups (e.g. suspected syncope, epilepsy or psychogenic non-epileptic seizures).

6.2 Introduction

This section is concerned with determining whether tilt-testing, ambulatory ECG and carotid sinus massage can be used to identify patients who may benefit from pacing because they are experiencing neurally mediated syncope with a cardioinhibitory response.

This assumes that pacemakers are effective in preventing a cardioinhibitory response in people with neurally mediated syncope, or in those who have carotid sinus hypersensitivity. So, firstly, we examine the assumption that pacemakers are clinically effective in these two populations (neurally mediated syncope and carotid sinus syncope) in two systematic reviews of interventions, and then we report a review of diagnostic test accuracy to determine the most useful tests for the diagnosis of neurally mediated syncope or carotid sinus syncope in which there is a cardioinhibitory response that would benefit from pacing.

6.3 Clinical Evidence Review: efficacy of pacemakers in people with suspected neurally mediated syncope with a cardioinhibitory response identified during tilt testing

The purpose of this review is to inform the question on the usefulness of tilt testing to identify people with neurally mediated syncope who could benefit from having a pacemaker. This question presupposes that pacemakers are effective in this population: that is, in people who have neurally mediated

syncope with a cardioinhibitory component, manifested as bradycardia and periods of asystole. Definitions of cardioinhibitory behaviour vary, but the GDG defined it as a heart rate of less than 40 beats per minute or asystole for at least 3 seconds.

If cardiac pacing is effective in NM syncope when a cardioinhibitory component is present (and is not effective in other NM populations), then a review of pacemakers for cardioinhibitory NM syncope can be used to investigate how well diagnostic tests distinguish this patient group from the other groups.

However, before continuing with this hypothesis, we need to determine whether pacemakers are effective in preventing recurrence of TLoC in this population. Having said this, we note that the degree of cardioinhibitory behaviour may vary from episode to episode within the same person, and we also recognise that a pacemaker will not prevent recurrence of TLoC if it derives from the vasodepressor component.

A review of pacemakers for recurrent vasovagal syncope has been conducted by Sud et al (Sud 2007), but this focussed largely on the effect of blinding in explaining the observed heterogeneity. We decided to investigate these factors further by carrying out a new systematic review for the population cardioinhibitory NM syncope.

6.3.1 Methods of the review – selection criteria

The following selection criteria were to be applied to studies to determine their suitability for inclusion in the reviews:

6.3.1.1 Types of studies

For intervention studies, the randomised trial (RCT) and quasi randomised trial (e.g. allocation by alternation, date of birth, etc) were to be the primary trial designs.

Studies were to be excluded if there were fewer than 20 patients in each arm.

Studies were limited to the English language, initially, with the exception of studies translated for Cochrane reviews.

6.3.1.2 Types of participants

Participants were to be adults (16 years and older) who had neurally mediated syncope in which there is a cardioinhibitory response. NM syncope was to be diagnosed by a positive tilt table test (any type), accompanied by bradycardia below 40 bpm and/or asystole of more than 3 seconds.

Indirect populations were to be adults (16 years and older) with NM syncope of any type (cardioinhibitory response not reported or present only for some of the population).

6.3.1.3 Types of intervention

The intervention was to be any type of pacemaker.

6.3.1.4 Types of comparisons

The following comparisons were to be included:

i) Pacemaker versus no pacemaker

ii) Pacemaker versus placebo pacemaker

iii) Pacemaker versus another intervention

In analyses, comparisons (i) and (ii) could be combined, but (iii) was to be treated separately.

6.3.1.5 Types of outcome measures

The primary outcome was to be time to recurrence of TLoC or number of patients with recurrence at 6, 12 and 24 months duration.

If there was heterogeneity between studies, the following subgroup analyses were proposed:

- Proportion of patients with cardioinhibitory NM syncope: 100% / 50-100% / less than 50%
- Type of pacemaker mode

- Type of tilt test used (including duration and angle of tilt and drugs used)
- Duration of study relative to frequency of TLoC

6.3.2 Description of studies

Nine reports of studies were evaluated for inclusion. Six were excluded because there were fewer than 20 patients in each arm (Ammirati 1998; Fitzpatrick 1999; Flammang 1999; Occhetta 2004 (INVASY); Raviele 2004 (SYNPACE); Sutton 2000 (VASIS)). Further details are given in Appendix F.

Three studies were included that had randomised designs (Ammirati 2001 (SYDIT); Connolly 1999 (VPS); Connolly 2003 (VPS II)).

6.3.2.1 Study design

None of the studies were conducted in the UK. One study was carried out in North America (Connolly 1999); one in Italy (Ammirati 2001) and one was a multicentre study carried out in Canada, Australia, USA and Colombia (Connolly 2003).

One study (Connolly 2003) received some funding from Medtronic Inc (pacemaker manufacturer) and the lead author also had an honorarium from them; the other two studies did not state a funding source.

All the studies had between 50 and 100 patients. Two of the studies were stopped early because of a significant effect for the treatment group (Ammirati 2001 (SYDIT); Connolly 1999 (VPS)).

6.3.2.2 Population

The mean age across the studies ranged from 43 to 61 years. The proportion of men in the studies ranged from 27% to 52%, with the Connolly (2003) study having 27% in the pacemaker group and 52% in the placebo pacemaker group. Ethnicity was not reported.

The number of previous TLoC episodes across studies varied from 3 to 130 per patient, with the median ranging from 7 (Ammirati 2001) to 35 (Connolly 1999); Connolly (1999) had a median of 14 (IQR 8-35) in the pacemaker

group and 35 (20-100) in the control group, which is a large difference (unclear if this is significant).

Ammirati (2001) had a median of 2 events (range 1-20) in the 6 months prior to enrolment; Connolly (2003) had a median of 4 (IQR 2-15) events in the previous year; and Connolly (1999) had a median of 3 (IQR 2-12) [pacemaker group] and 6 (3-40) [no pacemaker] events in the previous year.

All the studies selected patients with NM syncope. Each study required the patients to have had a 'positive' tilt test, but this included vasodepressor and mixed responses too (see definitions below). In the Ammirati (2001) study the patients had had extensive prior tests to exclude other causes (12-lead ECG, exercise, echo, 24-hour ECG, CSM, EEG plus CT, MRI, EP as necessary) and the Connolly (1999) study had also excluded patients with other causes of TLoC (arrhythmias, carotid sinus syndrome, seizures), which implies prior tests. The patients in the Connolly (2003) study were not reported to have had extensive prior tests. Both Connolly (1999) and Connolly (2003) included patients with a history of recurrent syncope.

The type of tilt test varied across studies: all had a passive phase followed by a drug induced phase if the passive phase was negative – the drug was isoproterenol for the two Connolly studies and the Ammirati (2001) study used isosorbide dinitrate; the proportion of patients receiving the drug varied from 44% (Connolly 2003) to 77% (Connolly 1999).

For a positive tilt test, all studies required patients to have had syncope or pre-syncope plus 'relative bradycardia', but exact definitions varied:

All patients in the Ammirati (2001) had syncope during the tilt test, but the other studies allowed both syncope and pre-syncope:

- Connolly (1999) had 77% with syncope during the tilt test in the pacemaker group and 63% in the no pacemaker group
- Connolly (2003) had 60% with syncope in the pacemaker group and 71% in the placebo group.

Relative bradycardia was defined as:

- the product of heart rate and systolic blood pressure to be less than 6000 mm Hg / min (Connolly 2003)
- trough heart rate less than 60 bpm if no isoproterenol used, less than 70 bpm if up to 2 mcg/min IPN used or less than 80 bpm if over 2 mcg/min used (Connolly 1999)
- trough heart rate less than 60 bpm (Ammirati 2001)

It terms of the direct population for this review (cardioinhibitory NM syncope), the studies reported the following:

- Ammirati (2001) had 60.2% patients with syncope in association with asystole of longer than 3 seconds (mean 16 seconds (SD18) pacemaker group; 18 s (SD 11) drug group)
- Connolly (2003) had 15% with bradycardia below 40 bpm in the pacemaker group and 23% in the placebo pacemaker group
- Connolly (1999) had 19% with bradycardia below 40 bpm in the pacemaker group and 26% in the no pacemaker group.

Thus, none of the studies completely represented the direct population for this review, although the majority of patients did for the Ammirati (2001) study.

6.3.2.3 Interventions

The included studies investigated the following interventions:

Dual chamber pacemaker with rate drop response (RDR)

- The Connolly (2003) study had an RDR defined by a drop size 20 beats, drop rate of 70 bpm and an intervention rate of 100 bpm for 2 min, duration 6 months
- The Connolly (1999) study had an RDR defined by a drop of 5 to 15 bpm over 20-40 beats, drop rate of 60 bpm and an intervention rate of 100 bpm for 2 min, duration mean 112 days (i.e. 3-4 months).
  - patients were also permitted usual care, but none was required

- The Ammirati (2001) study had an RDR programmed on the basis of heart rate behaviour on the tilt test plus a lower rate of 40 bpm and a minimum AV delay of 200 ms, median 390 days (IQR 360-420)

6.3.2.4 Comparators

The studies varied in their comparators:

- Dual chamber pacemaker set to sensing only, duration 6 months (Connolly 2003)
- Usual care, medical or nonmedical, at the discretion of the physician (none required), duration mean 54 days (Connolly 1999)
- Atenolol 50 mg once per day, then titrated up to 100 mg/day within 2-3 days, median 135 days (IQR 15-250) (Ammirati 2001)

In the Connolly (2003) study, concomitant pharmacological therapy was used during follow up: beta-blockers 19% pacemaker and 12% placebo pacemaker; fludrocortisone 2% and 10%; selective serotonin reuptake inhibitors 13% and 12%.

6.3.2.5 Comparisons

The following comparisons were carried out:

- Dual chamber pacemaker, with RDR pacing versus pacemaker in sensing only mode (i.e. placebo pacemaker; ODO mode) (Connolly 2003)
- Dual chamber pacemaker with RDR pacing + usual care versus no pacemaker + usual care (Connolly 1999)
- Dual chamber pacemaker with RDR pacing versus atenolol (Ammirati 2001)

6.3.2.6 Outcomes

The outcome measure for the studies was the recurrence of TLoC, which was defined similarly in all the studies as a transient state of unconsciousness characterised by spontaneous recovery. All of the studies showed Kaplan

Meier time-to-event plots and reported the number of patients with a first TLoC.

6.3.3 Methodological quality

The method of sequence generation was adequate in one study (Ammirati 2001), in which a computer generated method was used. The method of sequence generation was not stated in the other studies.

The method of allocation concealment was considered to be adequate in all studies because a central telephone facility was used in the two Connolly studies, and the Ammirati (2001) study reported the use of a central randomisation list.

In all studies the outcome was assessed by the patient, so both the outcome assessors and the patients were blinded only in the Connolly (2003) study, but unblinded in the other two. In all of the studies, some of the TLoC events were witnessed or there was evidence of minor injuries, however, it was unclear if the witnesses would have known to which groups the patients were assigned.

All of the studies reported an *a priori* sample size calculation. However, two studies were stopped early because of significant efficacy at the interim analysis (Ammirati 2001; Connolly 1999).

In all studies, patients in the two groups were comparable for age, number of TLoC events, tilt test variables, number with heart rate below 40 bpm or with asystole

- Connolly (2003) was not comparable for gender (the pacemaker group had a lower proportion of men (27% versus 52%))
- Ammirati (2001) was reported to have a trend towards pacemaker patients being older (61 versus 55 years) and having more TLoC related traumatic injuries (55 versus 36).
- Connolly (1999) was probably not comparable in the median number of lifetime TLoCs (14 versus 35 (no pacemaker)) nor in the median number of events in the previous year (3 versus 6).

None of the studies had missing data and all were intention to treat analyses (ITT), although 4% patients in the pacemaker group for the Connolly (2003) study had inhibited pacing instead of RDR and 2% in each group of the Ammirati (2001) study had drug side effects or refused the pacemaker.

Overall, two of the studies were considered to have high potential for bias (Ammirati 2001 and Connolly 1999) because of a lack of blinding and early stopping, and Connolly (1999) because of the difference in median number of TLoC events prior to the trial. Connolly (2003) had a significantly smaller proportion of men in the pacemaker group and may have had some confounding because the patients received differential concomitant drugs during the follow up period.

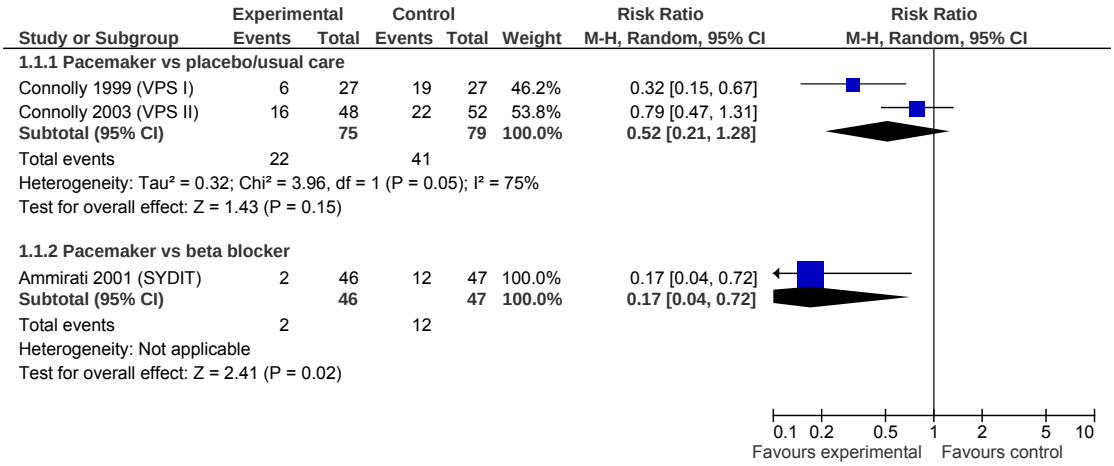
6.3.4 Results

6.3.4.1 Pacemaker versus placebo/no treatment

Outcome: recurrence of syncope

Two RCTs in 154 patients (Connolly 1999; Connolly 2003) compared a dual chamber pacemaker with rate drop response versus placebo pacemaker or no pacemaker, with a follow up period of up to 6 months (Connolly 1999 had a mean follow up time of 112 days and Connolly 2003 had 6 months). Meta-analysis (Figure 6-1, subgroup 1), showed significant heterogeneity (p=0.05, I^2=75%), representing different effects.

Figure 6-1: Recurrence of syncope



6.3.4.2 Pacemaker versus atenolol

One study in 93 patients (Ammirati 2001) showed a large significant difference between the two interventions at a mean follow up of 520 days (SD 266), but the confidence interval is wide because there are relatively few events.

6.3.5 Discussion and GRADE analysis

We considered the evidence in terms of the GRADE approach, looking at risk of bias, inconsistency, imprecision, indirectness and reporting bias.

Risk of bias: there are only three included studies in this review and all have limitations: the Connolly (1999) and Ammirati (2001) studies were at risk because of a lack of blinding and early stopping, and some differences at baseline for Connolly (1999); the Connolly (2003) study had baseline differences in the number of men and was possibly confounded because of differential concurrent drugs (in particular, more patients with beta-blockers and fewer with fludrocortisone in the intervention group). Both a lack of blinding and early stopping would be likely to increase the effect size.

Although there are two different types of comparators in these studies, which shouldn't be combined in a meta-analysis we can consider indirect comparisons. Normally, we would expect a comparison of two active interventions to have a smaller effect size than a comparison of an active intervention and placebo or no intervention. However, the reverse is true. The Ammirati (2001) authors refer to an apparent effect of beta-blockers to worsen

the tendency towards syncope. If this is the case, the confounding due to concurrent medication may be more serious in the Connolly (2003) study, and would tend to reduce the effect size.

Indirectness: the populations differed in the three studies and only the Ammirati (2001) study included more than 50% of patients with cardioinhibitory NM syncope. The other two studies had less than 30% of these patients and in each case there were more patients with cardioinhibitory (CI) NM syncope in the control group (15% versus 26% for Connolly (2003) and 19% versus 26% for Connolly (1999)). It is likely that if pacemakers only work in the direct group, the proportion of patients having events in the intervention group of the studies will be lower than if all the patients had CI NM syncope. Consequently the relative risk is expected to be higher (i.e. less effective) in this indirect population.

Inconsistency: for the two studies comparing pacemaker with no treatment or placebo, we can explain the observed heterogeneity in terms of the different comparators, study limitations (lack of blinding and early stopping) and possible confounding. Therefore, the two studies are considered separately, but the meta-analysis is reported too in the GRADE analysis.

Precision: for precision within guidelines, we consider whether the results are consistent with important differences and important harms. One of the studies (Connolly 2003) stated that a relative risk reduction of 50% would be needed to justify a recommendation of using this invasive procedure routinely in the NM syncope population, and so a minimum acceptable threshold of RR = 1.5 or 0.5 was set. If the confidence interval crosses one of these thresholds there is uncertainty in our confidence in the result, and the evidence is considered to be imprecise. Each of the studies crossed this threshold.

For the GRADE analysis we report the results of the meta-analysis and the results for the studies separately (

Table 30).

Table 30: GRADE evidence summary

Outcome	Details	Results	Findings	GRADE summary	Comments	Evidence Rating
Pacemaker versus placebo pacemaker or no pacemaker						
Recurrence of TLoC at 6 months	2 trials; 154 patients; from Meta analysis of RCTs	RR=0.52 (95%CI 0.21, 1.28); p=0.05; I2 =75%	not statistically significant	# Study limitations: serious - incomplete follow up # Indirectness: serious - indirect population # Imprecision: serious - CI crosses null and appreciable benefit threshold # Inconsistency: serious # Reporting bias: none	2 studies similar size, one had lack of blinding and stopped early; other had industry funding and possible confounding by concurrent drugs; both indirect population (< 30% cardioinhibitory NM syncope)	very low
Recurrence of TLoC at 6 months Placebo pacemaker	1trial; 100 patients; from RCT	RR=0.79 (95%CI 0.47, 1.31)	no significant difference between interventions	# Study limitations: serious - some confounding # Indirectness: serious - indirect population # Imprecision: serious - CI crosses null and appreciable benefit threshold # Inconsistency: none # Reporting bias: serious - industry funding	Baseline differences. May be confounded by differences in concurrent drugs. Blinded. Indirect population (<30% cardioinhibitory NM syncope). Industry funded.	very low
Recurrence of TLoC at 3-4 months No pacemaker	1trial; 54 patients; from RCT	RR=0.32 (95%CI 0.15, 0.67)	Significantly less recurrence for pacemaker group	# Study limitations: very serious # Indirectness: serious - indirect population # Imprecision: serious - CI crosses appreciable benefit threshold # Inconsistency: none # Reporting bias: none	Not blinded and early stopping. Indirect population (<30% cardioinhibitory NM syncope)	very low
Pacemaker versus beta-blocker						
Recurrence of TLoC at 17 months	1trial; 93 patients; from RCT	RR=0.17 (95%CI 0.04, 0.72)	large significant effect favouring pacemaker	# Study limitations: very serious # Indirectness: none # Imprecision: serious - CI crosses appreciable benefit threshold # Inconsistency: none # Reporting bias: none	Not blinded and early stopping. Majority of patients had cardioinhibitory NM syncope	very low

Overall, the evidence quality is considered to be very low for each of the studies, but may be graded as 'low' for the Connolly (2003) study depending on the importance of baseline differences and funding. In any case, our confidence in the estimates of effect is very uncertain.

In view of the poor evidence quality for the efficacy of pacemakers, it is difficult to draw conclusions on whether the tilt test is useful in determining patients who are suitable for pacemaker implants to prevent cardioinhibitory NM syncope.

A large (710 patients) trial (ISSUE 3) is currently underway to investigate pacemaker therapy versus placebo pacemaker therapy for patients with severe NM syncope (very frequent, so quality of life is affected; recurrent and

unpredictable with a high risk of trauma; or TLoC occurs during high risk activity such as driving), with an asystolic component (Brignole 2007). Patients receive an implantable event recorder and are also given tilt testing and carotid sinus massage during the screening phase before randomisation in order to identify people with asystolic syncope. One of the trial's secondary objectives is to investigate the value of asystolic tilt testing responses in predicting spontaneous asystolic events. This trial is likely to be completed in late 2010 (http://clinicaltrials.gov/ct2/show/NCT00359203).

6.4 Clinical Evidence Review: efficacy of pacemakers in people with suspected neurally mediated syncope with a cardioinhibitory response to carotid sinus massage

6.4.1 Methods of the review: selection criteria

The following selection criteria were to be applied to studies to determine their suitability for inclusion in the reviews:

6.4.1.1 Types of studies

For intervention studies, the randomised trial (RCT) and quasi randomised trial (e.g. allocation by alternation, date of birth, etc) were to be the primary trial designs.

Studies were to be excluded if there were fewer than 20 patients in each arm, and were to be limited to the English language.

6.4.1.2 Types of participants

Participants were to be adults (16 years and older) who had carotid sinus syncope in which there was a cardioinhibitory response which would potentially benefit from pacing. Carotid sinus syncope was to be diagnosed by a positive response to carotid sinus massage (any type of CSM), accompanied by bradycardia below 40 bpm and/or asystole of more than 3 seconds.

Indirect populations were to be adults (16 years and older) with NM syncope of any type (cardioinhibitory response not reported or present only for some of the population).

6.4.1.3 Types of intervention

The intervention was to be any type of pacemaker.

6.4.1.4 Types of comparisons

The following comparisons were to be included:

i) Pacemaker versus no pacemaker

ii) Pacemaker versus placebo pacemaker

iii) Pacemaker versus another intervention

In analyses, comparisons (i) and (ii) could be combined, but (iii) was to be treated separately.

6.4.1.5 Types of outcome measures

The primary outcome was to be the time to recurrence of TLoC or the number of patients with recurrence at the end of follow up.

6.4.1.6 Subgroup analyses

If there was heterogeneity between studies, the following subgroup analyses were proposed:

- 100% cardioinhibitory NM syncope/ 50-100% / less than 50%
- Type of pacemaker mode
- Type of carotid sinus massage (e.g. different angle of tilt during procedure)
- Duration of study relative to frequency of TLoC

6.4.2 Description of studies

Sixty papers were evaluated for inclusion. Fifty-seven studies were excluded: 19 because there were fewer than 20 patients in each arm. Further details

are given in the Appendix D1. Three RCTs were included (Claesson 2007, Kenny 2001).

6.4.2.1 Study Design

One of the studies was conducted in the UK (Kenny 2001); one in Italy (Brignole 1992c); and one in Sweden (Claesson 2007).

One study (Kenny 2001) received some funding from an educational grant from Medtronic Inc. (a pacemaker manufacturer) as well as from the National Health Service Cardiovascular research and development programme; one (Claesson 2007) from the Skaraborg Institute for Research and Development; the other study did not state a funding source.

The studies had between 60 and 175 patients in total.

6.4.2.2 Population

The mean age across the studies ranged from 69 to 75 years. The proportion of men in the studies ranged from 41% to 84%. Ethnicity was not reported.

The mean number of TLoC episodes per patient across studies was around 2 to 4 episodes.

All the studies included patients who had induced cardioinhibitory carotid sinus syndrome, with asystole of more than 3 seconds, in response to carotid sinus stimulation; in the Kenny (2001) study patients were recruited from a cohort that had non-accidental falls and were attending the Emergency Department, and had not necessarily had TLoC (this may indicate an indirect population). The Brignole (1992) study selected patients with carotid sinus syndrome, whose symptoms were judged to involve risk of major trauma or death, or interfered with their daily activity (because of frequency or intensity); the patients had either a cardioinhibitory response or a mixed response on CSM (about 50% of each).

In the Brignole (1992c) and Kenny (2001) studies, the patients had had extensive prior tests to exclude other causes: e.g. by history, examination, and neurological and cardiological tests, including ambulatory ECG monitoring

for at least 24 hours in Brignole (1992c). Claesson (2007) did not mention neurological tests although patients had had history, examination, 12 lead ECG, orthostatic test, HUT and 24-hour ambulatory Holter monitoring; positive results did not lead to their exclusion from the trial.

Claesson (2007) simply reported that patients had a carotid sinus stimulation test; the test was conducted both supine and erect in the remaining studies. For a positive CSM, all studies required patients to have had asystole of 3 seconds or more (although about half the patients in Brignole (1992) had a mixed response).

6.4.2.3 Interventions

In one study, all paced patients received a rate drop response dual chamber pacemaker (Kenny 2001: paced if the heart rate fell below 50 beats per minute; paced at 100 beats per minute for a fixed time period, gradually decreasing by 5 beats per minute at 1-minute intervals to a programmed lower rate, or until the patient's own rate intervened). In the Brignole (1992c) study, 18 patients received a ventricular inhibited (VVI) pacemaker, while 14 had a dual chamber (DDD) pacemaker.

In the Claesson (2007) study, 24 patients had a pacemaker operating in DDDR mode, 5 in VVIR mode and one in AAIR mode.

The duration of follow up ranged from 12 months (Brignole 1992c and Claesson 2007) to 36 months (Brignole 1992c); the latter study had a different follow up for the paced (mean 34 months (SD 10)) versus the non-paced group (mean 36 months (SD 10)), although recurrence rates were also reported at 1, 2, 3, and 4 years..

6.4.2.4 Comparisons

All the studies compared pacemaker versus no pacemaker; in the Claesson (2007) study patients were allowed to cross over from the no pacemaker group after they had had syncope or pre-syncope occurred (one-third did crossover, but this did not affect the results for recurrence of TLoC, except perhaps psychologically). In the Brignole (1992c) study, 19 (68%) patients in

the non-paced group received a pacemaker after a mean of 8.2 months (SD 10) follow up; in 15 cases this was because of TLoC recurrence.

6.4.2.5 Outcomes

The outcome measure for the studies was the recurrence of TLoC, which was defined similarly in all the studies as a transient state of unconsciousness characterised by spontaneous recovery.

6.4.3 Methodological quality

The method of sequence generation was adequate in two studies (Claesson 2007: envelopes, shuffled 21 times; Brignole 1992c: table of random numbers) and unclear in one study (Kenny 2001: block randomisation).

The method of allocation concealment was considered to be adequate in one study (Claesson 2007; sequentially numbered, opaque, sealed envelopes); it was unclear in the other RCTs.

The patients and outcome assessors were not blinded in any of the studies.

One study (Kenny 2001) reported an *a priori* sample size calculation, based on detecting a 40% difference in the number of falls (from 10 to 6 falls per year), assuming an SD of 8 falls per year; 85 participants per group gave a 90% power to detect this difference at alpha=0.05. None of the other studies reported a power calculation.

In all studies, patients in the two groups were comparable for age and gender. Other variables that were stated as comparable across the studies included number of previous TLoCs, ECG findings, duration of asystole with CSM, cardiovascular drugs and co-morbidities; no studies reported fundamental differences between the groups on any recorded variable.

None of the studies had missing data except Kenny (2001), in which 95% of patients completed the study in the pacemaker group and 86% in the control group; there was no significant difference in the frequency of falls between the completers and non-completers. Diaries recording the outcome measure in

these patients were returned in 85% and 92% patients respectively (i.e. there were results for 81% and 79% of the randomised patients for the paced and non-paced groups respectively). In the Brignole (1992c) study, 68% patients in the non-paced group crossed to the pacemaker group after a mean of 8.2 months (SD 10) follow up; in 15 cases this was because of TLoC recurrence. This is likely to bias the later results (after crossover).

Overall, all of the studies were considered to have some potential for bias because of a lack of blinding of patients and outcome assessors. The Kenny (2001) study also had unclear allocation concealment and some missing data (although this is not considered significant). The Brignole (1992c) study is likely to have risk of bias at later times because of crossover from the no pacemaker arm, but this is expected to reduce the effect size.

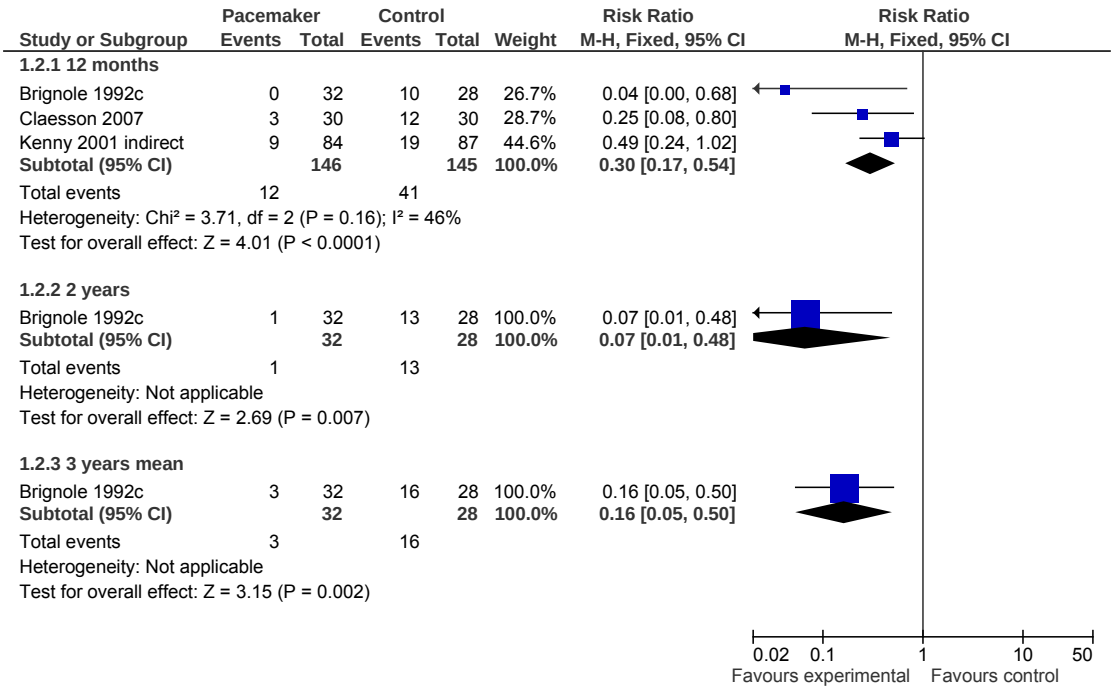
6.4.4 Results

6.4.4.1 Outcome: recurrence of TLoC

Three RCTs in 155 patients reported recurrence of TLoC at different time periods for a pacemaker versus no pacemaker.;The number of patients with recurrence of TLoC was calculated for the Kenny (2001) study from the proportion of patients reported; the denominators were the numbers reported by the authors.

Meta-analysis (Figure 6-2) showed a significant benefit of pacemakers, with some heterogeneity at 12 months follow up.

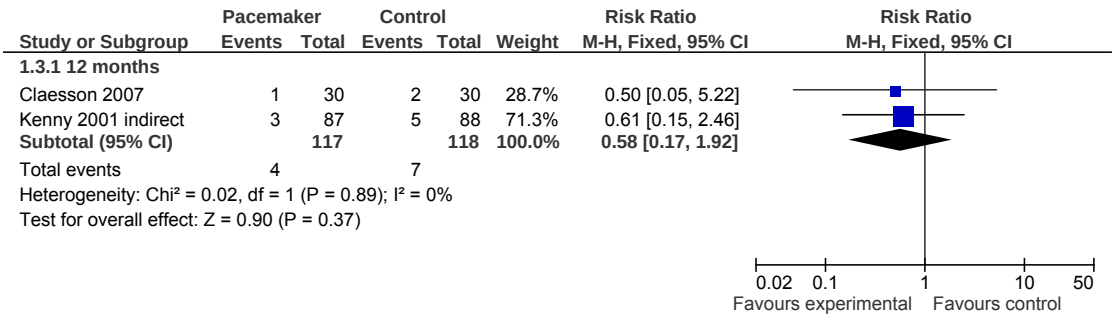
Figure 6-2: Pacemaker versus no pacemaker, recurrence of TLoC



6.4.4.2 Outcome: death and other adverse events

Two studies reported the incidence of death at 12 months and one at 5 years (Brignole 1992c). The latter was likely to be confounded by crossover to the pacemaker arm and is not included here. Meta-analysis showed no significant benefit, but there was much uncertainty (Figure 6-3).

Figure 6-3: death rate at 12 months for pacemaker versus no pacemaker



Advice from the GDG's consultant in this field, indicated that CSM is safe, and that published risk data are remarkably uniform across centres (slightly less than 1:1000 risk of an adverse neurological event). However, the severity of the potential adverse event means that informed consent should be obtained

from the patient before performing CSM. Not all centres do so though. The incidence of adverse events with CSM has diminished since resting the patients for 15 minutes after CSM became standard practice. CSM should always be done sequentially, right then left (more likely to be positive on the right), supine then upright.

6.4.4.3 GRADE analysis

The GRADE analysis for this outcome is shown below: the evidence is of low quality, but shows a large effect in favour of pacemakers for preventing recurrence (

Table 31).

Table 31: GRADE evidence summary

Outcome	Details	Results	Findings	GRADE summary	Comments	Evidence Rating
Recurrence of TLoC at 12 months	3 trials; 291 patients; from Meta analysis of RCTs	RR=0.3 (95%CI 0.17, 0.54); p=0.16; I2 =46%	large effect in favour of pacemaker	# Study limitations: serious - not blinded # Indirectness: none # Imprecision: serious - crosses line of appreciable benefit # Inconsistency: none # Reporting bias: none	No study blinded; 44% of weight is indirect population (partly); some heterogeneity but all in same direction. Crosses appreciable benefit threshold. Biggest study (44% weight) funded by Medtronic.	Low
Recurrence of TLoC at 2 years	1trial; 60 patients; from RCT	RR=0.07 (95%CI 0.01, 0.48)	large effect in favour of pacemaker	# Study limitations: very serious - not blinded and probably confounded # Indirectness: none # Imprecision: serious - number of events < 300 # Inconsistency: none # Reporting bias: none	Not blinded; likely to be confounded by crossover from non-pacemaker group. Not crossing appreciable benefit threshold but insufficient events	Very low
Recurrence of TLoC at mean 3 years	1trial; 60 patients; from RCT	RR=0.16 (95%CI 0.05, 0.5)	large effect in favour of pacemaker	# Study limitations: very serious - not blinded and probably confounded # Indirectness: none # Imprecision: serious - number of events < 300 # Inconsistency: none # Reporting bias: none	Not blinded; likely to be confounded by crossover from non-pacemaker group. Not crossing appreciable benefit threshold but insufficient events	Very low
Death	2 trials; 235 patients; from Meta analysis of RCTs	RR=0.58 (95%CI 0.17, 1.92); p=0.89; I2 =0%	no significant difference	# Study limitations: none # Indirectness: serious - indirect population # Imprecision: very serious - CI crosses both appreciable harm and benefit thresholds # Inconsistency: none # Reporting bias: none	Bigger study (71%) in partially indirect population and funded by Medtronic; blinding and industry funding not considered important for this outcome; very imprecise - crosses both appreciable benefit and appreciable harm thresholds	Very low

6.5 Clinical Evidence Review: people with suspected neurally mediated syncope after initial assessment - accuracy of tilt-testing, ambulatory ECG and carotid sinus massage to direct pacing therapy

6.5.1 Methods of the review: selection criteria

6.5.1.1 Population

Adults in secondary care with TLoC, in whom neurally mediated syncope is suspected after the initial assessment (patient history and eye witness accounts, physical examination including upright and supine BP and 12-lead ECG). No clear alternative diagnosis based on patient history or physical examination. Inadequate response to first-line therapy (patient education, mediation review). Subgroups (1) above 65 years (2) below 65 years.

6.5.1.2 Prior tests

12-lead ECG normal or any identified abnormality not likely to be the cause of TLoC.

6.5.1.3 The target condition

Neurally mediated syncope in which there is a cardioinhibitory response which would benefit from pacing.

6.5.1.4 The index test

Tilt Table test (all types)

6.5.1.5 The comparator test

Ambulatory ECG or carotid sinus massage

6.5.1.6 The reference standard

Symptom free after pacing

6.5.2 Characteristics of included studies (Appendix D1)

Twenty-eight studies were identified as being potentially relevant to this review, because they reported at least one of the index tests and the number of patients started on pacemaker therapy. Five of these were excluded (Appendix F) and the rest were included. (Boersma 2004 (ECG), Brignole 2001 (ECG), Brignole 2004 (ECG), Brignole 2005 (ECG), Brignole 2006 (ECG), Deharo 2006 (ECG), Donateo 2003 (ECG), Ermis 2003 (ECG), Farwell 2006 (ECG), Garcia-Civera 2005 (ECG), Gatzoulis 2003 (Tilt), Grubb 1991b (Tilt), Krahn 1998 (ECG), Krahn 2002 (ECG), Krahn 2004 (ECG), Lagi 1991 (CSM), Lombardi 2005 (ECG), Menozzi 2002 (ECG), Moya 2001 (ECG), Nierop 2000 (ECG), Pezewas 2007 (ECG), Pierre 2008 (ECG), Seidl 2000 (ECG)).

However, only seven of these studies reported the results of pacemaker therapy (Brignole 2005, Brignole 2006, Farwell 2006, Gatzoulis 2003, Krahn 1998, Lagi 1991, Pierre 2008), so the other studies were not considered further in this review (but are included in other reviews). Four of these seven studies, (Brignole 2005, Farwell 2006, Krahn 1998, Pierre 2008), all of which were in an indirect population (people with unexplained syncope), gave a pacemaker only to the IER positive patients, so test accuracy statistics can not be determined. These studies are not reported further here, except to note that, in each study, there was significantly less TLoC recurrence after pacemaker implantation than before.

The three main included studies each investigated a different index test compared with the reference standard, symptom free after pacing: Tilt test: Gatzoulis (2003); IER: Brignole (2006) and CSM: Lagi (1991).

6.5.2.1 Population

None of the studies reported whether the patients had received first line therapy for NM syncope before tilting, which may have made the population slightly indirect.

The populations of the three studies differed: only one was in people with suspected neurally mediated syncope (Brignole 2006), and the other two were

in an indirect population of unexplained syncope (Gatzoulis 2003); or suspected cardiac arrhythmia syncope or unexplained syncope (Lagi 1991): indeed, the Lagi (1991) study explicitly stated that patients were excluded if they had a diagnosis of vasovagal syncope on initial assessment.

Patients in the Gatzoulis (2003) study received several prior tests: history and physical examination, full neurological assessment, standard laboratory tests, supine and upright blood pressure measurements, 12-lead ECG, CSM, 24-hour Holter monitoring and echocardiography, plus other tests as indictated. Those with sinus bradycardia below 50 bpm, conduction defects and other ECG abnormalities were excluded. Syncope was unexplained after these tests. There were 123 people in the study. Their mean age was 41 years (range 20 to 70); 52% of them were men. None of the patients had underlying organic heart disease, as assessed initially. The mean number of previous TLoC events per patient was 4 (range 2 to 8), with the most recent episode in the last 6 months.

The Brignole (2006) study (ISSUE 2) was carried out in a population with more severe NM syncope. Inclusion criteria were: three or more episodes of suspected NM syncope in the past 2 years, each with a severe clinical presentation because of a high number of episodes that affected the patient's quality of life or they were at high risk for physical injury due to unpredictable occurrence. Patients were included if they had 'suggestive data' on initial assessment and the following differential diagnoses had been ruled out: suspected or definite heart disease or cardiac syncope; orthostatic hypotension; non-syncopal TLoC (e.g. epilepsy); subclavian steal syndrome. All patients had received CSM and those with CSS were excluded. The study included 392 patients; their mean age was 66 years (SD 14) and 45% were men. Patients had a median of 6 previous episodes of TLoC (range 4 to 10) and had had 4 (range 3 to 5) in the past 2 years; their mean age at first TLoC was 54 years (SD 20). We note that the study was funded by Medtronic Inc., who also provided a study manager to supervise its conduct.

The inclusion criteria for the Lagi (1991) study were: patients with suspected cardiac arrhythmia (75%) or unexplained syncope after history, examination,

12-lead ECG, chest x-ray, blood and urine chemistry, 24-hour Holter, and EEG; some patients also had exercise test, echo, cardiac catheter, CT head and 24-hour EEG. Exclusion criteria were a diagnosis of epilepsy or 'vasodepressive' syncope (diagnosed on the basis of characteristic precipitating factors and prodromes; short loss of consciousness and complete recovery after lying down for less than 5 minutes, without neurological sequelae) after the testing procedure outlined above. Other exclusions were carotid artery disease, or a history of cerebrovascular accident. Patients had to have had at least one episode of syncope (isolated or recurrent; it was not stated how many patients were in each category). The study included 56 patients. Their mean age was 66 years (range 47 to 82). The gender distribution of the patients was not stated; 75% of the patients had heart disease, including 39% coronary artery disease and 30% hypertensive heart disease, but 24-hour Holter monitoring did not demonstrate the need for permanent pacemaker therapy. All patients had had at least one previous TLoC.

6.5.2.2 Index tests and treatment

All patients in the Gatzoulis (2003) study received a standardised tilt protocol of 10 minutes supine, then 20 minutes at 80 degrees tilt, then, in the absence of symptoms, isoproterenol was infused in successive stages of increasing doses. Patients were treated according to their symptoms and those with a cardioinhibitory response (asystole more than 3 seconds or bradycardia less than 40 bpm) were considered for permanent pacing. Three patients fell into the cardioinhibitory category and were followed for a mean of 24 months (SD 7).

One of these patients was given beta-blocker therapy and the other two were offered a pacemaker; one of the latter declined the pacemaker. The study did not state if there were any differences between those patients offered a beta-blocker and those offered a pacemaker, but decision-making could have been symptom-led or severity-led. The patients' decisions whether to accept the pacemaker could also have been biased.

In the Brignole (2006) study, patients received an IER and were followed for a median time of 9 months (IQR 3 to 17). The study reported that 103/392 patients had an ECG recorded during TLoC, and of these, 47 were treated by cardiac pacing because they had asystole or bradycardia; and 6 received catheter ablation, ICD or anti-arrhythmic therapy because they had tachyarrythmias. The remaining 50 patients, those with normal or slight rhythm variations or progressive sinus tachycardia with TLoC, were given counselling and non-specific therapy; the latter group included 14 patients who did not receive appropriate treatment despite recording asystole or bradycardia (13) or tachycardia (1). It is not clear why the 14 patients did not receive appropriate treatment, which may have been for biased reasons.

The index test (carotid sinus massage) in the Lagi (1991) study consisted of massage to each right and left carotid sinus for about 5 seconds with the neck hyperextended and the patient lying supine. Cardioinhibitory carotid sinus hypersensitivity was the target condition and was defined by the authors as a variation of the cardiac rhythm or ventricular asystole over 3 seconds, with or without a decrease in blood pressure. The 41 people who had a positive result on CSM were given a pacemaker if they also had asystole for more than 3 seconds; this applied to 34 people. Three CSM negative patients also received a pacemaker because they had recurrent symptoms with ECG indication of heart disease. Therefore, pacemaker treatment was used in a symptom-led way in this study as well. Patients were followed for a mean of 11 months (SD 8).

6.5.3 Methodological quality of included studies

All the studies were prospective. Two patients were lost to follow up out of 56 (4%) in the Lagi (1991) study and 3/103 (3%) in the Brignole (2006) study; the Gatzoulis (2003) study had no loss to follow up.

The studies were assessed using the QUADAS criteria for studies of diagnostic test accuracy: in all of the studies, a selected sample of patients received a pacemaker following the index test, usually dependent on the results of the index test. Thus, there was differential verification bias (different reference standards). Interpretation of the reference standard results were not

blinded from the index test results. The studies were given a "-" QUADAS rating.

6.5.4 Results

As discussed above, the reference standard for this review is flawed in that not all patients received a pacemaker, and those that did were given one dependent on their symptoms. Therefore, the opportunity to determine if patients with a negative index test result had a lack of symptoms following pacing was very limited and probably led to bias for the diagnostic test accuracy statistics, resulting in likely artificially inflated values for both sensitivity and specificity. A negative result for the reference standard included both the patients who received a pacemaker and had symptoms, and those who did not receive a pacemaker.

The Gatzoulis (2003) study reported that 3/123 (2%) patients with unexplained syncope had asystolic pauses on tilt testing, one of whom was given a pacemaker and the other two were not. The patient receiving the pacemaker had no recurrence of TLoC, and the other two did have recurrence.

The Brignole (2006) study reported that 61/392 (16%) patients with suspected neurally mediated syncope with a severe presentation had asystole or bradyarrhythmia on IER testing, 47 of whom were given a pacemaker and 13 were not (there appeared to be 1 patient lost to follow up). Recurrence occurred in 4 patients in each group (9% and 31% respectively).

Table 32: Time to recurrence data for Brignole (2006) study

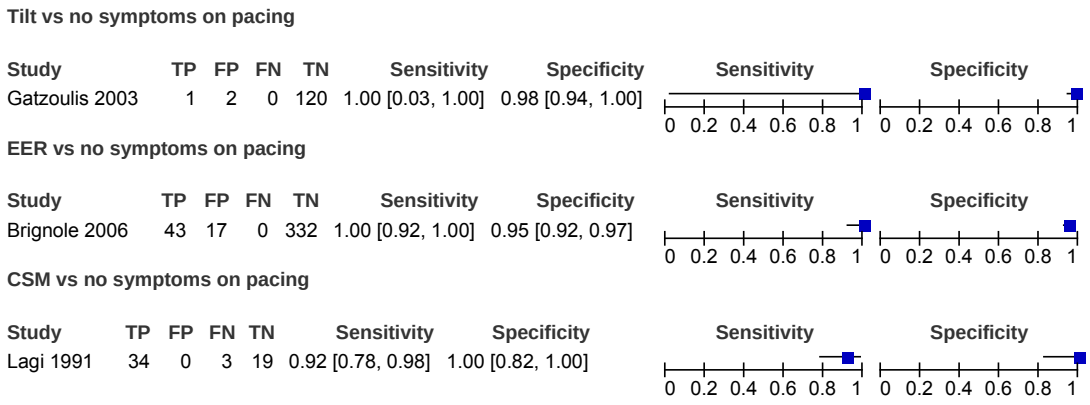
Population	Time to first recurrence of syncope (post IER implantation) (HR)	Time to second recurrence of syncope, i.e. recurrence following initiation of treatment
All patients with asystole/bradycardia on IER. Pacemaker versus no pacemaker	Not significant (p = 0.60)	Significantly lower rate of recurrence for pacemaker group: HR 0.10 (95%CI 0.02 to 0.43)
All patients with IER recordings: Pacemaker (asystole/bradycardia) versus no asystole/bradycardia (and no pacemaker)	Not significant (p = 0.72)	Significantly lower rate of recurrence for pacemaker group: HR 0.20 (95%CI 0.07 to 0.55)

The Brignole (2006) study also reported time to (second) recurrence data in 103 patients who had symptom correlation recordings on IER: 47 patients given a pacemaker for asystole or bradycardia findings; 13 patients who had asystole or bradycardia findings, but were not given a pacemaker (for reasons unstated); and 36 patients who had no or slight rhythm variations or progressive sinus tachycardia. The study reported the hazard ratio for comparisons between the groups and these are given in Table 33, together with the non-significant results for time to first recurrence (i.e. after IER implantation, but before therapy).

The Lagi (1991) study reported that 34/56 (61%) patients with suspected cardiac syncope or unexplained syncope had asystole on CSM testing, all of whom received a pacemaker; three other patients received a pacemaker because of recurrent syncope with organic heart disease. Recurrence occurred in none of the patients treated with a pacemaker during a mean follow up period of 11 months (range 8 to 24 months).

Each of the studies showed high sensitivity and specificity, although the confidence interval was very wide for the Gatzoulis (2003) study (Figure 6-4).

Figure 6-4. Diagnosic test accuracy: CSM, tilt testing and IER versus symptom-free after pacing



These results are likely to overestimate both the sensitivity and specificity because the number of false negatives was not assessed appropriately (i.e.

people with a negative index test result were not usually treated with a pacemaker, so would automatically have a true negative result).

6.6 Diagnostic test accuracy of tilt testing versus IER as a reference standard for the diagnosis of cardioinhibitory, neurally mediated syncope

6.6.1 Introduction

In view of the bias described about the above studies because of the reference standard, lack of symptoms on pacing (section 6.4), we decided, post hoc, to review the evidence for tilt testing with the reference standard of IER for the diagnosis of cardioinhibitory neurally mediated syncope.

The adoption of the IER as the reference standard was based on two main assumptions: that the IER is 100% sensitive in detecting a cardioinhibitory response during syncope; and, secondly, that a diagnosis of a cardioinhibitory response is a good predictor for which patients will benefit from pacing. The latter assumption was addressed by the review on pacemakers for cardioinhibitory neurally mediated syncope (section 6.2), but was inconclusive because there is much uncertainty in the evidence, so this remains an assumption. The former assumption is considered below (section 6.5.3).

6.6.2 Description of studies

Three studies gave sufficient data to compare, at least in part, the tilt test directly with ambulatory ECG for the diagnosis of cardioinhibitory syncope; this was for the neurally mediated syncope population in one study (Brignole 2006), and for an indirect population in two other studies (Garcia-Civera 2005 in suspected arrhythmia syncope; Farwell 2005 in unexplained syncope).

The characteristics of included studies have been described previously in sections 5.3 and 6.4.

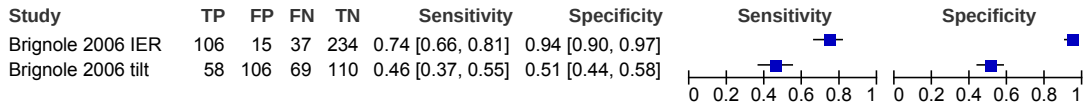
6.6.3 Results: diagnostic test accuracy versus follow up (TLoC incidence)

The Brignole (2006) study reported the correlation between (a) a positive tilt test result (induced TLoC) and (b) an IER positive recording in the same patients, versus the reference standard of occurrence of spontaneous TLoC during a mean follow up of 12 months. The test accuracy statistics are shown in Figure 6-5.

For the tilt test, the sensitivity is 46% and the specificity is 51%; the positive predictive value is 35%, i.e. a positive result on a tilt test does not predict well the incidence of spontaneous syncope.

The IER has a sensitivity of 74% and a specificity of 94%, with a positive predictive value of 88%, however it is notable that the IER did not record on every occasion that there was a TLoC in this study (9% overall missed). The diagnostic yield for no ECG recorded during TLoC was between 0 and 11% for IER, across the studies in the ambulatory ECG review (section 5.3). This is a limitation when using an IER as a reference standard.

Figure 6-5: forest plot for sensitivity and specificity for a positive tilt test and arrhythmia on ambulatory ECG for recurrence of syncope



6.6.4 Diagnostic test accuracy of tilt test with IER as the reference standard for cardioinhibitory NM syncope

In this setting, asystole can be regarded as an extreme bradycardia, but we report results separately for the target conditions, asystole alone and asystole plus bradycardia.

Two studies gave the patients both a tilt test and an IER and reported correlations between types of arrhythmias reported. One study (Brignole 2006) was in the direct population of suspected NM syncope, although the patients were restricted to those who had a severe presentation. The other study (Farwell 2005, 2006) was in patients with unexplained syncope following initial tests and 24-hour Holter monitoring; patients were excluded if they were thought to be at high risk of further syncope and injury, i.e. the Brignole (2006) and Farwell (2005, 2006) study populations were probably mutually exclusive.

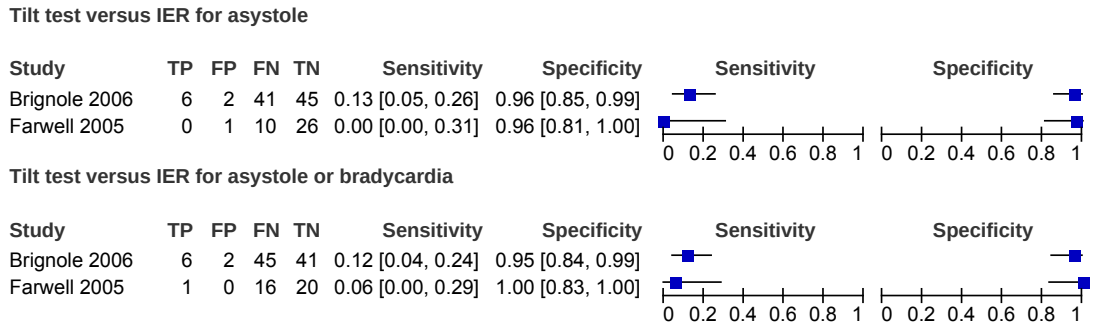
Correlations were reported for a sample of the patients in each study: patients were compared if they had a TLoC recorded by the IER and a tilt test result. The proportion of the study sample was 94/343 (27%) in Brignole (2006) and 37/103 (36%) in Farwell (2006). Diagnostic test accuracy statistics are reported for the two studies in Figure 6-6. The Farwell (2005) study reports similar results in this population to the Brignole (2006) study, but the latter is in the correct population for this review (although severe NM syncope).

For the Brignole (2006) study, the sensitivity of the tilt test is low (13% and 12% for asystole and asystole plus bradycardia respectively), but the specificity is high (96 and 95%) and the positive predictive value is 75% for both; the pre- and post-test probabilities are 50% and 75% for asystole only, and 54% and 75% for asystole plus bradycardia.

For the Farwell (2005) study the diagnostic test accuracy statistics were as follows for asystole and asystole or bradycardia: sensitivity 0% (95%CI 0 to 31%) and 6% (0 to 29%); specificity 96% (81 to 100%) and 100% (83 to 100%). Three of 26 (12%) patients with a negative tilt test result were found to have tachycardia.

The GDG considered it worth investigating if the tilt test could be used as a cost effective ‘triage’ test, so that people who were positive on a tilt test could be offered a pacemaker if appropriate and those who were negative could possibly be offered further tests, if cost effective.

Figure 6-6: Sensitivity and specificity of Tilt test versus IER

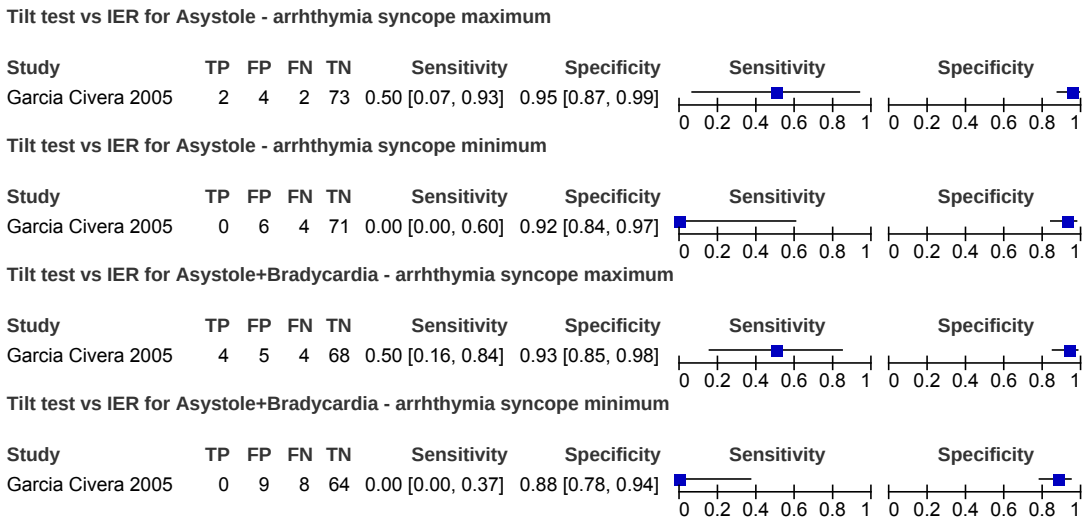


A similar analysis was carried out for a further study (Garcia-Civera 2005) in 81 people with suspected cardiac arrhythmia syncope. The study reported that the patients with a positive tilt could be subdivided into types of syncope: cardioinhibitory with asystole in 6 (16%) patients, cardioinhibitory with bradycardia in 3 (8%) patients, vasodepressor in 11 (28%) patients and mixed (no asystole or bradycardia) in 18 (47%) patients. The positive tilt results corresponded to the following rhythms on IER: 2 with asystole, 2 with sinus bradycardia, 2 with normal sinus rhythm, 2 with AV block and 30 with no spontaneous TLoC events. The negative tilt results corresponded to 2 people with asystole, 2 with bradycardia, 1 with normal sinus rhythm, 6 with AV block (14% of tilt negative), 6 with VT (14%) and 26 with no TLoC. Correlations within patient were not reported, but minimum and maximum sensitivities and specificities could be estimated from the false negative results (Figure 6-7).

The sensitivity and specificity for the maximum scenario for asystole were 50% (with a wide confidence interval) and 95% respectively, with a positive predictive value of 33% and the pre- and post-test probabilities were 5 and 33% respectively. For the asystole plus bradycardia target condition, the sensitivity and specificity were 50% (wide CI) and 93% respectively, the positive predictive value is 44% and the pre- and post-test probabilities were 5 and 27%. Although the specificity is high (93 and 95%), the post test probability is low, and the GDG did not wish to consider the tilt test for this population, even as a triage test, because they were concerned that the tilt test was unable to identify primary cardiac arrhythmias, and that missing these would put the patient at unacceptable risk. The GDG therefore decided

to investigate the cost effectiveness only for ambulatory ECG in this population.

Figure 6-7. Tilt test versus ambulatory ECG as the reference standard



6.7 Economic evaluation of testing strategies to direct pacing therapy

The GDG wished to investigate the cost-effectiveness of using tilt-testing, ambulatory ECG or sequences of these tests to identify patients who may benefit from pacing. Given the benign prognosis of vasovagal syncope, pacemakers are only likely to be considered as a treatment option in patients who continue to experience frequent episodes of TLoC or episodes that place them at significant risk of injury despite receiving conventional management for vasovagal syncope. The GDG felt that pacing would be likely to be most beneficial in patients who experience a cardioinhibitory response during vasovagal syncope either in the form of a period of asystole or bradycardia. They felt that patients with a mixed or vasodepressor response would be less likely to benefit from pacing as the pacing would not prevent a drop in blood pressure causing TLoC. In the basecase analysis we assumed that only those patients with an asystole recorded during tilt-testing or asystole recorded during spontaneous TLoC would receive a pacemaker. In a sensitivity analysis we relaxed this assumption to include bradycardia during a tilt induced or spontaneous TLoC.

In order to determine the optimum strategy for testing to identify patients for pacing, we needed to know the diagnostic yield and accuracy of different strategies. We have assumed that recording an ECG during a spontaneous TLoC is the reference standard for diagnosing or excluding an arrhythmic cause of TLoC. However, not all patients will experience a spontaneous event during monitoring, so some patients may not receive a diagnostic outcome from ambulatory ECG. An alternative approach would be to use a tilt-test to determine whether there is an arrhythmia during tilt-induced syncope. This is likely to have a higher yield as most tests can be classified as either positive or negative, but as this test isn't the reference standard for diagnosing an arrhythmic cause of TLoC, evidence is needed on the correlation between the arrhythmias diagnosed on tilt-testing and the arrhythmias diagnosed using ambulatory ECG. Only one study (Brignole 2006) provided sufficient information to determine the accuracy of tilt-testing against the reference standard of ambulatory ECG in the population with suspected vasovagal syncope. To be eligible for this study, patients had to have experienced, in the last 2 years, three or more syncope episodes with a severe clinical presentation (either a high number of episodes that affect the patient's quality of life or a high risk for physical injury) requiring treatment initiation. Therefore this study was considered to be a directly relevant to this economic model.

The Brignole 2006 study showed that the tilt-test was very specific (96%) in excluding asystole during spontaneous TLoC if a negative tilt-test was defined as either no TLoC during tilt-testing or a TLoC in which there was either a mixed or vasodepressor response or bradycardia without asystole. However, the tilt-test was not very sensitive (13%) and could therefore miss patients with asystole during spontaneous TLoC. Given the poor sensitivity and good specificity for tilt-testing compared to IER, the GDG therefore felt that it was worth investigating the cost-effectiveness of a tilt-test followed by an IER when the tilt-test failed to show asystole. They wished to determine whether this was more cost-effective than using a tilt-test alone or an IER alone. They also wanted to know the cost-effectiveness of all of these strategies compared to a strategy of no further testing.

The event rates for the Brignole 2006 study according to IER diagnosis are shown in Table 33 alongside the total event rates for the 3 studies available in patients with suspected vasovagal syncope. The Brignole 2006 study was the largest of the three studies and the probabilities derived from this study alone closely matched those derived from all 3 studies. Of the 77 arrhythmias diagnosed by IER in the Brignole 2006 study, 57 of these were classified as asystole, 4 as bradycardia and 16 as tachycardia. We assumed that the prevalence of arrhythmias found by IER diagnosis reflected the prevalence of arrhythmias in the population being tested including those patients who did not have a spontaneous TLoC recorded by IER. We then applied the sensitivity and specificity data derived from the study to determine the rate of false and true positives and false and true negatives for tilt-testing in this population. It should be noted that only 94 patients out of the 392 enrolled in Brignole 2006 had both a tilt-table test and a spontaneous event recorded on IER, so the sensitivity and specificity data has been calculated using this subset of patients which has been assumed to be representative of the population as a whole. We undertook a sensitivity analysis in which we assumed that pacing would be offered to those with either an asystolic or bradycaridic rhythm during TLoC. For this broader outcome, the sensitivity and specificity were 12% and 95% respectively.

Table 33

Population	N Studies	Prob of TLoC, P-1	Prob of outcomes in patient having TLoC during monitoring			Prob of arrhythmia in patient not having TLoC during monitoring, P4
			Arrhythmia, P2	Normal, P3	No ECG, (1-P2-P-3)	
Implantable event recorder						
All studies for suspected vasovagal syncope	3[a]	165/446 =0.37	90/165 =0.55	36/165 =0.22	39/165 =0.24	0/281 =0.00
Brignole 2006	1	143/392 =0.36	77/143 =0.54	29/143= 0.20	37/143 =0.26	0/249 =0.00

[a] Brignole 2006, Deharo 2006, Moya 2001

6.7.1 Modelling prognosis in diagnosed and undiagnosed cases

In order to model the post testing outcomes, we used the data from Brignole 2006 to estimate the proportion of patients with asystole who had AV block (28%) or sick sinus syndrome (72%). For patients who were correctly paced we used the same approach as applied in the ambulatory ECG model to estimate their post diagnostic costs and health outcomes (see sections 5.9.6 and 5.9.7). For patients who were incorrectly paced, we assumed that they incurred the same treatment costs as correctly paced patients but that there was no change in recurrence rate, HRQoL or survival (for AV block). For patients with asystole that was not identified by testing, we used the same approach as applied in the ambulatory ECG model to estimate their post diagnostic costs and health outcomes. For the strategies that included IER testing, we also included the post diagnostic costs and health outcomes of diagnosing VT on IER (see section 5.9.8).

6.7.2 Cost of diagnostic testing

6.7.2.1 IER monitoring

This was estimated by adding the device cost to the NHS reference costs for implantation and removal as described in section 5.9.1 for the ambulatory ECG model.

6.7.2.2 Tilt-testing

This falls under the same HRG code (EA47Z) as ambulatory ECG. The GDG advised that this is likely to be done as an outpatient procedure and the relevant outpatient reference cost for this HRG is £117 (IQR £64 – 156).

6.7.3 Cost-effectiveness results for testing strategies to direct pacing therapy

The basecase results are summarised in Table 34. The results show that whilst the strategy of using tilt-testing alone results in some patients receiving inappropriate pacemaker therapy, the rate of this outcome is low (<2.5% of those tested) and the benefits of correctly identifying patients who can be

paced outweighs the costs of testing and the costs of pacing in patients who may not benefit. The strategy of using an IER alone does not result in any patients receiving inappropriate pacemaker therapy but the costs of testing make this strategy less cost-effective. The incremental cost-effectiveness of IER compared to tilt-testing is £57,520 per QALY. The strategy of using a tilt-test first and an IER for those patients with a negative tilt-test has an incremental cost-effectiveness ratio of £30,620 compared to tilt-testing alone.

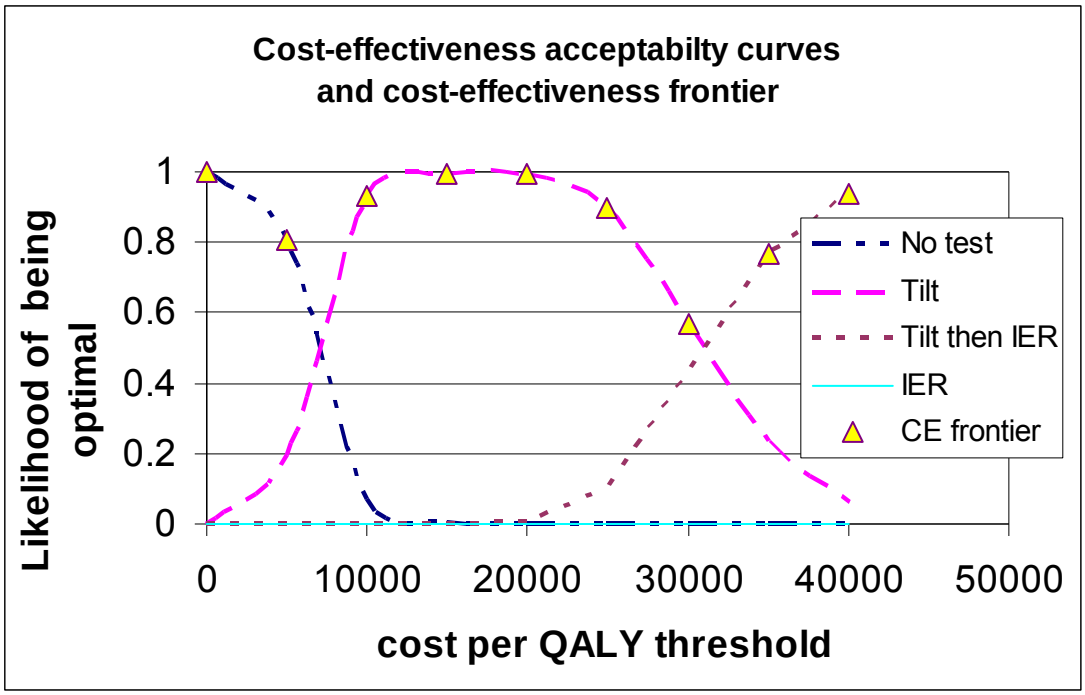
Table 34

		No testing	Tilt	Tilt then IER if tilt negative	IER
Deterministic estimates of diagnostic outcomes per 1000 patients tested					
Arrhythmia correctly paced		0	69	195	145
Pacing used inappropriately		0	22	22	0
Missed arrhythmia that could be paced		538	469	342	392
Diagnosed VT		0	0	11	11
Undiagnosed VT		151	151	140	140
Other rhythm left untreated		311	290	290	311
Deterministic estimates of costs and QALYs per patient tested					
Cost of testing		0	£117	£3,775	£4,021
Cost of post testing outcomes		£2,236	£2,668	£3,757	£3,414
Total costs		£2,236	£2,785	£7,533	£7,435
QALY gained		4.241	4.332	4.519	4.453
Probabilistic estimates per patient tested					
Total cost		£2,240	£2,790	£7,310	£7,200
Total QALY		4.241	4.331	4.479	4.407
Incremental cost per QALY vs no testing		NA	£6,060	£21,300	£29,670
Incremental cost per QALY vs tilt-testing		NA	NA	£30,620	£57,520
Incremental net benefit compared to no testing at;	20k per QALY	NA	£1,260	-£310	£-1610
	£30K per QALY	NA	£2,160	£2,070	£50
Likelihood of being optimal strategy at	20k per QALY	<1%	99.4%	<1%	<1%
	£30K per QALY	<1%	56.8%	43.2%	<1%

Figure 6-8 shows the likelihood that each strategy is cost-effective across 10,000 probabilistic samples for various different monetary values of a QALY. It also shows the cost-effectiveness frontier, which is the strategy which is optimal, for various different monetary values of a QALY, based on its average cost-effectiveness across 10,000 samples. From this figure we can

see that the strategy of using a tilt-test then an IER for patients with a negative tilt-test only becomes the optimal strategy if we are willing to value a gain of 1 QALY at more than £30,000. The strategy of using IER as the first-line test is not optimal for any willingness to pay threshold.

Figure 6-8 The cost-effectiveness acceptability curve and frontier



A number of scenario sensitivity analyses were conducted to determine how sensitive the model results are to the various assumptions used to populate the model. Tilt-testing continued to be cost-effective under all of the scenarios examined and IER continued to be not cost-effective compared to tilt-testing for all of the scenarios. The ICER for tilt-testing followed by IER in patients with a negative tilt-test compared to tilt-testing alone did fall below £30,000 per QALY for a few of the scenarios but it did not fall substantially in any of them. The ICERs for tilt-testing then IER compared to tilt-testing alone increased significantly when applying the lower range of the estimate for HRQoL improvement following pacing. This shows that the cost-effectiveness of tilt-testing to direct pacing therapy is sensitive to the improvement in HRQoL experienced after pacing.

Table 35: Scenario sensitivity analysis

	Incremental cost per QALY		
Scenario	Tilt-testing vs no testing	Tilt then IER if negative vs tilt	IER vs tilt
Basecase	£6,060	£30,620	£57,520
Bradycardia treated with pacemaker as well as asystole	£6,120	£29,340	£51,350
Recurrences continue beyond 2 years in unpaced patients with AV block or SSS	£5,920	£30,590	£57,900
Recurrences results in short stay admission	£6,030	£30,750	£58,030
Continued recurrences beyond 2 years that results in short stay admission	£5,690	£30,360	£57,840
Unpaced patients with AV block or SSS experience an average of one admission per annum	£4,175	£29,010	£56,300
Lower limit for utility gain after pacing and no utility gain after ICD therapy	£7,710	£39,940	£77,000
No uplift in IER device cost since 2004 (£1,400 instead of £1,600)	£6,060	£29,490	£55,380
Costs and benefits of pacing estimated over 6 year horizon	£8,650	£42,980	£78,290

6.7.4 Limitations of the analysis

Many assumptions have been made to populate this model. For example, we have assumed that the prevalence of arrhythmias in patients who didn't have an event recorded by IER during the Brignole 2006 study is the same as the prevalence in patients who did have an event recorded. It should also be noted that the sensitivity and specificity values used in this study were calculated from a subset of the Brignole 2006 patient cohort (94/392) who had an event reported using both tests. By not including any benefits for patients who have an arrhythmia diagnosed other than SSS, AV block or VT and not including any benefits for patients who have an arrhythmic cause excluded, the model probably underestimates the cost-effectiveness of testing. However, the estimates of post testing costs and benefits for SSS and AV block have been estimated using unadjusted estimates of survival from non-randomised trials and should therefore be treated with caution. The estimates of post testing costs and benefits for patients with VT have been generated by

adjusting the outputs of another economic model which considered a different comparison and therefore should also be treated with caution. It should also be noted that the cost-effectiveness results are not based on a randomised controlled trial and have been generated by using evidence from a single trial to estimate the diagnostic outcomes for tilt-testing and IER and by making assumptions regarding the diagnostic outcomes in patients who receive no further testing.

6.7.5 Conclusions

The cost-effectiveness model results show that tilt-testing is cost-effective compared to no further testing in patients with suspected vasovagal syncope who are being considered for pacemaker therapy due to experiencing high frequency TLoC episodes or episodes of TLoC that place them at risk of experiencing significant injury. This strategy is more cost-effective than a strategy of using IER and it is more cost-effective than a strategy of using tilt-testing followed by IER when tilt-testing is negative. However, it should be noted that many assumptions have been used to populate the model and the GDG took these into account when interpreting the cost-effectiveness evidence and forming their recommendations.

6.8 Evidence Statements

The evidence is summarised as follows:

6.8.1.1 Effectiveness of pacemakers in people with cardioinhibitory NM syncope diagnosed using a tilt test

There is very low-quality, indirect evidence from randomised trials on the effectiveness of pacemakers in preventing recurrence of TLoC in people with cardioinhibitory neurally mediated syncope. There may be a positive effect, but our confidence in this is very uncertain.

6.8.1.2 Effectiveness of pacemakers in people with cardioinhibitory carotid sinus syncope

There is low-quality evidence from randomised trials on the effectiveness of pacemakers in preventing recurrence of TLoC at 12 months in people with cardioinhibitory carotid sinus syncope. Three trials showed a large effect favouring pacemakers. Evidence was uncertain regarding the death rate at 12 months.

6.8.1.3 Diagnostic test accuracy of tilt, CSM and IER tests to direct pacing therapy in people with suspected NM syncope

There is very low-quality evidence from three non-randomised studies on the diagnostic test accuracy of tilt, CSM and IER for directing pacing therapy in people with suspected NM syncope. Pacemakers were generally not given to people with negative test results and so the sensitivity (particularly) and the specificity were likely to be overestimated.

There was much uncertainty in the sensitivity for tilt testing in directing pacing in people with unexplained syncope

There was 100% sensitivity and 95% specificity for IER in directing pacing therapy in a suspected NM syncope population with a severe presentation

There was 92% sensitivity and 100% specificity for CSM in directing pacing therapy in a population predominantly with a suspected arrhythmia cause of syncope.

6.8.1.4 Diagnostic test accuracy of tilt testing versus IER as a reference standard for predicting spontaneous syncope

There is moderate quality evidence from a single study to show that the sensitivity and specificity for the occurrence of spontaneous TLoC during follow up are 74% and 94% respectively for the IER and 46% and 51% for the tilt test, for a population with a severe presentation of suspected NM syncope.

6.8.1.5 Diagnostic test accuracy of tilt testing versus IER as a reference standard for the diagnosis of cardioinhibitory, neurally mediated syncope

There is low-quality evidence from 3 studies examining the test accuracy statistics for a tilt test with IER as the reference standard for the diagnosis of cardioinhibitory NN syncope. The limitation of these results is that between 0 and 11% patients given an IER do not have an ECG recording during TLoC. The evidence is as follows:

A sample population from one study (Brignole 2006) gave a low sensitivity [13% (95%CI 5 to 26)] and a high specificity [96% (95%CI 85 to 99)] for an asystolic cardioinhibitory response on the tilt test relative to IER; the population had to have had three or more episodes of suspected NM syncope in the past two years, each with a severe clinical presentation because of a high number of episodes that affected the patient's quality of life or they were at high risk for physical injury due to unpredictable occurrence. For an asystolic or bradycardic response on tilt testing the sensitivity was 12% and the specificity 95%.

There is low-quality evidence from a small sample population from one study (Farwell 2005) to show a very low sensitivity [0% (95%CI 0 to 31)] and high specificity [96% (95%CI 81 to 100)] for an asystolic cardioinhibitory response on the tilt test relative to IER; the population was unexplained syncope following initial tests, but people were excluded if they were thought to be at high risk of further syncope and injury. For an asystolic or bradycardic response on tilt testing the sensitivity was 6% (95%CI 0 to 29%) and the specificity 100% (83 to 100%).

There is low-quality evidence from a one study (Garcia-Civera 2005) to show a moderate sensitivity with a wide confidence interval [50% (95%CI 7 to 93); maximum value], a high specificity [95% (95%CI 87 to 99)] and a low positive predictive value (33%) for an asystolic cardioinhibitory response on the tilt test relative to IER; the population was suspected arrhythmia cause of syncope. For an asystolic or bradycardic response on tilt testing the sensitivity was 50% (95%CI 16 to 84%; maximum), the specificity 93% (85 to 98%) and the

positive predictive value 44%. False negative tilt results included 14% with VT (of the tilt negative population).

6.9 Evidence to Recommendations

6.9.1 General Points

The specialist cardiology stage investigates the value of further diagnostic tests for people who do not have a firm diagnosis of orthostatic hypotension, uncomplicated faint or situational syncope following the initial assessment stage and who do not have features strongly suggestive of epilepsy. The GDG recommended that a specialist cardiology assessment should be carried out for these people, and noted that this group includes people referred as an emergency as well as those who do not have a diagnosis following the initial stage.

People who have structural heart disease suspected as a result of the initial assessment should have further diagnostic testing directed according to these findings. Further tests for structural heart disease were not reviewed in this guideline (e.g. echocardiography), but the GDG wished to indicate that appropriate tests should be conducted and so made recommendation 1.2.2.1. The GDG advised that if the structural heart disease is considered not to be the cause of the person's TLoC, they would then be investigated with other populations who do not have a firm diagnosis after the initial stage.

The GDG decided that people without a diagnosis should be divided into three groups, those with:

- Suspected cardiac arrhythmic syncope
- Suspected neurally mediated syncope
- Unexplained syncope after the initial assessment

and they made separate recommendations for each group.

'People with unexplained syncope after the initial assessment' is also represented indirectly by the population, 'people with unexplained syncope after secondary tests'.

The GDG's reasons for treating the three main groups separately were as follows. They took into consideration evidence from the narrative review covering prognosis (Appendix D6) and noted that the one-year mortality for people with a cardiac cause of syncope (which includes both structural heart disease and/or arrhythmia) is significantly higher for this group (18% to 33%, including sudden death 14–24%) than for people with non-cardiac syncope or syncope of undetermined aetiology (3% to 6%); many studies reported that people with NM syncope do not have an increased risk of death.

The GDG also noted from the evidence on ambulatory ECG (section 5.3) and the prognosis narrative review that the recurrence rate of TLoC varies amongst the different groups: this was demonstrated, in the ambulatory ECG indirect comparisons, by a lower incidence of TLoC for the group with suspected NM syncope.

In the light of these pieces of evidence, the GDG, therefore, deemed it necessary to treat the three population groups separately. Having said this, the GDG noted that the suspected NM syncope group was particularly distinct from the other groups in terms of prognosis for both death and recurrence.

The GDG wanted to find out which diagnostic tests, or series of diagnostic tests, are the most useful and cost effective for diagnosing the likely causes of TLoC. This investigation was carried out separately for the different population groups.

6.9.2 Re-assessment at the start of the specialist cardiology stage

The GDG agreed that there was a need, at the start of the specialist cardiology stage, to reinforce the importance of a full review of the information obtained at the initial stage assessment, and recommended a reassessment of the patient's medical history, family history of cardiac disease, history of

previous TLoC events and any drug therapy. They also wanted to ensure that the specialist assessment included a clinical examination and repeat 12-lead ECG, with interpretation by a cardiologist. Once the clinician had conducted this reassessment of the patient, the GDG recommended that the clinician should decide if they suspected an arrhythmic or structural heart disease or neurally mediated cause (on the basis of positive as well as negative findings) or whether there was still considerable uncertainty regarding the suspected cause, in which case the clinician should consider the TLoC cause to be unexplained. Further testing should be directed by the clinician's suspicions and according to the recommendations. The GDG noted that other diagnostic tests (e.g. echocardiography) not reviewed in this guideline may be used to investigate any likely structural heart disease before conducting the second stage tests discussed below.

6.9.3 Recommendations for people with exercise-induced syncope

The GDG treated separately people with exercise-induced syncope and considered the low-quality evidence from one small case-control study in the exercise testing review, noting that the sensitivity of the test is moderately high (78%) for diagnosing arrhythmias in people with exercise-induced syncope; the test had moderate specificity for ruling out people with exercise-unrelated syncope (73%).

The cost of exercise testing is considered to be similar to Holter monitoring or external event recording as it falls under the same HRG code for outpatient testing. The direct access cost for exercise testing is £68 (IQR £42 to £79) (NHS reference costs 07/08 for DA15). This test was not prioritised for further economic evaluation as it was considered that the population who may benefit from exercise testing, those with exercise induced syncope, are a small subset of the whole TLoC population. In the absence of an economic model the GDG considered the likely balance of costs, benefits and any potential harms, in a qualitative manner. Given the clinical importance of identifying cardiac arrhythmia (or rarely, evidence of myocardial ischaemia) as the cause of syncope that occurs during exercise, the GDG considered that exercise

testing is likely to be cost-effective compared to no testing for people with exercise-induced syncope.

The GDG noted that exercise testing should not be a first-line investigation in people who present with exercise-induced syncope and who have clinical or other evidence of severe aortic stenosis or hypertrophic cardiomyopathy. In such people, echocardiography should be carried out as a first-line investigation.

The GDG also noted that exercise testing does not always identify the cause of TLoC in people with exercise-induced syncope, and recognised that syncope during exercise is a serious occurrence and that further investigations or treatment should be carried out as clinically appropriate for each individual, regardless of their results on exercise testing.

Overall, the GDG considered that exercise testing gave useful diagnostic information in people who had exercise-induced TLoC and could enable the clinician to determine the mechanism responsible for TLoC. Therefore, they recommended exercise testing in this population, with the reservations given above (recommendations 1.2.2.2 and 1.2.2.3).

6.9.4 Recommendations for people with a suspected cardiac arrhythmic cause of syncope

6.9.4.1 Tilt testing not to be used in this population

The GDG advised that the reference standard for diagnosing an arrhythmic cause of TLoC is an ECG recorded during spontaneous TLoC. As tilt-testing does not record spontaneous TLoC, they were concerned as to whether a tilt-test provided accurate information in this population. They were therefore interested to know the accuracy of tilt-testing.

The GDG noted the evidence from one low-quality study, which showed that the maximum sensitivity and specificity values for tilt test, versus IER as the reference standard, were 50% and 95% respectively for the target condition of

asystole; the positive predictive value and the post test probability were both low (33%). The GDG was concerned that people with a positive response to tilt could be falsely reassured that they had vasovagal syncope, when in fact they were at risk of a life-threatening arrhythmia. In addition, the study showed that 14% of those with a negative tilt test had ventricular tachycardia, which might have put the person at risk of serious events if left untreated. Taking into account the diagnostic test accuracy of tilt testing and its likely sequelae, the GDG recommended that tilt testing should not be used in a population in whom an arrhythmic cause is suspected.

6.9.4.2 Ambulatory ECG in this population

The GDG then considered whether there was sufficient evidence of clinical and cost-effectiveness to recommend ambulatory ECG in this population. There are three types of ambulatory ECG devices which work in different ways and can provide slightly different information. The differences are described in Chapter 5.

The GDG considered the fact that a Holter monitor may give additional information on the patient's condition and may be more likely to detect arrhythmias not occurring during TLoC, which may help with diagnosis. However, it is only in place for a short period. On the other hand, the evidence shows that EER and IER devices may fail to keep a record of the ECG during TLoC if they are not activated or if they are activated multiple times causing useful data to be overwritten. In their discussions, the GDG took into consideration the fact that the IER is an invasive device, although noted, from the ambulatory ECG review, that adverse effects (e.g. infections) were rare.

The GDG advised that the principal aim of ambulatory ECG recording is to obtain an ECG recording at the time of TLoC. On the basis of their consensus experience, the GDG formed the hypothesis that it was preferable to match the type of device used with the frequency of previous episodes experienced in order to achieve a good probability of documenting the cardiac rhythm at the time of TLoC during the monitoring period. This hypothesis was examined in the ambulatory ECG reviews, however, much of the evidence for Holter monitors and EERs appeared to be in the infrequent TLoC population

(although sometimes the frequency of events was not reported). Some studies reported the time to recurrence of TLoC instead of the frequency. One study did fall into the frequent TLoC category (Rothman 2007) and had a median time to diagnosis of 10 days for the external event recorder.

The GDG considered the following low-quality evidence for the suspected cardiac arrhythmic group, and also drew on the extensive predominantly low-quality evidence for the population with unexplained TLoC after secondary tests:

- Indirect comparisons of the various devices in the non-frequent TLoC population:
  - ◊ There were fewer TLoC events during Holter monitoring than during IER monitoring for the same population group
  - ◊ The proportion of patients with symptomatic arrhythmias recorded by the IER was much higher than that of the Holter monitor
  - ◊ For the IER across the studies in the combined suspected arrhythmic and unexplained groups, there appeared to be a correlation between the diagnostic yield for TLoC-occurring-during-monitoring and the mean frequency of previousTLoC
- Direct comparison of EER versus 48-hour Holter monitoring in the non-frequent TLoC population: there was moderate-quality evidence from one RCT in people with ‘unexplained TLoC after secondary tests’, which showed a significantly higher diagnostic yield for EER versus 48-hour Holter monitoring
- The external event recorder in the fairly frequent population (i.e. appropriate population) for the suspected arrhythmia group recorded about two-thirds of TLoC events, and recorded symptomatic arrhythmias in 41% of the population.

Thus, the GDG concluded that the evidence supported their hypothesis that the type of device should be tailored to the frequency of previous TLoC and that it was inappropriate to compare head-to-head the different ambulatory ECG devices; this rationale was carried forward into the cost-effectiveness analyses. We note that the evidence is indirect for the Holter monitor and the

EER because the populations in the available studies did not have frequent TLoC. In addition, many of the studies looking at external and implantable event recorders recruited patients who had had a previous negative Holter test. Therefore the evidence is indirect, both in terms of the frequency of events in the population and in terms of the use of prior testing – this may underestimate the diagnostic yield.

Cost-effectiveness analysis was directed towards determining whether the device was cost-effective when used in patients with the appropriate frequency of TLoC episodes. The cost-effectiveness analysis did not compare the different ambulatory ECG devices head-to-head for the reasons discussed above. The economic modelling results suggest that ambulatory ECG is likely to be cost-effective compared to no further testing in patients with suspected arrhythmic syncope and these results were robust under the sensitivity analyses conducted. However, it should be noted that the economic analysis had various limitations which the GDG took into account when interpreting the cost-effectiveness evidence and forming their recommendations.

The GDG recognised that the cost-effectiveness estimates for Holter monitoring were based on studies in which the population was not selected on the basis of having highly frequent TLoC. Therefore the model probably underestimates the cost-effectiveness of Holter monitoring in people with very frequent events.

The GDG also considered whether it would be appropriate to repeat the test in people who had not had TLoC during the monitoring time. The GDG drew on one study (Arya 2005) that compared 24-hour monitoring with 48-hour monitoring in the same patients. The diagnostic yield was approximately doubled for the 48-hour period. Indirect evidence from another population (patients who had unexplained TLoC after initial tests) in one study (Kapoor 1991) showed that 72-hour Holter monitoring did not add to the diagnostic yield for 48-hour monitoring: in this study the cumulative diagnostic yield approximately doubled from 24-hours to 48-hours, but was essentially unchanged after a further 24 hours.

Given that the sensitivity analyses showed that the cost-effectiveness was not particularly sensitive to increases in the cost of Holter monitoring, (approximately doubling the cost of testing did not increase the ICER substantially), the GDG concluded that using the device twice would still be cost effective and they recommended that repeat Holter monitoring could be carried out in people with a negative 24-hour Holter, up to 48 hours.

The GDG also considered whether it would be useful to use a Holter monitor followed by an external or implantable event recorder if the initial Holter did not document a clear cause of TLoC, and referred to one moderate-quality study (Rockx 2005) in an indirect population (people with infrequent TLoC that were unexplained after further tests). This study compared EER followed by Holter monitoring (patient choice) versus Holter followed by EER (patient choice) in people with negative results on the first test. The EER followed by Holter monitoring had a significantly higher yield than Holter followed by EER, but there was no significant difference between the EER alone and the Holter followed by EER. The GDG considered that the costs of using either EER or Holter were likely to be similar and the same cost had been applied within the economic model. The GDG did not think that the study was very helpful because the Holter device was not appropriate to the population, but took the study results into account in clinically interpreting the evidence.

The GDG concluded that the first choice of device should be based on the frequency of TLoC events previously experienced by the individual and that if this fails to capture an event a device which monitors for a longer period should be considered at the discretion of the expert clinician, bearing in mind the clinical context and the patient's preference. Consequently the GDG shaped the recommendation with this practical application in mind.

6.9.5 People with suspected carotid sinus syncope

The GDG considered the low-quality evidence from RCTs on the effectiveness of carotid sinus massage (CSM) in people with suspected carotid sinus syncope (CSS) or with unexplained syncope. The review concluded that pacemakers were effective in people identified using CSM to have a cardioinhibitory basis for CSS.

Carotid sinus massage was not considered to be a priority for further economic modelling as the GDG believed that conducting a CSM test would not significantly increase the costs of the second stage assessment. Given that there was some evidence, albeit low quality, showing that pacemakers are effective in treating patients identified using CSM, the GDG thought that using CSM was likely to be cost-effective provided that it was used in a population with a reasonable pre-test probability of carotid sinus syncope (i.e. in all people with symptoms indicating CSS or in people with unexplained TLoC aged 60 years and over).

6.9.6 People with suspected NM syncope

The GDG considered the clinical and cost effectiveness of carrying out different tests in people with suspected neurally mediated syncope for the purpose of diagnosing the cause of TLoC.

6.9.6.1 Tilt test not to be used to confirm NM syncope

There was a large volume of low-quality evidence from the tilt test review, which was largely based on case-control studies in people with neurally mediated syncope on the basis of initial assessment and controls who were generally people who had not had syncope. There was uncertainty about how useful the tilt test was because of the poor evidence quality (case-control studies), although in this unrepresentative population, the tilt test performed fairly well. One low-quality case-control study (Parry 2008) showed that the tilt test had poor diagnostic test accuracy in a population from which people were excluded if they had likely neurally mediated syncope following history-taking.

The GDG also took into account the good prognosis for most people with NM syncope, both in terms of mortality and recurrence of symptoms. They also considered the potential benefits to the person of confirmation that their TLoC was vasovagal and not likely to have a poor prognosis. Although other treatments for neurally mediated syncope were not reviewed (as these were outside the scope of the guideline), the GDG noted that there was a lack of evidence in this area for people with neurally mediated syncope.

The GDG also took into consideration the potential adverse effects of drugs used for the tilt test, the fact that some people find that the tilt-test is an unpleasant experience and there is a small risk consequent on asystole being induced by the test.

Finally, the GDG had confidence in the initial assessment for vasovagal syncope, which led them to prefer this as a diagnostic test.

The GDG took into consideration all these benefits and harms and concluded that the tilt test should not be used simply to confirm neurally mediated syncope .

6.9.6.2 Tilt test not to be used in all people with cardioinhibitory NM syncope

The GDG then considered whether tilt-testing had particular benefits in any subgroup of people with vasovagal syncope. In particular, whether people with a cardioinhibitory form of vasovagal syncope might benefit from diagnosis and subsequent treatment, including pacing.

The evidence was uncertain on the clinical effectiveness of pacemakers in people with cardioinhibitory vasovagal syncope identified by tilt testing. Furthermore, the evidence reviewed on the diagnostic test accuracy of tilt testing to select patients for pacing was considered to be biased.

The GDG also considered the evidence for risks associated with implantation of a permanent pacemaker, particularly in young people who may have a pacemaker for many years. Immediate complications include infection (0.2-1.8%), haematoma formation, pneumothorax (1.0%), lead displacement (1.5-2.4%) and lead perforation (0.5%) (Carlson 2006). The average longevity of a pacemaker was found to be 7.3± 3.1 years (range: less than 1 day to 26 years) (Hauser 2007). Permanent pacemakers can malfunction and may have to be replaced or, rarely, explanted. Data compiled between 1990 and 2002 indicated that this complication occurred for between 0.4 and 9.0 per 1000 pacemakers implanted. The implanted pacemaker leads can also develop defects over time: ten year lead survival for unipolar and bipolar pacemaker leads varies from 96.5 to 97.8% respectively. If leads need to be extracted,

the procedure can be associated with complications of lead extraction of 1.4% including that of death of 0.6%. (Maisel 2009; Wilkoff 2009).

The GDG took into account the benefits and harms of pacemaker implantation in people with cardioinhibitory vasovagal syncope, including the good prognosis for this group, and concluded that the decision to implant a pacemaker, especially in a young individual should not be undertaken lightly.

6.9.6.3 Tilt testing in people with a high symptom burden associated with poor quality of life and/or high risk of injury, for whom a pacemaker could be considered ('severe vasovagal syncope' population)

Finally, the GDG considered whether diagnostic tests should be carried out in people with a greater clinical need, notably those with a high symptom burden who had poor quality of life and/or were at high risk of injury, and for whom pacing could be considered as an option. They therefore examined the evidence for this population group for two diagnostic tests, tilt and ambulatory ECG.

One low-quality study (Fitchet 2003) in an indirect population (people with suspected vasovagal syncope who were not selected on the basis of a high symptom burden) performed 48-hour Holter monitoring and tilt testing. The Holter monitoring detected no-one with symptomatic asystole or bradycardia and the tilt test recorded 3 (8%) with a cardioinhibitory positive tilt. There was thus a significantly higher diagnostic yield for the tilt test in giving a positive result, but there was no significant difference between tests for diagnosing an arrhythmia during TLoC. Insufficient information was reported to determine the diagnostic test.accuracy. The GDG decided to consider only the IER in comparison to tilt testing for this patient group.

The Brignole (2006) study reported a sensitivity of 13% and specificity of 96% for the tilt test for the target condition, asystole, in the severe vasovagal syncope population, and values of 12% and 95% for the target condition, asystole or bradycardia. In both cases the reference standard was the target arrhythmia found by IER during spontaneous TLoC. We note that the IER did not make a diagnosis for all TLoCs (26% missed of those with a TLoC), so the

accuracy in people without a spontaneous TLoC recorded during IER is unknown. In the economic model we assumed that the people with a spontaneous event recorded during IER monitoring were similar to those without a spontaneous event recorded during IER monitoring.

The GDG decided that the population described in the Brignole (2006) study was representative of people to whom they might consider offering a pacemaker and they wished to determine the cost effectiveness of tilt-testing and IER for a diagnosis of asystole and/or bradycardia, rather than vasovagal syncope in general. Each test would be compared with no further testing. In view of the high specificity and relatively low sensitivity of the tilt test (few false positives but more false negatives), the GDG considered that another option might be to use the tilt test first and then offer an IER test in those with a negative test result, whilst considering a pacemaker for those with a positive result..

The cost-effectiveness model results showed that tilt-testing is cost-effective compared to no further testing in people with suspected vasovagal syncope who are being considered for pacemaker therapy due to experiencing high frequency TLoC or episodes of TLoC that place them at risk of experiencing significant injury and who have a cardioinhibitory response to tilt testing. This strategy was more cost-effective than a strategy of performing an IER test and was more cost-effective than a strategy of using tilt-testing followed by IER when tilt-testing is negative. These conclusions did not change materially when various assumptions used in the model were tested through sensitivity analysis. However, it should be noted that the economic analysis had various limitations which the GDG took into account when interpreting the cost-effectiveness evidence and forming their recommendations.

6.9.7 People with unexplained syncope

6.9.7.1 CSM in people aged 60 years and over

The GDG recommended that CSM should also be offered to people aged 60 years and over with unexplained syncope in addition to those with suspected carotid sinus syncope, and that CSM should be done before ambulatory ECG in this population. People under 60 years should be offered ambulatory ECG as appropriate and CSM should not be performed on them. The GDG noted that a diagnosis could be made of carotid sinus syncope if CSM induced syncope (usually with a cardioinhibitory response).

6.9.7.2 Directness of evidence for other tests in this population

The GDG defined the population for these tests as people with unexplained TLoC following initial tests, who are either 60 years and over and negative on CSM, or those who are younger than 60 years.

When considering the evidence in people with unexplained TLoC, studies were split into two populations: those with unexplained TLoC following initial assessment (patient history, clinical examination and 12-lead ECG) and those who had had more extensive tests, which could include tilt testing, Holter monitoring, electrophysiology etc (section 5.3). The latter set of studies also varied according to whether the previous tests led to exclusion of patients, e.g. people with a positive tilt test being excluded from the population receiving an IER. The GDG wished to determine which tests should be performed in the population, unexplained TLoC following initial assessment, however, there was limited evidence for these people. Consequently, studies in the population with unexplained syncope after secondary tests, were used as indirect evidence.

6.9.7.3 Tilt testing should not be used in this population

The GDG considered whether a tilt test should be used in this group, and noted that the prognosis for death in this population was not zero and that same arguments applied for this population as for those with a suspected arrhythmic cause. One study (Farwell 2005) compared a tilt test and IER in a population with unexplained syncope. This UK-based study showed a similar

effect as the Brignole (2006) study, i.e. low sensitivity (0 and 6%) and high specificity (96 and 100% respectively) for asystole and asystole plus bradycardia. The limitation of this study is that their population was selected, and not necessarily representative of the unexplained TLoC group because people with asystolic tilt results who were considered to be at high risk of injury received a pacemaker and did not go on to have an IER implanted (13 out of 214 who received the tilt test). Even if we assume that all of these people would have had asystole during IER monitoring, the sensitivity of the tilt test for detecting asystole or bradycardia would have been less than 50% in this population. In addition, 3 of the 26 people who had a negative tilt result went on to have a tachyarrhythmia recorded by IER. The GDG decided that a tilt test should not be offered in the population with unexplained TLoC.

Two moderate quality RCTs (Farwell 2006, Krahn 2001) compared an IER with conventional testing – the latter arm was not well described in the UK-based Farwell (2006) study, and included an external event recorder, tilt test and electrophysiology in the Krahn (2001) study. Both studies showed a significantly larger diagnostic yield for the IER group and both were funded by Medtronic Inc.

The Farwell (2006) study carried out a test-and-treat randomised trial, with patients being given treatments depending on their test results, and showed that the IER test-and-treat strategy resulted in a significantly longer time to second recurrence of syncope (p=0.04).The second recurrence is important because treatment may delay or prevent the second recurrence if diagnosis is achieved at the first recurrence during monitoring. There was no significant difference in the number of deaths at censorship nor in the quality of life SF-12 score, but the IER group had a significant improvement in a visual analogue general well-being score.

The economic modeling results suggest that ambulatory ECG is likely to be cost-effective compared to no further testing in people with unexplained TLoC and these results were robust under the sensitivity analyses conducted. IER was also found to be cost-effective compared with conventional testing based on the Farwell 2006 results. However, it should be noted that the economic

analysis had various limitations which the GDG took into account when interpreting the cost-effectiveness evidence and forming their recommendations.

The GDG decided to recommend ambulatory ECG in this population, with CSM being recommended first-line for older patients in whom the incidence of carotid sinus hypersensitivity is higher. The GDG also decided that their previous discussion regarding targeting the type of ambulatory ECG to match the frequency of events was equally applicable to this population as it was to the population with a suspected arrhythmic cause of syncope.

6.9.8 General recommendations on the use of ambulatory ECG

The evidence showed that IERs failed to record an event in a median of 6% of all people tested (range 0 to 31%). The Farwell (2006) study reported that 37% failed to capture their first syncopal event, and this was due either to a failure to activate the IER or to a delay between the TLoC and subsequent device interrogation, resulting in overwriting of the event data by subsequently captured data. The study noted that after longer-term follow-up this figure reduced to 5%. The Farwell (2006) study noted that the diagnostic yield was improved by the used of automatic IERs (19% of all IER diagnoses) and the Ermis (2003) study showed that 5 times as many symptomatic arrhythmias were captured by the automatic activation mode than the patient-activated mode, although different arrhythmias were captured.

The authors of the Farwell (2006) study recommended that people with an IER should be regularly followed up in order to:

- interrogate the device
- fine-tune the sensitivity for auto-activation
- re-educate people about the technique of manual activation
- encourage early presentation after any TLoC event to prevent overwriting of the recorded rhythms and the loss of diagnostic data.

The GDG concluded that this was good advice and added some details to their recommendation to help people with an IER.

6.10 Recommendations

Hyperlink to recommendations Section 1.2.2 - Diagnostic tests for different types of syncope

7 Reference List

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8 Appendices A–H are separate files