Transient loss of consciousness (TLoC) management in adults

Full Guideline

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If you wish to make a comment, please quote page and line number

Citation

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KEY PRIORITIES FOR IMPLEMENTATION

Note: Each guideline is allowed by NICE to select 10 recommendations which will have the maximum impact on patient care. These 'Key Priorities for Implementation' are listed below. It is particularly apparent in this a guideline which is a diagnostic pathway, that these recommendations are taken out of context. Please refer to the full list of recommendation, which follows this section, to see how these recommendations relate to others.

Initial assessment

- 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 by telephone witnesses who are not present. Record details about:
  - circumstances of the event
  - person's posture immediately before loss of consciousness
  - prodromal symptoms (such as sweating or feeling warm/hot)
  - appearance (for example, whether eyes were open or shut) and colour of the person during the event
  - presence or absence of movement during the event (for example, limb-jerking and its duration)
  - any tongue-biting (record whether the side or the tip of the tongue was bitten)
  - injury occurring during the event (record site and severity)
  - duration of the event (onset to regaining consciousness)
  - presence or absence of confusion during the recovery period. **[1.1.1.2]**
- When recording a description of the suspected TLoC from the patient or 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. **[1.1.1.3]**
- Record a 12-lead electrocardiogram (ECG) using automated interpretation. Treat as a red flag (see recommendation 1.1.5.2) if any of the following abnormalities are reported on the ECG printout:
  - conduction abnormality (for example, complete right or left bundle branch block or any degree of heart block)
  - evidence of delayed atrio-ventricular conduction, including bundle branch block
  - evidence of a long or short QT interval, **or**

- any ST segment or T wave abnormalities. **[1.1.3.1]**

- Refer within 24 hours for specialist cardiovascular assessment by the most appropriate local service, anyone with TLoC who also has any of the following.
  - An ECG abnormality (see recommendation 1.1.3.1).
  - Heart failure (history or physical signs).
  - TLoC during exertion.
  - Family history of sudden cardiac death in people aged younger than 40 years and/or an inherited cardiac condition.
  - New or unexplained breathlessness.
  - A heart murmur.

  Consider referring within 24 hours for cardiovascular assessment, as above, anyone aged older than 65 years who has experienced TLoC without prodromal symptoms. **[1.1.5.2]**

- Diagnose uncomplicated faint (uncomplicated vasovagal syncope) on the basis of the initial assessment when:
  - there are no features 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 suggestive of uncomplicated faint (the 3 'P's) such as:
    - ◊ **P**osture – prolonged standing or similar episodes that have been prevented by lying down
    - ◊ **P**rovoking factors (such as pain or a medical procedure)
    - ◊ **P**rodromal symptoms (such as sweating or feeling warm/hot before TLoC).

  [1.1.5.3]

Further assessment and referral

- 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 2 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.
  - Head-turning to one side during TLoC.

- No memory of abnormal behaviour witnessed by someone else.
- Unusual posturing.
- Prolonged limb-jerking (note that brief seizure-like activity can often occur during uncomplicated faints).
- Confusion following the event.
- Prodromal déjà vu, or jamais vu (see glossary).

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

- Prodromal symptoms that on other occasions have been abolished by sitting or lying down.
- Sweating.
- Prolonged standing that appeared to precipitate the TLoC.
- Pallor during the episode.

Do not routinely use electroencephalogram (EEG) in the investigation of TLoC (see 'The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care' [NICE clinical guideline 20]). **[1.2.2.1]**

Specialist cardiovascular assessment and diagnosis

- Carry out a specialist cardiovascular assessment as follows.
  - Reassess the person's:
    - ◊ detailed history of TLoC including any previous events
    - ◊ medical history and any family history of cardiac disease or an inherited cardiac condition
    - ◊ drug therapy at the time of TLoC and any subsequent changes.
  - Conduct a clinical examination, including full cardiovascular examination and, if clinically appropriate, measurement of lying and standing blood pressure.
  - Repeat 12-lead ECG and obtain and examine previous ECG recordings.

On the basis of this assessment, assign the person to one of the following causes of syncope.

- Suspected structural heart disease.
- Suspected cardiac arrhythmic.
- Suspected neurally mediated.
- Unexplained.

Offer further testing as directed by recommendations 1.3.2.1 to 1.3.2.10 or other tests as clinically appropriate. **[1.3.1.1]**

- For people with a suspected cardiac arrhythmic cause of syncope, offer an ambulatory ECG and do not offer a tilt test as a first-line investigation. The type of ambulatory ECG offered should be chosen on the basis of the person's history (and, in particular, frequency) of TLoC. For people who have:
  - TLoC at least several times a week, 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.
  - 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.
  - TLoC infrequently (less than once 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. **[1.3.2.4]**

- Do not offer a tilt test to people who have a diagnosis of vasovagal syncope on initial assessment. **[1.3.2.5]**
- For all people with unexplained syncope (including after negative carotid sinus massage test in those for whom this is appropriate), offer ambulatory ECG (see recommendation 1.3.2.4). Do not offer a tilt test before the ambulatory ECG. **[1.3.2.9]**

RECOMMENDATIONS

1.1 Initial assessment

1.1.1 Gathering information about the event and initial decision making

Hyperlink to Chapter 3 - Initial Assessment and Diagnosis

1.1.1.1 If the person with suspected transient loss of consciousness (TLoC) has sustained an injury or they have not made a full recovery of consciousness, use clinical judgement to determine appropriate management and the urgency of treatment.

1.1.1.2 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 by telephone witnesses who are not present. Record details about:

- circumstances of the event
- person's posture immediately before loss of consciousness
- prodromal symptoms (such as sweating or feeling warm/hot)
- appearance (for example, whether eyes were open or shut) and colour of the person during the event
- presence or absence of movement during the event (for example, limb-jerking and its duration)
- any tongue-biting (record whether the side or the tip of the tongue was bitten)
- injury occurring during the event (record site and severity)
- duration of the event (onset to regaining consciousness)
- presence or absence of confusion during the recovery period.

1.1.1.3 When recording a description of the suspected TLoC from the patient or 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.

Determining whether the person had TLoC

1.1.1.4 Use information gathered from all accounts of the suspected TLoC (see recommendation 1.1.1.2) to confirm whether or not TLoC has occurred. If this is uncertain it should be assumed that they had TLoC until proven otherwise. But, if the person did not have TLoC, instigate suitable management (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 Obtaining patient history, physical examination and tests

Hyperlink to Chapter 3 - Initial Assessment and Diagnosis

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 that may have contributed to TLoC (for example, diuretics)
- vital signs (for example, pulse rate, respiratory rate and temperature) – repeat if clinically indicated
- lying and standing blood pressure if clinically appropriate
- other cardiovascular and neurological signs.

1.1.2.2 If during the initial assessment, there is suspicion of an underlying problem causing TLoC, or additional to TLoC, carry out relevant examinations and investigations (for example, check blood glucose levels if hypoglycaemia is suspected, or haemoglobin levels if anaemia or bleeding is suspected).

1.1.3 Recording a 12-lead electrocardiogram (ECG)

Hyperlink to Chapter 4 - 12 Lead ECG

1.1.3.1 Record a 12-lead electrocardiogram (ECG) using automated interpretation. Treat as a red flag (see recommendation 1.1.5.2) if any of the following abnormalities are reported on the ECG printout:

- conduction abnormality (for example, complete right or left bundle branch block or any degree of heart block)
- evidence of delayed atrio-ventricular conduction, including bundle branch block
- evidence of a long or short QT interval, **or**
- any ST segment or T wave abnormalities.

1.1.3.2 If a 12-lead ECG with automated interpretation is not available, take a manual 12-lead ECG reading and have this reviewed by a healthcare professional trained and competent in identifying the following abnormalities.

- Inappropriate persistent bradycardia.
- Any ventricular arrhythmia (including ventricular ectopic beats).
- Long QT (corrected QT > 450 ms) and short QT (corrected 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.

1.1.4 Recording the event information and transfer of records

1.1.4.1 Record carefully the information obtained from all accounts of the TLoC. Include paramedic records with this information. Give copies of the ECG record and the patient report form to the receiving clinician when care is transferred, and to the person who had the TLoC.

1.1.5 Making a judgement based on initial assessment

Red flags: people requiring urgent assessment and treatment

Hyperlink to Chapter 3 - Initial Assessment and Diagnosis

1.1.5.1 If TLoC is secondary to a condition that requires immediate action, use clinical judgement to determine appropriate management and the urgency of treatment.

1.1.5.2 Refer within 24 hours for specialist cardiovascular assessment by the most appropriate local service, anyone with TLoC who also has any of the following.

- An ECG abnormality (see recommendation 1.1.3.1).
- Heart failure (history or physical signs).
- TLoC during exertion.
- Family history of sudden cardiac death in people aged younger than 40 years and/or an inherited cardiac condition.
- New or unexplained breathlessness.
- A heart murmur.

Consider referring within 24 hours for cardiovascular assessment, as above, anyone aged older than 65 years who has experienced TLoC without prodromal symptoms.

No further immediate management required

Hyperlink to Chapter 3 - Initial Assessment and Diagnosis

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

- there are no features 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 suggestive of uncomplicated faint (the 3 'P's) such as:
  - **P**osture – prolonged standing or similar episodes that have been prevented by lying down
  - **P**rovoking factors (such as pain or a medical procedure)
  - **P**rodromal symptoms (such as sweating or feeling warm/hot before TLoC).

1.1.5.4 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 straining during micturition (usually while standing) or by coughing or swallowing.

1.1.5.5 If a diagnosis of uncomplicated faint or situational syncope is made, and there is nothing in the initial assessment to raise clinical or social concern, no further immediate management is required. If the presentation is not to the GP, the healthcare professional should:

- advise the person to take a copy of the patient report form and the ECG record to their GP
- inform the GP about the diagnosis, directly if possible; if an ECG has not been recorded, the GP should arrange an ECG (and its interpretation as described in recommendation 1.1.3.2) within 3 days.

Further immediate management required

1.1.5.6 If the person presents to the ambulance service, take them to the Emergency Department unless a diagnosis of an uncomplicated faint or situational syncope is clear.

1.2 Further assessment and referral

Hyperlink to Chapter 5 Specialist Assessment

1.2.1 Suspected orthostatic hypotension

1.2.1.1 Suspect orthostatic hypotension on the basis of the initial assessment when:

- there are no features suggesting an alternative diagnosis **and**
- the history is typical.

If these criteria are met, measure lying and standing blood pressure (with repeated measurements while standing for 3 minutes). If clinical measurements do not confirm orthostatic hypotension despite a suggestive history, refer the person for further specialist cardiovascular assessment.

If orthostatic hypotension is confirmed, consider likely causes, including drug therapy, and 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]).

1.2.2 Suspected epilepsy

1.2.2.1 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 2 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.
- Head-turning to one side during TLoC.
- No memory of abnormal behaviour witnessed by someone else.
- Unusual posturing.
- Prolonged limb-jerking (note that brief seizure-like activity can often occur during uncomplicated faints).
- Confusion following the event.
- Prodromal déjà vu, or jamais vu (see glossary).

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

- Prodromal symptoms that on other occasions have been abolished by sitting or lying down.
- Sweating.
- Prolonged standing that appeared to precipitate the TLoC.
- Pallor during the episode.

Do not routinely use electroencephalogram (EEG) in the investigation of TLoC (see 'The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care' [NICE clinical guideline 20]).

1.2.3 Referral for specialist cardiovascular assessment

1.2.3.1 Refer all people with TLoC (apart from the exceptions below) for a specialist cardiovascular assessment by the most appropriate local service. Exceptions are:

- people with a firm diagnosis, after the initial assessment, of:
  - uncomplicated faint
  - situational syncope
  - orthostatic hypotension
- people whose presentation is strongly suggestive of epileptic seizures.

1.3 Specialist cardiovascular assessment and diagonosis

Hyperlink to Chapter 6 Diagnostic Tests

1.3.1 Assessment and assignment to type of syncope

1.3.1.1 Carry out a specialist cardiovascular assessment as follows.

- Reassess the person's:
  - detailed history of TLoC including any previous events
  - medical history and any family history of cardiac disease or an inherited cardiac condition
  - drug therapy at the time of TLoC and any subsequent changes.
- Conduct a clinical examination, including full cardiovascular examination and, if clinically appropriate, measurement of lying and standing blood pressure.
- Repeat 12-lead ECG and obtain and examine previous ECG recordings.

On the basis of this assessment, assign the person to one of the following causes of syncope.

- Suspected structural heart disease.
- Suspected cardiac arrhythmic.
- Suspected neurally mediated.
- Unexplained.

Offer further testing as directed by recommendations 1.3.2.1 to 1.3.2.10 or other tests as clinically appropriate.

1.3.1.2 For people with suspected structural heart disease, investigate appropriately (for example, cardiac imaging). Because other mechanisms for syncope are possible in this group, investigate also for a cardiac arrhythmic cause (as described in recommendation 1.3.2.4), and consider investigating for orthostatic hypotension (often caused/exacerbated by drug therapy – see recommendation 1.2.1.1) or for neurally mediated syncope (see recommendations 1.3.2.5 and 1.3.2.6).

1.3.2 Diagnostic tests for different types of syncope

1.3.2.1 Use the person's history to distinguish people whose exercise-induced syncope occurred **during exercise** (when a cardiac arrhythmic cause is probable) from those whose syncope occurred **shortly after stopping exercise** (when a vasovagal cause is more likely).

1.3.2.2 For people who have experienced syncope during exercise, offer urgent (within 7 days) exercise testing, unless there is a possible contraindication (such as suspected aortic stenosis or hypertrophic cardiomyopathy requiring initial assessment by imaging). Advise the person to refrain from exercise until informed otherwise following further assessment.

1.3.2.3 If the mechanism for exercise-induced syncope is identified by exercise testing, carry out further investigation or treatment as appropriate in each individual clinical context. Otherwise, carry out further investigations assuming a suspected cardiac arrhythmic cause.

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

- TLoC at least several times a week, 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.

- 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.
- TLoC infrequently (less than once 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.

1.3.2.5 Do not offer a tilt test to people who have a diagnosis of vasovagal syncope on initial assessment.

1.3.2.6 For people with suspected vasovagal syncope with recurrent episodes of TLoC adversely affecting their quality of life, or representing a high risk of injury, consider a tilt test to assess whether the syncope is accompanied by a severe cardioinhibitory response (usually asystole).

1.3.2.7 For people with suspected carotid sinus syncope and for people with unexplained syncope who are aged 60 years or older, offer carotid sinus massage as a first-line investigation. This should be conducted in a controlled environment, with ECG recording, and with resuscitation equipment and a skilled team immediately available.

1.3.2.8 Diagnose carotid sinus syncope if carotid sinus massage reproduces syncope due to marked bradycardia/asystole and/or marked hypotension. Do not diagnose carotid sinus syncope if carotid sinus massage causes asymptomatic transient bradycardia or hypotension (see recommendation 1.3.2.9).

1.3.2.9 For all people with unexplained syncope (including after negative carotid sinus massage test in those for whom this is appropriate), offer ambulatory ECG (see recommendation 1.3.2.4). Do not offer a tilt test before the ambulatory ECG.

1.3.2.10 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[1] follow-up (data interrogation of the device) after they have any further TLoC.

1.4 If the cause of TLoC remains uncertain

1.4.1.1 If after further assessment the cause of TLoC remains uncertain or the person has not responded to treatment, consider other causes including the possibility that more than one pathology may co-exist (for example, ictal arrhythmias).

1.4.1.2 If a person has persistent TLoC, consider psychogenic non-epileptic seizures (PNES) or psychogenic syncope if, for example:

- the nature of the event changes over time
- there are multiple unexplained physical symptoms
- there are unusually prolonged events.

The distinction between epilepsy and non-epileptic seizures is complex; therefore refer for neurological assessment if either PNES or psychogenic syncope is suspected.

1.4.1.3 Advise people who have experienced TLoC to try to record any future events (for example, a video recording or a detailed witness account of the event), particularly if the diagnosis is unclear or taking a history is difficult.

1.5 Information for people with TLoC

1.5.1 General information

1.5.1.1 When communicating with the person who had TLoC, clearly explain:

- the possible causes of their TLoC
- test results and the need for any further investigations
- and discuss the nature and extent of uncertainty in the diagnosis.

1.5.2 Driving

1.5.2.1 Give advice about eligibility to drive when a person first presents with TLoC[2].

[1] The timing of the follow-up is dependent on the storage on the device and the condition of the person.

1.5.2.2 Advise all people who have experienced TLoC that they must not drive while waiting for a specialist assessment. Following specialist assessment, the healthcare professional should advise the person of their obligations regarding reporting the TLoC event to the Driver and Vehicle Licensing Agency (DVLA)[2].

1.5.3 Health and safety at work

1.5.3.1 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 that of other people[3].

1.5.4 Safety advice for people who have had TLoC

1.5.4.1 For people with an uncomplicated faint (uncomplicated vasovagal syncope) or situational syncope:

- explain the mechanisms causing their syncope
- advise on possible trigger events, and strategies for avoiding them. If the trigger events are unclear, advise people 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
- reassure them that their prognosis is good
- advise them to consult their GP if they experience further TLoC, particularly if this differs from their recent episode.

1.5.4.2 For people with orthostatic hypotension:

- explain the mechanisms causing their syncope
- discuss and review possible causes, especially drug therapy
- discuss the prognostic implications and treatment options available
- advise people what to do if they experience another TLoC.

1.5.4.3 Advise people waiting for a specialist cardiovascular assessment:

- what they should do if they have another event

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[2] Please refer to the DVLA for further information at www.dft.gov.uk/dvla/medical/medical_advisory_information/medicaladvisory_meetings/pmembers_nervous_system.aspx

[3] Please refer to 'Health and Safety at Work etc Act 1974' available at www.hse.gov.uk/legislation/hswa.htm

- if appropriate, how they should modify their activity (for example, by avoiding physical exertion if relevant) and not to drive[4].

1.5.4.4 Offer advice to people waiting for specialist neurological assessment for their TLoC as recommended in 'The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care' (NICE clinical guideline 20).

CARE PATHWAYS

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[4] Please refer to the DVLA for further information at www.dft.gov.uk/dvla/medical/medical_advisory_information/medicaladvisory_meetings/pmembers_nervous_system.aspx

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. Record details about:

- circumstances of the event
- person's posture immediately before loss of consciousness
- prodromal symptoms (such as sweating or feeling warm/hot)
- appearance (for example, whether eyes were open or shut) and colour of the person during the event
- presence or absence of movement during the event (for example: limb-jerking and its duration)
- any tongue-biting (record whether the side or the tip of the tongue was bitten)
- injury occurring during the event, (record site and severity)
- duration of the event (onset to regaining consciousness)
- presence or absence of confusion during the recovery period

Box B

If an automated interpretation is not available, the unreported 12-lead ECG should be reviewed by a healthcare professional trained and competent in identifying the following abnormalities.

- Inappropriate persistent bradycardia.
- Any ventricular arrhythmia (including ventricular ectopic beats).
- Long QT (corrected QT > 450 ms) and short QT (corrected 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.

Box C

- ECG abnormality (as specified in Box B)
- Heart failure (history or physical signs)
- TLoC during exertion
- Family history of sudden cardiac death under 40 years and/or inherited cardiac condition
- New or unexplained breathlessness
- Heart murmur

Consider referring within 24 hours for cardiovascular assessment , as above, anyone aged older than 65 years who has experienced TLoC without prodromal symptoms.

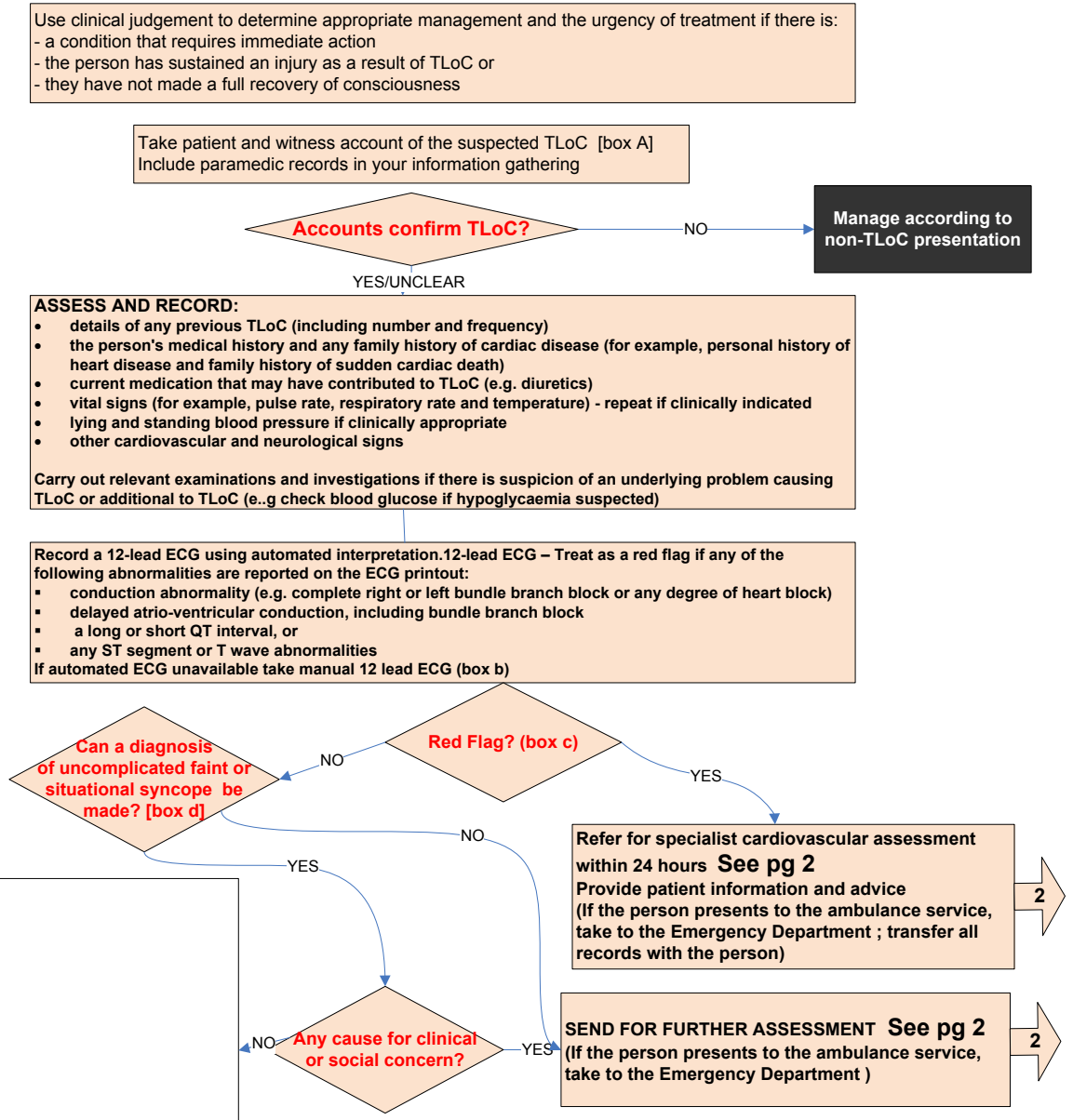
Box D

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

- There are no features that suggest an alternative diagnosis ……..AND
- there are features suggestive of uncomplicated faint such as;
  - Posture - prolonged standing or similar episodes which have been prevented by lying down.
  - Provoking factors (such as pain or a medical procedure).
  - Prodromal symptoms (such as sweating or feeling warm/hot before TLoC).

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 straining during micturition (usually while standing) or by coughing or swallowing.



Further Assessment and Referral

Suspected orthostatic hypotension on the basis of the initial assessment when:
- there are no features suggesting an alternative diagnosis, and
- the history is typical

Yes

Measure lying and standing blood pressure (with repeated measurements whilst standing for 3 minutes)

Orthostatic hypotension is confirmed?

NO

YES

If orthostatic hypotension is confirmed, consider likely causes, including drug therapy, and 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]).

Refer all people with TLoC (apart from the exceptions below) for a specialist cardiovascular assessment by the most appropriate local service. Exceptions are:
people with a firm diagnosis after the initial assessment of:
- **uncomplicated faint**
- **situational syncope**
- **orthostatic hypotension**

and people whose presentation is strongly suggestive of epileptic seizures.

Advise people waiting for specialist cardiovascular assessment.
- **What they should do if they have another event.**
- **If appropriate, how they should modify their activity (for example, by avoiding physical exertion)**
- **They should not drive prior to seeing cardiovascular assessment**

Suspected epilepsy - 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 2 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.
- Head-turning to one side during TLoC.
- No memory of abnormal behaviour witnessed by someone else,
- Unusual posturing
- Prolonged limb jerking (note that brief seizure-like activity can often occur during uncomplicated faints)
- Confusion following the event.
- Prodromal déjà vu or jamais vu (see glossary)

Consider that the episode may not be related to epilepsy if any of the following
- Prodromal symptoms which on other occasions have been abolished by sitting or lying down.
- Sweating.
- Prolonged standing that appeared to precipitate TLoC
- Pallor during the episode

- **EEG should not be used routinely in the investigation of TLoC [see CG20]**
- **Offer advice to people waiting for a specialist neurological assessment for their TLoC [see CG20]**

Specialist cardiovascular assessment

HISTORY AND EXAMINATION
Carry out a specialist cardiovascular assessment as follows.
- Reassess the person's:
  - detailed history of TLoC including any previous events
  - medical history and any family history of cardiac disease or inherited cardiac condition
  - drug therapy at the time of TLoC and any subsequent changes.
- Conduct a clinical examination, including full cardiovascular examination and, if clinically appropriate, measurement of lying 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 causes of syncope:
- suspected structural heart disease
- suspected cardiac arrhythmic
- suspected neurally mediated, or
- unexplained.

Offer further testing **see page 3** or other tests as clinically appropriate.

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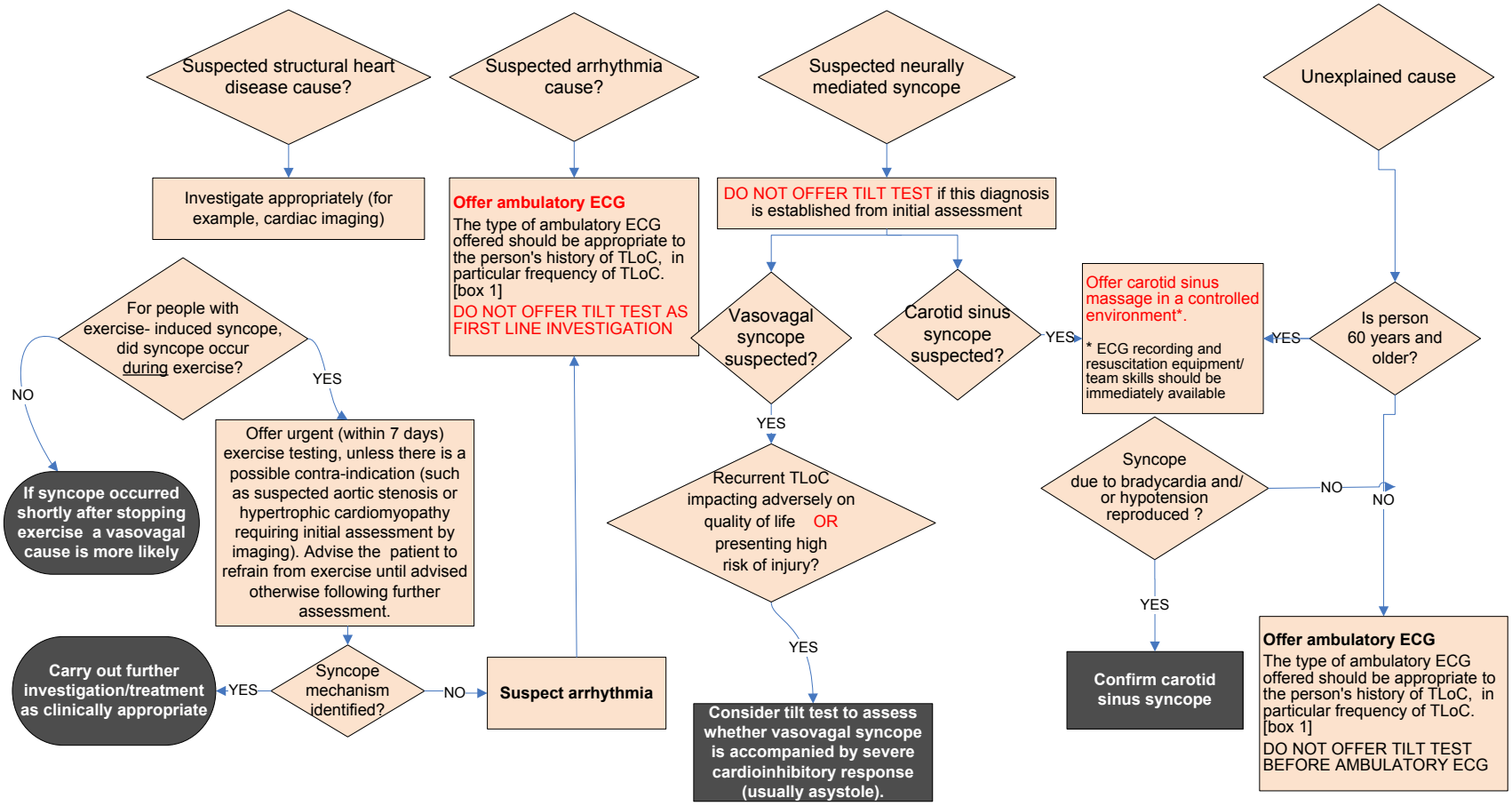


BOX 1
For people who have:

- TLoC at least several times a week, 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.
- 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.
- TLoC infrequently,(less than once 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** follow-up (data interrogation of the device) after they have any further TLoC.
**The timing of the follow-up is dependent on the storage on the device and the condition of the person.

If the cause remains uncertain or the person has not responded to treatment

- Consider other causes of TLoC, including the possibility that more than one pathology may co-exist, for example Ictal arrythmias
- Consider PNES or Psychogenic syncope if a person has persistent TLoC and if, for example,
  - the nature of the event changes over time
  - there are multiple unexplained physical symptoms
  - there are unusually prolonged events

  Refer for neurological assessment

Advise people who have experienced TLoC to try to record any future events (for example, a video recording or a detailed witness account of the event) particularly if the diagnosis is unclear or taking a history is difficult

1

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

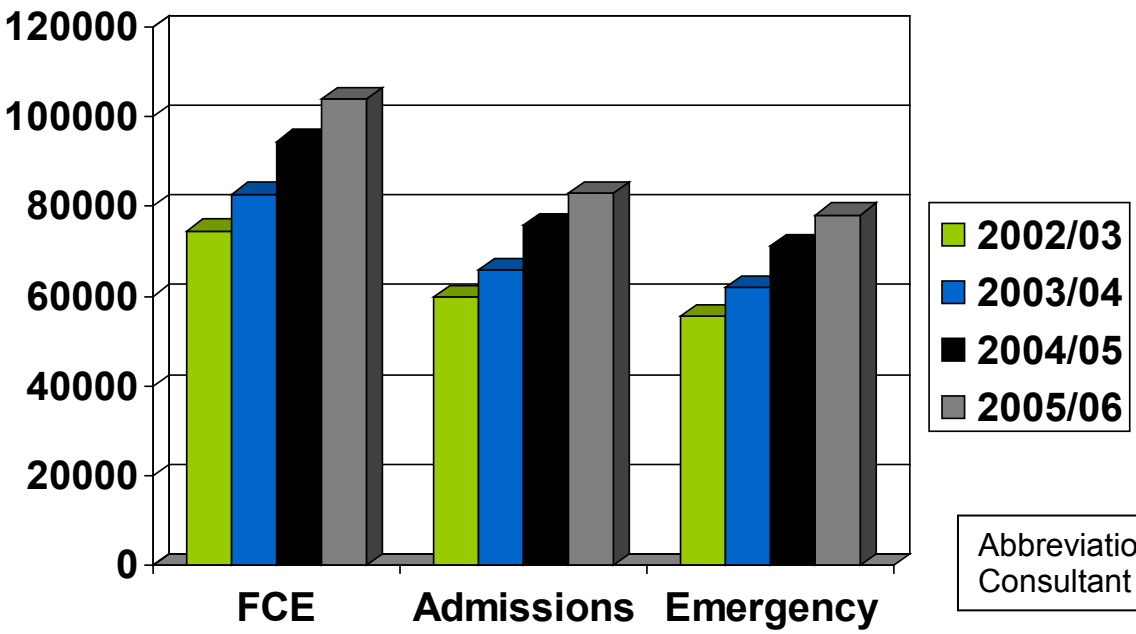
LV Dysfunction: included the following specific codes: I25.5 Ischemic cardiomyopathy, I42.0 Dilated cardiomyopathy, I50.0 Congestive heart failure

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

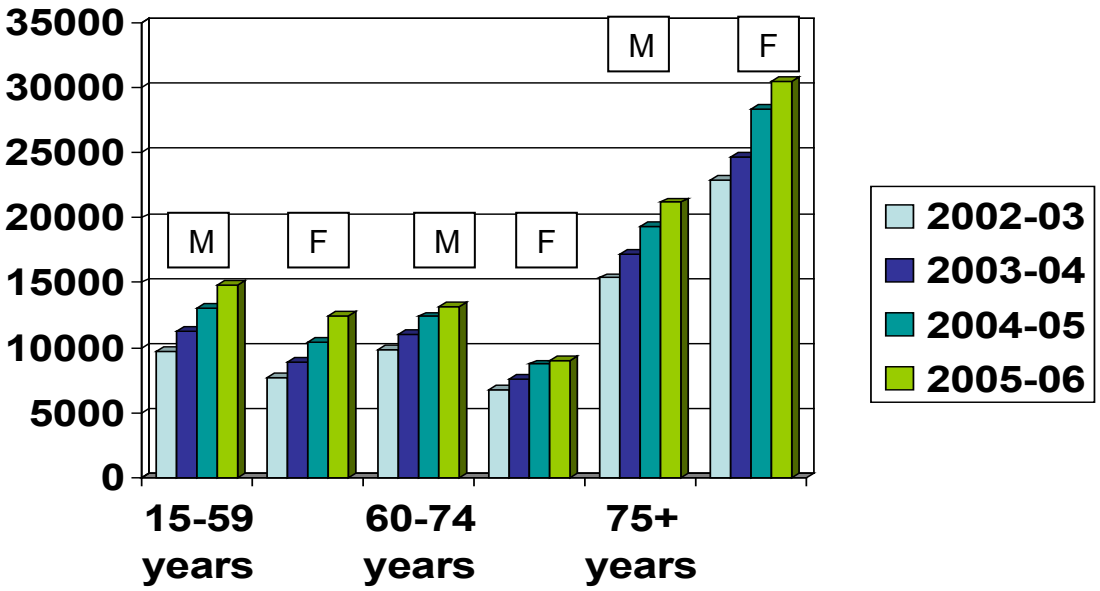


Year	Finished Consultant Episodes	Admissions	Emergency	Mean length of stay (days)	Median Episode Duration (days)	Mean Age (years)
2005/06	103825 (↑ 39%*)	82999 (↑ 38.6%*)	78146 (↑ 40.4%*)	3.9 (↓ 36%*)	1	67
2004/05	94486	75850	71311	4.6	1	68
2003/04	82773	65986	61982	5.5	2	68
2002/03	74576	59851	55651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

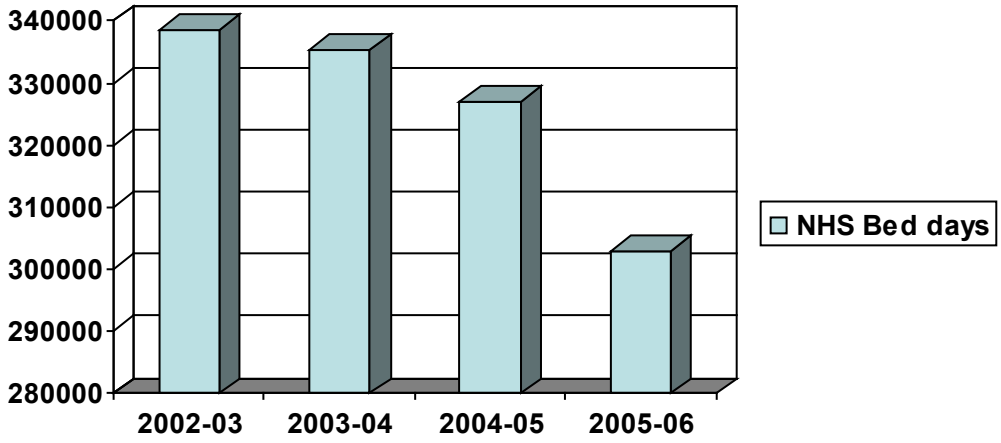


Abbreviations: M=Male, F=Female

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

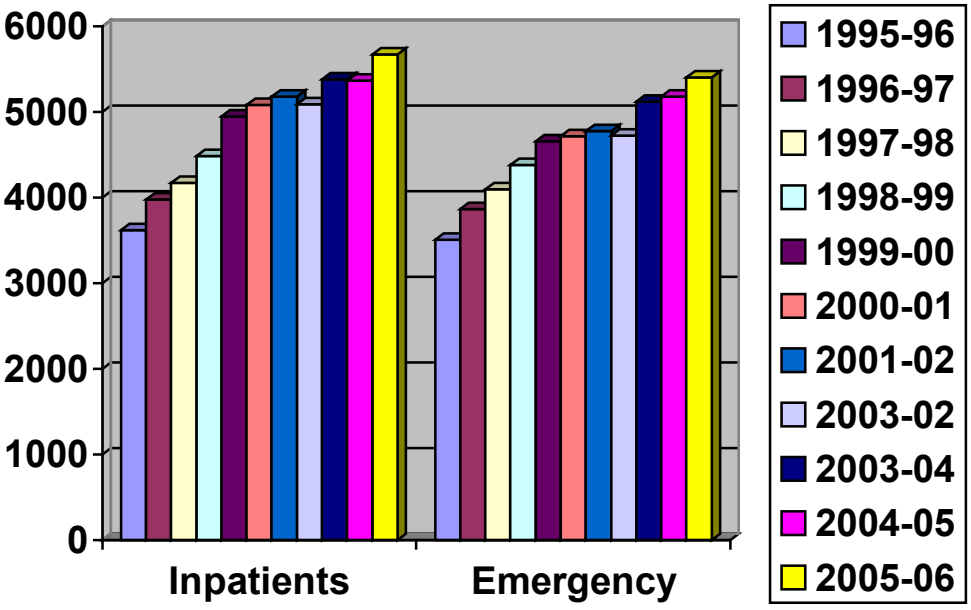
*relative to year 2002/03

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%).



1 The number of bed days used for this condition has decreased over the period
2 2002-2006 as a result of the decrease in the mean length of stay and the
3 median episode duration.

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



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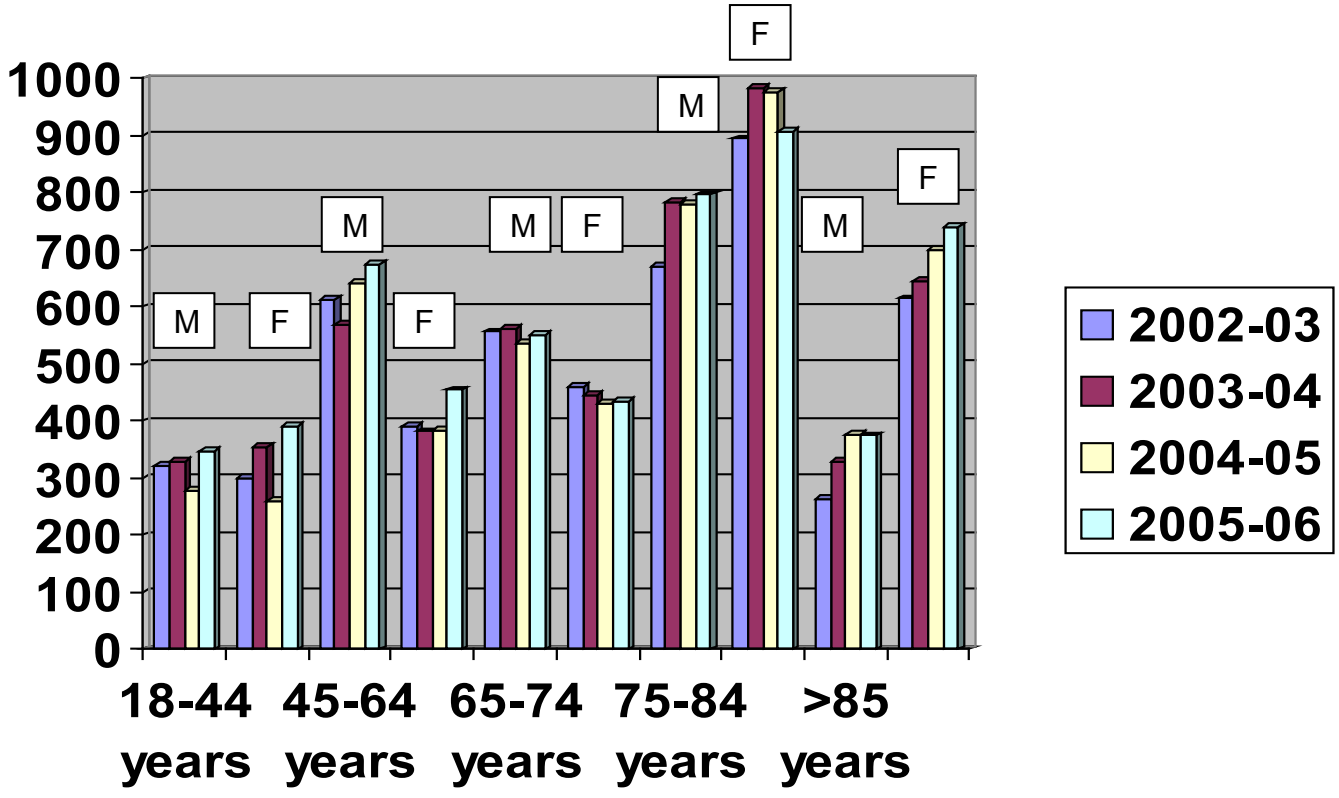
Year	Inpatient Episodes	Emergency	Mean length of stay (days)
2005/06	5671 (↑ 36.2%*)	5398 (95.2%)	7.3
2004/05	5361	5174 (96.5%)	7.8
2003/04	5380	5120 (95.2%)	7.3
2002/03	5088	4720 (92.8%)	6.8
2001/02	5177	4777 (92.3%)	6.8
2000/01	5080	4716 (92.8%)	7.2
1999/00	4948	4653 (94.0%)	8.0
1998/99	4481	4381(97.8%)	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.

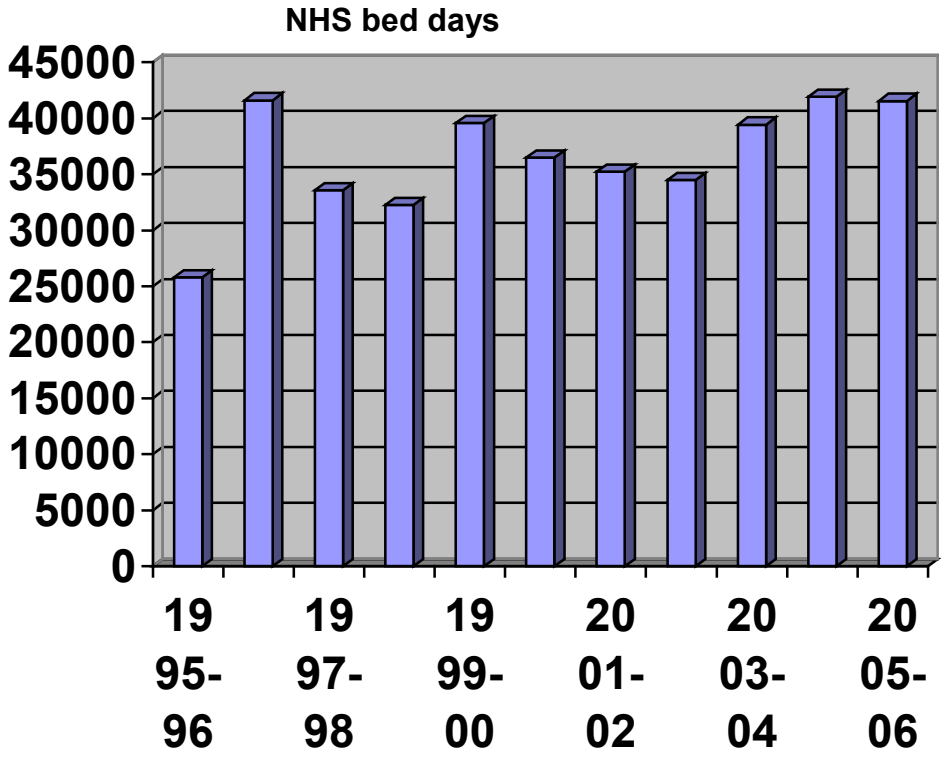
Year	Finished Consultant Episodes	18-44 years	45-64 years	65-74 years	75-84 years	>85 years
2005/06	5671 (↑ 36.2%*)	738 (↑ 30.8%*)	1130 (↑ 5.7%*)	985 (↑18.6%*)	1704 (↑40.5%*)	1114 (↑49.5%*)
2004/05	5361	538	1028	966	1754	1075
2003/04	5380	682	951	1008	1766	973
2002/03	5088	622	1004	1018	1566	878
2001/02	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



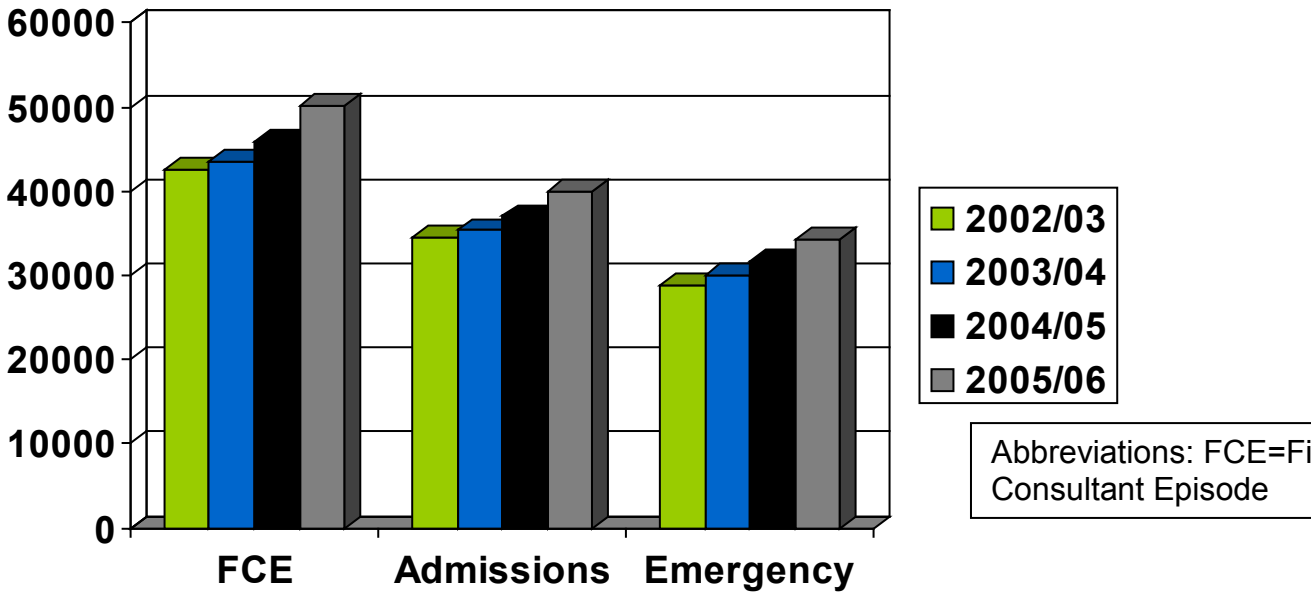
2 Unlike the data available for England, more detailed age-specific data were
3 available for Wales. These data show that the number of patients presenting
4 with R55 Syncope and Collapse (ICD 10) has increased across all age groups

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

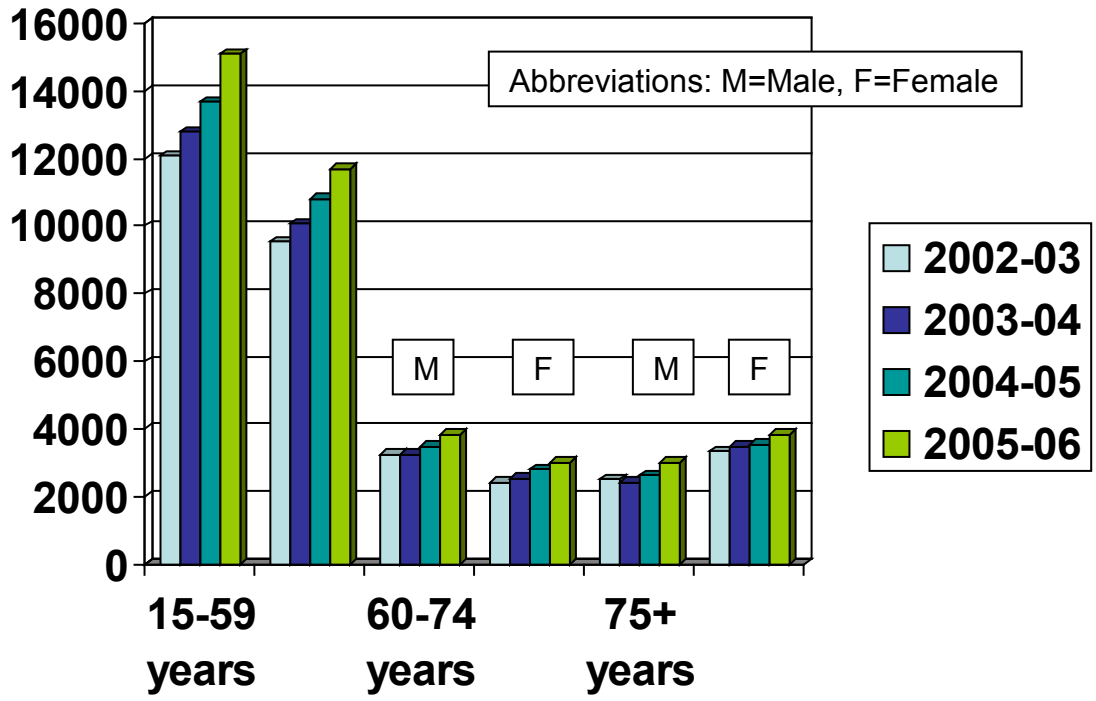


Year	Finished Consultant Episodes	Admissions	Emergency	Mean length of stay (days)	Median Episode Duration (days)	Mean Age (years)
2005/06	50112 (↑15.2%*)	39871 (↑13.3%*)	34226 (↑15.8%*)	5.0 (↓12.3%*)	1	42
2004/05	45811	36984	31722	5.5	1	41
2003/04	43453	35327	29989	5.5	2	41
2002/03	42473	34580	28818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



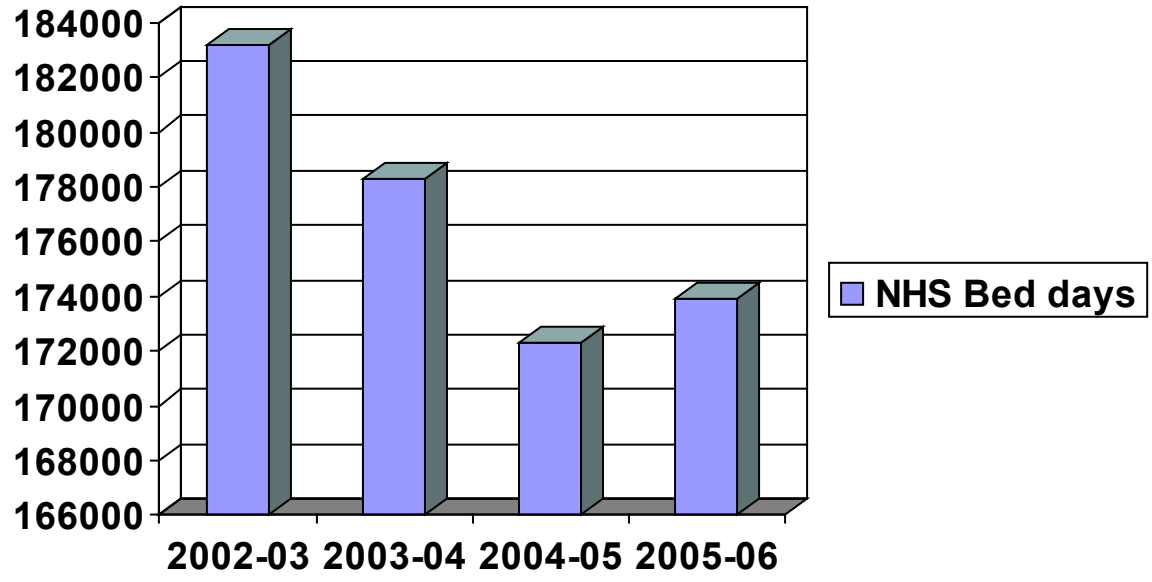
(42 years versus 67 years) than patients with R55 Syncope and Collapse. There has been a slight increase in the mean age of the patients with epilepsy over the corresponding period from 40 years to 42 years.

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.

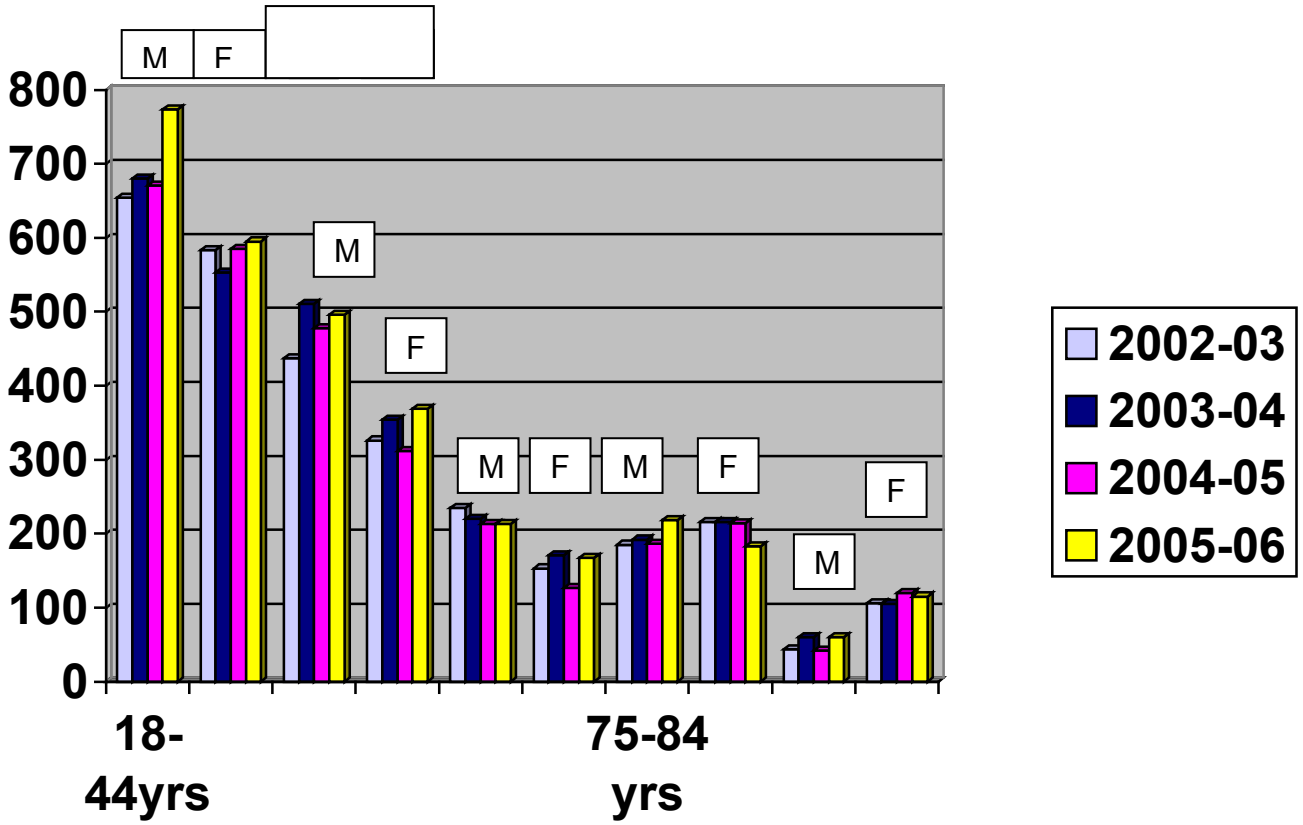


Similar to the trend observed with R55 Syncope and Collapse, overall, between the years 2002 and 2006, there has been a downward trend in the number of NHS bed days, driven by the decrease in the mean length of stay and the median episode duration.

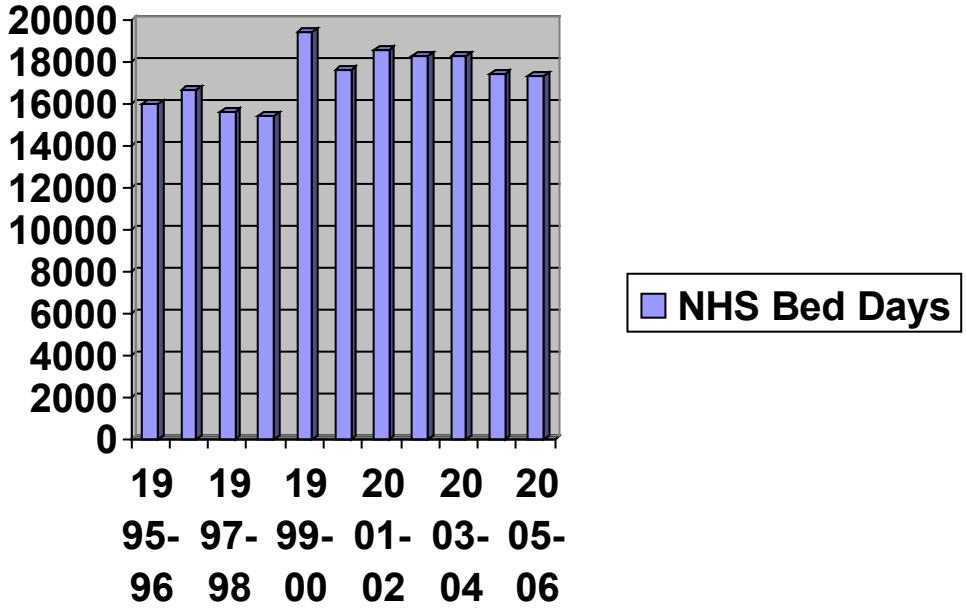
(d) G40 Epilepsy and R56.8 Other and unspecified convulsions (ICD-10) – data for Wales

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.

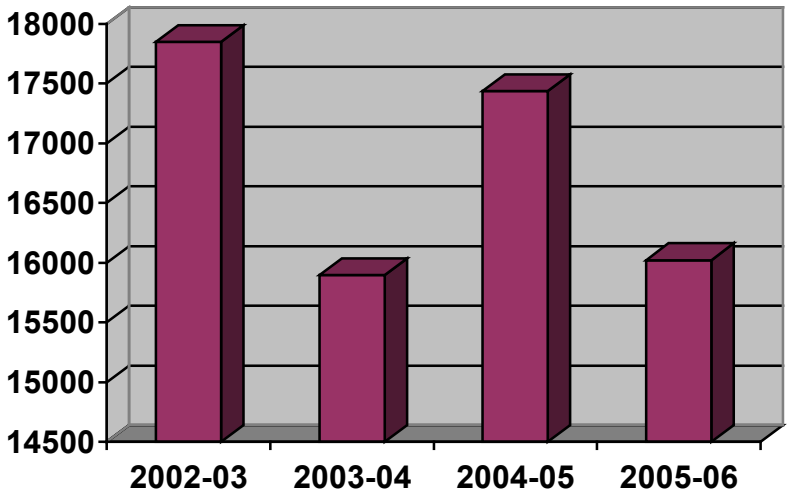
(e) F44 Dissociative disorders (ICD 10) – Data for England

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%)	849 (0.12%)	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

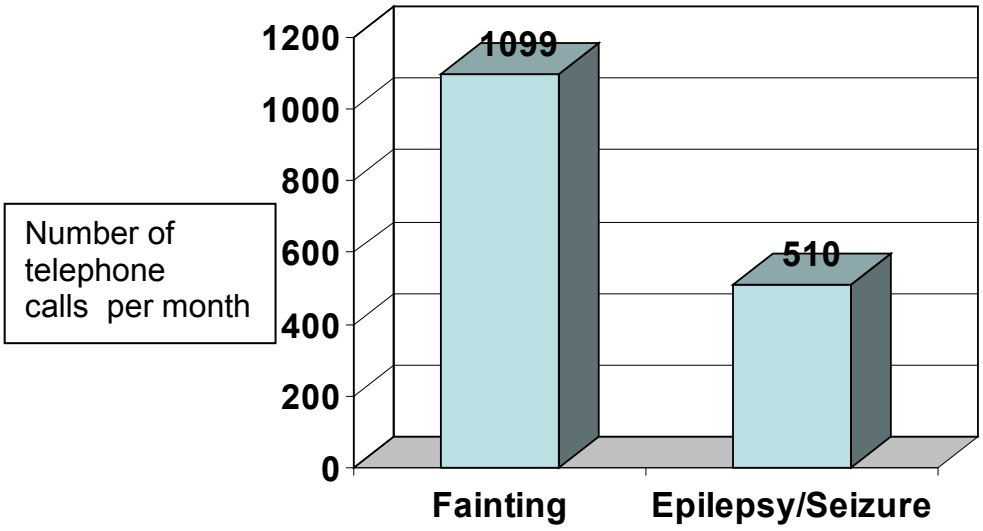
make decisions about their healthcare and that of their families'. It is estimated that over 2 million people use NHS Direct every month. Services are delivered via telephone, through their website and also through the NHS Direct digital television services.

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.

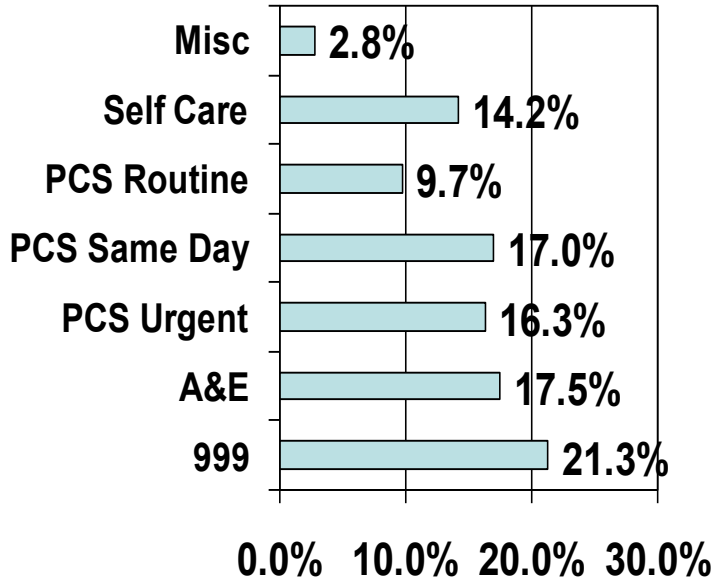
NHS Direct England:
Information on only 'fainting' and 'epilepsy' was available as the term 'syncope' did not fit into their algorithm. Though information for the last 5 years was sought, prior to January 2006, different regions making up NHS Direct England were using different versions of the database 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:

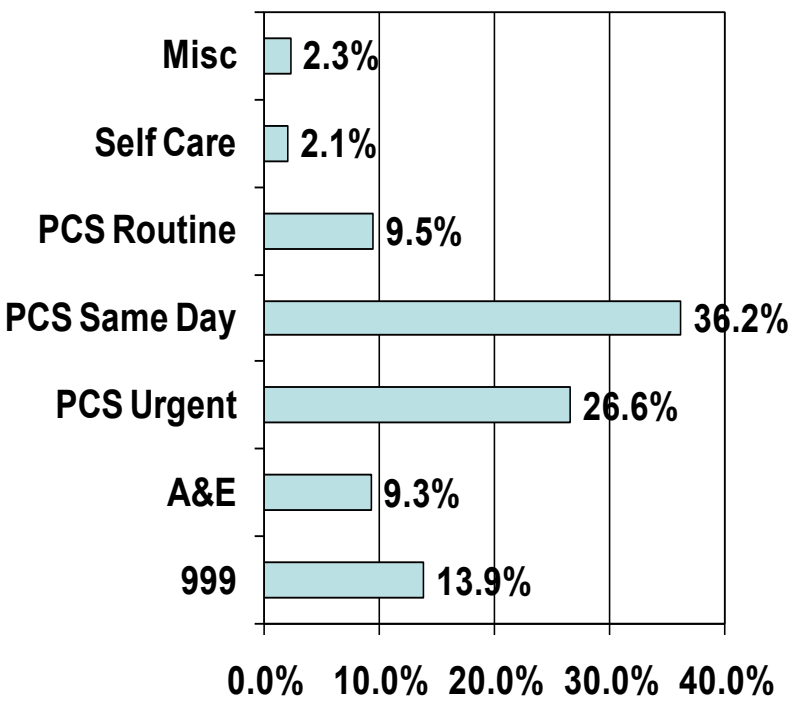
‘Fainting’



Percentage distribution of calls /month for ‘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’:



Percentage distribution of calls /month for ‘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.

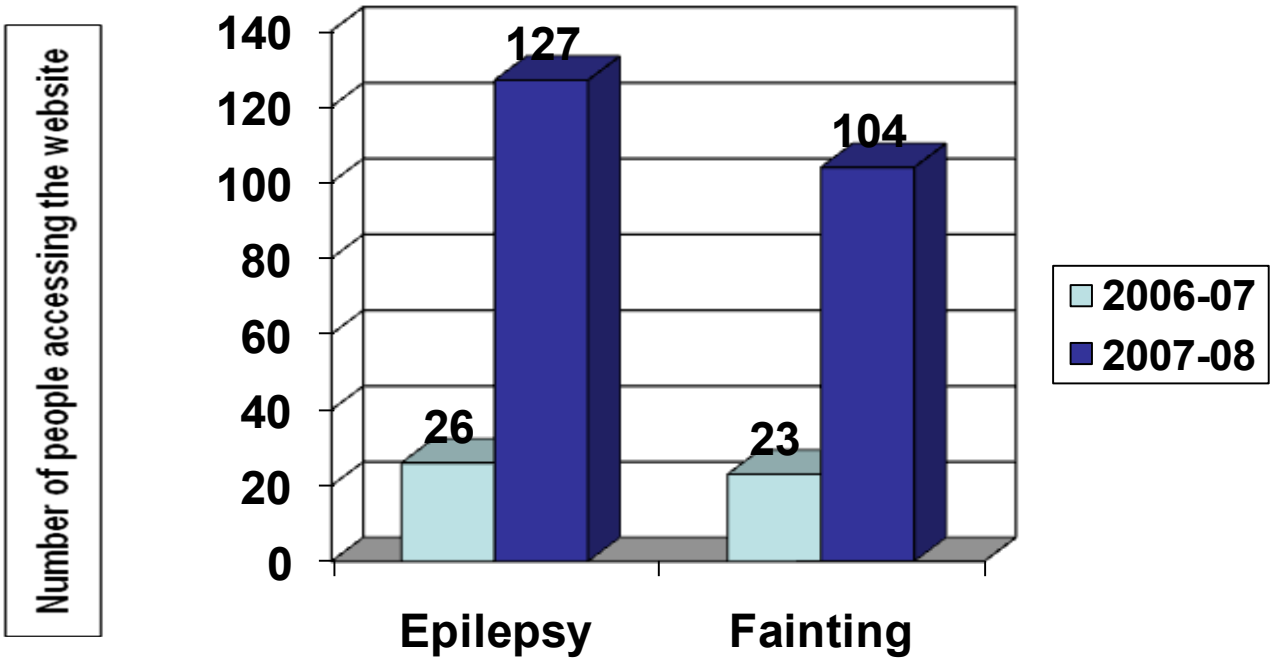
'Epilepsy':

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 hypotension
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 hypotension 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 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. However, some additional papers published post-consultation by stakeholders were included because they affected the recommendations.

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 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 and some of these were checked by a second reviewer.
- 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 there was doubt, 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 much of the extraction was 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. Further details are given in the NICE Guidelines Manual and the Cochrane Handbook for Systematic Reviews of Interventions (http://www.cochrane-handbook.org) :

- 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 TLoC 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 χ^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; unexplained heterogeneous results were summarised using a random effects model.

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

- Methodological quality
- 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, and for which the confidence interval did not cross 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. For many of the studies, the proportion was close to 0 or 1, and for these outcomes it was necessary to calculate asymmetric confidence intervals, rather than using a simple formula for the standard error. We calculated asymmetric confidence intervals for all outcomes and devised graphs to report the proportion with its confidence interval, similar in appearance to forest plots. Any heterogeneity was assessed by inspecting the overlap of confidence intervals.

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. In practice, the two intervention reviews consisted entirely of RCTs, and this is reflected in the discussion below. We note that the intervention reviews were conducted simply to aid interpretation of the diagnostic evidence on specialist assessment tests and not to inform treatment recommendations.

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 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

‡ GRADE – Grading of Recommendations Assessment, Development and Evaluation

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 the pacemaker review (chapter 6), the dichotomous outcome, recurrence of TLoC, one of the included 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. The GDG concurred with this assessment and so a minimum acceptable threshold of RR = 1.5 or 0.5 was set..
- 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. The latter is a ‘rule of thumb’ that is satisfactory for a relative risk reduction (RRR) of 30%

regardless of baseline risk and for a RRR of 25% with a baseline risk above 25%; smaller RRRs require either a high baseline risk or give rise to larger optimum sample sizes. The rule of thumb is derived from the work of Mueller 2007. These criteria appeared to be met for the majority of studies and meta-analyses, but we note that none of them had more than 63 events.

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.

The GRADE scheme was not applied to diagnostic evidence in the guideline because this analytical method is still under development. However, a GRADE-like approach was applied to diagnostic evidence to take account of imprecision, inconsistency, indirectness and study limitations. This is described further in the evidence chapters.

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. While 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 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 subgroup 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 subgroup wished to provide the person with information on what may have caused their TLoC; what they should do while 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 subgroup 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 subgroup 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 subgroup 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 subgroup 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, 1.1.2.3, 1.1.3.3, 1.2.3.1 and 1.3.1.1 were chosen because they are expected to improve care, decrease variation in practice and promote safer practice

Recommendations 1.1.3.4, 1.3.2.5 and 1.3.2.10 were chosen because they are expected to decrease variation in practice, promote safer practice and use resources more effectively

Recommendation 1.3.2.6 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

- Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction. NICE clinical guideline 94. (2010) Available from http://guidance.nice.org.uk/CG94.

Under development

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

- 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 2011.

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. Good-quality trials in people with TLoC are needed to establish whether providing specific information to people with TLoC and their carers helps healthcare professionals to reach a correct diagnosis more quickly and improves outcomes for the patient. The information should address which details of TLoC are required to aid diagnosis. This would also identify those patients who have been inadvertently 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 during the lifetime of a person living 70yrs is estimated to be approximately 42%. The Framingham study[5], 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 quality of interpretation depended 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 published scientific studies are available in a population selected for TLoC. It is therefore recommended that studies be undertaken in adults who had TLoC to assess the accuracy of automatically interpreted ECGs versus those interpreted by experts 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?

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[5] Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ, Levy D. Incidence and prognosis of syncope. N Engl J Med 2002;347:878–885.

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 people 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

NOTE: Please refer to '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 for a more detailed glossary of terms related to epilepsy.

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 feeling or sensation which imediately precedes an episode (*From the Greek, meaning: "A breath of wind")*
Blackout	Sudden and spontaneous transient loss of consciousness with complete recovery. In this context complete recovery would involve full recovery of consciousness without any residual neurological deficit..
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 a bradyarrhythmia (abnormal rhythm with a slow heart rate) or a tachyarrhythmia (abnormal rhythm with a fast heart rate).
Carotid sinus massage	A procedure in which the carotid sinus is stimulated (by firm massage with a thumb during continuous ECG and blood pressure monitoring in both supine and upright positions) to investigate suspected or possible carotid sinus syncope.
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.
Convulsive syncope	Loss of consciousness caused by transient insufficiency of blood supply to the brain accompanied by jerky or posturing movements, generally involving the limbs
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 be a manifestation of a partial seizure" (rather than "occurring immediately before 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, Excludes event recorders that do not perform continuous ECG monitoring (and therefore are not capable of documenting cardiac rhythm at the moment of TLoC).
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.
Implantable event recorder	Small implantable device capable of monitoring and storing ECG recordings of the heart's rhythm. It may also known as an Implantable/Insertable Loop Recorder.
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 89haracterized 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 hypotensive response and/or reflex bradycardic response to a number of causes; this category includes 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.
Psychogenic Non Epileptic Seizure (PNES)	Episodes of altered movement, sensation or experience similar to epilepsy, but caused by a psychological process and not associated with abnormal electrical discharges in the brain.
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.
Red flags	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
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 specific situations (e.g. cough syncope, micturition syncope, swallowing 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
Structural heart disease	Any disease of the heart in which the structural components of the heart are abnormal. This encompasses heart muscle disease, valve disease and congenital heart disease.
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
FCE	Finished Consultant Episode
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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3 Initial assessment and diagnosis of people who 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, neurally mediated or orthostatic hypotension), 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, neurally mediated or orthostatic hypotension), 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, neurally mediated or orthostatic hypotension), 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. A patient profile was shared with the GDG by an actor and four GDG members role-played a consultation. Different approaches to diagnosis were discussed, and the exercise and findings are reported in Appendix D5.

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)
- neurally mediated syncope
- 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 three main categories, cardiac syncope, neurally mediated syncope and orthostatic hypotension (see glossary).

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
- Multivariable 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 multivariable 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 multivariable predictors in the decision rule in one population (derivation cohort) and validate the tool in a second population (validation cohort). We 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 and its 95% confidence interval
- Specificity and its 95% confidence interval
- 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; however, if the confidence interval crossed 1 the findings were not considered to be a good or strong test)
- Pre- and post test probabilities
- Diagnostic odds ratio

3.3.3 Description of studies (Appendix D1)

Twenty-eight reports of 27 studies were included (Alboni 2001; Ammirati 2000; Benbadis 1995; Birnbaum 2008; Colivicchi 2003; Cosgriff 2007; Costantino 2008; Crane 2002; del Rosso 2008; Elseber 2005; Graf 2008; Grossman 2007; Hoefnagels 1991; Quinn 2004; Quinn 2005; Quinn 2006; Quinn 2008; Reed 2007; Reed 2010; Romme 2008; Romme 2009; 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. Two reports (Reed 2010; Romme 2009) were included following stakeholder comments. Both of these were published after the guideline was submitted for consultation, however, the GDG decided to include them because they provided further evidence in an evidence-poor area. The Reed (2007) study was said to be a pilot for the Reed (2010) study, but the former was concerned only with feasibility of recruitment and study method, rather than reporting pilot results. Thus the two Reed studies are independent. The Romme (2009) study states that it used data collected for the van Dijk (2008) study, but aimed to validate the 'Calgary Score' derived in the Sheldon (2006) study. A further study (Costantino 2008) was identified from the reference list of the Romme (2009) study.

3.3.3.1 Study Design

A summary of study design features across studies is given in the table and further details of individual studies in Appendix D1.

Characteristics	Details

Design	• 2 cross sectional studies (del Rosso 2008; Sarasin 2003)
	• 2 case control studies (Sheldon 2002 and 2006)
	  ○ Both excluded patients with more than one plausible cause of TLoC
	  ○ Sheldon (2002) excluded patients with epileptic seizures not supported by EEG
	  ○ Sheldon (2006) included only patients with an apparent absence of structural heart disease and did not analyse patients with no apparent cause of TLoC and a negative tilt test.
	• 3 retrospective cohort, index tests vs follow up (Crane 2002; Elseber 2005; Schladenhaufen 2008); index test results from patient records
	• 1 study for which it is unclear if the decision score was applied retrospectively to prospectively collected data (Romme 2009)
	• The rest were prospective cohort studies.

Design 2	• 12 compared 2 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) • 1 gave 2 tests for different target conditions (del Rosso

	2008).

Country of study	• 3 in the UK (Crane 2002; Reed 2007; Reed 2010) • 11 in USA (Birnbaum 2008; Elseber 2005; Grossman 2007; Quinn 2004; Quinn 2005; Quinn 2006; Quinn 2008; Sarasin 2003 (part); Schladenhaufen 2008; Sun 2007; Sun 2008) • 4 in Italy (Alboni 2001; Colivicchi 2003; Costatino 2008; del Rosso 2008) • 2 in Canada (Sheldon 2002; Sheldon 2006) • 2 each in Switzerland (Graf 2008; Sarasin 2003 (part)) and The Netherlands (Romme 2009; van Dijk 2008). • 1 in Australia (Cosgriff 2007)
Funding and possible conflicts of interest	• 6 had some funding from Medronic (del Rosso 2008; Elseber 2005; Reed 2007; Sheldon 2002; Sheldon 2006; van Dijk 2008) - considered unlikely to be important • 4 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. • 1 gave results for the derivation cohort (Colivicchi 2003).
Sample size	• 2 studies had fewer than 100 patients (Graf 2008 validation cohort, n=65; Reed 2007, n=99). • 9 had more than 500 (Birnbaum 2008; Costantino 2008; Quinn 2004; Quinn 2005; Quinn 2006; Quinn 2008; Reed 2010; Schladenhaufen 2008; Sun 2007; van Dijk 2008) • The rest had between 250 and 500 patients.

3.3.3.2

3.3.3.3 Population

A summary of population characteristics across studies is given in the table below and further details of individual studies in Appendix D1.

Characteristics	Details

Setting	• Majority of studies in the emergency department (ED).
	• 2 in tertiary referral and acute care facilities only (Sheldon 2002 and Sheldon 2006)
	• 2 included patients from neurology, cardiology, internal medicine, cardiac emergency room and ED (Romme 2009; van Dijk 2008).
	• 2 in a syncope unit, to which patients were referred (Alboni 2001; Graf 2008).
	  ○ Patients in Graf (2008) study had unexplained syncope
	  ○ Unclear why patients referred in Alboni (2001).

Prior tests	• 4 studies stated that all the patients had received prior tests (Graf 2008; Sarasin 2003; Sheldon 2002; Sheldon 2006) • 2 reported some patients had prior tests (Romme 2009; van Dijk 2008). • 2 stated that no patients had prior tests (Grossman 2007; Reed 2007) • The remaining studies did not report on prior tests.
Age	• 2 studies also included children (Quinn 2004; Quinn 2006) • 1 study was restricted to people over 65 years (Schladenhaufen 2008) • 2 included adults with a mean age of over 65 years (Cosgriff 2007; Reed 2007 (median) • 4 had a mean age around 65 years (del Rosso 2008; Elseber 2005; Quinn 2008; Reed 2010; Sarasin 2003) • The rest had a mean age under 65 years
Ethnicity	• 3 reported ethnicity (Birnbaum 2008; Sun 2007; Sun 2008) ○ Birnbaum (2008) included 39% Hispanic patients and 38% black patients, and so would not necessarily be representative for the guideline's UK population
.History of heart disease	• 4 studies did not state if there was heart disease (Alboni 2001; Quinn 2006; Quinn 2008; Schladenhaufen 2008); the rest had some patients with heart disease. The proportions in the latter ranged from 8% to 35%.

Type of TLoC

A summary of TLoC details across studies is given in the table below and further details of individual studies in Appendix D1.

Characteristics	Details
Definition	• 7 studies included patients with syncope or near syncope (Birnbaum 2008; Quinn 2004; Quinn 2005; Quinn 2008; Schladenhaufen 2008; Sun 2007; Sun 2008) • The rest did not appear to include pre-syncope
Selection of patients	• The majority of studies included unselected patients presenting to the ED. • Reed (2007) 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. • Crane (2002), had 33% on cardioactive or psychotropic drugs. • Sarasin (2003) included patients who had no clear suspicion of the cause of syncope from initial tests (history, physical examination, blood pressure measurements, 12-lead ECG).
Inclusion of patients with epileptic seizures	• 3 included patients with epileptic seizures o about 2% diagnosed with epilepsy in van Dijk (2008) and 4% in Crane (2002) o Sarasin (2003) reported 9% and 13% patients had seizures or psychiatric diagnoses in the validation and derivation cohorts respectively • 17 excluded patients having epileptic seizures o 7 with a definite seizure (Birnbaum 2008; Cosgriff 2007; Quinn 2004; Quinn 2005; Quinn 2006; Quinn 2008; Sarasin 2003) o 7 with seizures or 'typical seizure presentations' (Costantino 2008; del Rosso 2008; Elseber 2005; Graf 2008; Grossman 2007; Romme 2009; Schladenhaufen 2008) o 2 with a witnessed seizure (Sun 2007; Sun 2008) o 1 with seizure activity with > 15 min witness reported post-ictal phase (Reed 2010) • 6 excluded patients with some types of epileptic seizures o 1 with epileptic seizures not diagnosed by EEG (Sheldon 2002) o 3 with a known seizure disorder (Colivicchi 2003; Crane 2002 (also those with focal neurological signs); Sheldon 2006) o 2 with a history of seizure with a prolonged post-ictal phase (Reed 2007; Reed 2010) • 1 excluded patients from the analysis with a neurological or psychiatric cause (Alboni 2001)

Characteristics	Details

Inclusion of psychogenic pseudosyncope or psychogenic non-epileptic seizures (PNES)	• 5 studies included patients with psychogenic TLoC
	  ○ 1 study had 17% patients with psychogenic pseudosyncope (Graf 2008), 1 had 6% (Romme 2009) and 1 had 3% (van Dijk 2008)
	  ○ 1 reported that 2% patients had a 'psychiatric diagnosis' (Crane 2002)
	  ○ 1 reported 1% patients with neurologic or psychiatric causes of syncope (Alboni 2001) and 1 had 13% (Sarasin 2003)
	• 2 excluded patients with 'pseudoseizures' (PNES; Sheldon 2002; Sheldon 2006);
	• 1 study excluded patients with non-syncopal causes of TLoC (del Rosso 2008)

Previous episodes of TLoC	• 1 study reported that all patients had had at least 1 previous episode (Grossman 2007) • 8 reported that some patients had recurrent TLoC (Alboni 2001; Colivicchi 2003; del Rosso 2008; Elseber 2005; Reed 2010; Romme 2009; Sarasin 2003; van Dijk 2008) ○ Elseber (2005) stated that 19% had at least 2 episodes in the previous month • The rest did not say if the TLoC was recurrent.

3.3.3.4 Index tests and reference standards

A range of index tests was investigated, ranging from aspects of patient history (predictors) to diagnostic algorithms. Additional details of the index tests are given in Appendix D1.

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. Summary descriptions of the index tests and reference standards are given at the start of the appropriate results sections.

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:

- Seventeen studies were considered to have potential for spectrum bias (Alboni 2001; Benbadis 1995; Birnbaum 2008; Cosgriff 2007; Costantino 2008; del Rosso 2008; Graf 2008; Hing 2005; Hoefnagels 1991; Quinn 2004; Quinn 2006; Reed 2007; Romme 2009 (borderline); Sarasin 2003; Schladenhaufen 2008; Sheldon 2002; Sheldon 2006; Sun 2008; van Dijk 2008)
- Selection bias: three studies were case control, with selected groups of patients (Benbadis 1995; Sheldon 2002; Sheldon 2006)
- Three studies were retrospective and therefore considered at risk of bias (Crane 2002; Elseber 2005; Schladenhaufen 2008); one study had a retrospective syncope group (Benbadis 1995); the validation cohort of the Sarasin 2003 study appeared to be retrospectively assessed (carried out 10 years before derivation study)
- Two studies were considered to have inadequate reference standards (Hing 2005; Sheldon 2002)
- Verification bias: in two studies the reference standard was follow up and there were more than 20% missing data, which the GDG considered unacceptable (Cosgriff 2007; del Rosso 2008)
- 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; Romme 2009; van Dijk 2008)
- Partial verification bias: four studies were unclear (Alboni 2001; del Rosso 2008; Graf 2008; van Dijk 2008)
- Incorporation bias: eight studies included the index test as part of the reference standard (Alboni 2001; del Rosso 2008; Elseber 2005; Graf 2008; Hoefnagels 1991; Romme 2009; van Dijk 2008). In three of these,

this referred only to the 12-lead ECG results, and in the other studies 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 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 six studies the reference standard assessors were not blinded because the index test was part of the reference standard (Alboni 2001; Cosgriff 2007; del Rosso 2008; Graf 2008; Hoefnagels 1991; Romme 2009).

Overall, the GDG considered that 24 tests in 15 studies were potentially or at risk of bias (Alboni 2001; Benbadis 1995; Cosgriff 2007; Crane 2002; del Rosso 2008; Elseber 2005; Graf 2008; Hing 2005; Hoefnagels 1991; Reed 2007; Romme 2009 (borderline risk); Sarasin 2003; Schladenhaufen 2008; Sheldon 2002; Sheldon 2006). The three case control studies (Sheldon 2002, 2006 and Benbadis 1995) were considered to be most at risk. These studies were considered in sensitivity analyses.

3.3.5 Evidence for predictive factors for diagnosis

We report the evidence for predictors for one diagnosis over other.

Although some studies reported results for the different types of syncope separately, 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 individual diagnoses. Values were calculated accordingly.

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

Patient history for diagnosis: epileptic seizures versus syncope

Two case control studies (Benbadis 1995 (n=108); Sheldon 2002 (n=270)) and one cohort study (Hoefnagels 1991(n=94)) reported the value of patient history in distinguishing between epileptic seizures and syncope in selected patients.

Sheldon (2002)

- Population – selected (patients were excluded if they had epileptic seizures not diagnosed by EEG, and if they had psychogenic non-epileptic seizures)
- 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
- 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). Patients with an unclear cause of syncope were excluded from the analysis.

- 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)

Benbadis (1995)

- Population: highly selected (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).
- Index tests: tongue biting and lateral tongue biting
- Case control design
- Reference standard: 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.

Hoefnagels 1991

- Population: patients referred to the neurology department (i.e. selected patients, non-seizure patients mainly had vasovagal syncope or hyperventilation)
- Index test: individual signs and symptoms before the event, after the event and during the event (as observed by an eye witness)
- Reference standard was eye witness observations of initial signs and symptoms (described below), that was not changed by follow up and secondary tests (including general and neurological examinations, routine laboratory tests, EEG and ECG; CT scan and 24h cardiac monitoring as

appropriate). It was not stated what was the basis of deciding which signs and symptoms were predictive of seizures, but they were:

- 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 was motionless and later reported an unequivocal aura, such as a strange smell

Firstly, univariate likelihood ratios across studies 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, multivariable 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.

Signs and symptoms that are considered to be good and strong univariate predictors are shown in Table 1 as likelihood ratios with their 95% confidence intervals. Multivariable predictors for and against seizures are shown in Table 2. Full results are recorded in Appendix D3.

We also give an evidence quality rating based on:

- Indirectness: Sheldon (2006) was restricted to patients who had an established diagnosis of TLoC; patients with epilepsy not diagnosed by EEG were excluded. Benbadis (1995) was in highly selected patients from an epilepsy clinic plus syncope patients of known cause. Hoefnagels (1991) included only referrals to a neurology department and the non-seizure patients mainly had vasovagal syncope or hyperventilation.

- Limitations: inadequate reference standard in Sheldon (2002) – reliance on EEG; incorporation bias and review bias (index test as part of the reference standard) in Hoefnagels (1991); selection bias (case control) in Benbadis (1991) and Sheldon (2002)
- Inconsistency between studies is indicated as a footnote
- Imprecision: for likelihood ratios, we defined imprecision as a confidence interval that crossed 5 or 0.2 for stong tests and 3 or 0.3 for a good test. If, for a good test, the lower confidence limit crossed 1 we did not include the study in the table). Imprecision is indicated with one or two asterisks (latter means very imprecise).

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 **low** [1, 7] LR 12.9 (5.4 to 30.8) • Cut tongue during TLoC (all 3 studies) **low** [1, 2, 3, 7] Sheldon LR 16.5 (7.1 - 38.3) Benbadis** LR 17.4 (2.3 - 134) Hoefnagels* (good predictor) LR 7.3 (2.3 - 23.3)Cut tongue lateral during TLoC (Benbadis) **very low** [2, 4, 7] LR 36.4 (2.2 to 613)** • Head turning during TLoC **low** [1,7] LR: 13.5 (6.1 to 29.9)	• History coronary heart disease **very low** [1,4,7] LR 0.08 (0.01 - 0.55)** • TLoC with prolonged sitting or standing **very low** [1,4,7] LR 0.05 (0.01 - 0.35)** But Hoefnagels sitting pre TLoC* & standing* not sig. (**very low**) • Dypsnoea pre-TLoC **very low** [1,4,7] LR 0.08 (0.01 - 0.58)**
Good predictors 5<LR<10 or 0.2>LR>0.1	• Younger age **low** [1, 3, 7] mean difference: Sheldon: -18.0 y (-22.2 to -13.8) Hoefnagels: -16.0 (-24.1 to -7.9) • Limb jerking noted by others during TLoC **low** [1,7] LR 5.6 (3.7 to 8.3) • Blue colour observed by bystander (2 studies) **very low** [1, 3, 4, 5, 7] Sheldon LR 5.7 (2.9 -11.3)* Hoefnagels 16.9 (2.3 -124.1)** • 'Bedwetting' **very low** [1,4,7] Sheldon LR 6.4 (2.8 -14.9)*	• Presyncope with prolonged sitting or standing **very low** [1, 4, 7] LR 0.18 (0.06 to 0.55)* • Diaphoresis pre-TLoC* **very low** [1,3,4,7] Sheldon LR 0.17 (0.06 - 0.52)* Hoefnagels LR 0.07 (0.01- 0.49)** • Palpitations pre-TLoC **very low** [1,4,7] LR 0.12 (0.03 - 0.46)* • Nausea pre-TloC
Key [1] Sheldon 2002 – case control study, patients with non-established diagnoses excluded [2] Benbadis 1995 - case control study, highly selected population [3] Hoefnagels – indirect population (only neurology referrals) [4] Imprecision (one or		

two asterisks) [5] Inconsistency between studies (minor or same direction) [6] Inconsistency between studies (major) [7]study limitations	c.f. Urinary incontinence Hoefnagels (not significant) LR 0.65 (0.29-1.45) • Disoriented post TLoC (patient reported) **very low** [3, 4, 7] Hoefnagels LR 5.4 (2.2 -13.2)* • Disoriented post TLoC (witness reported) **very low** [3, 4, 7] Hoefnagels LR 5.0 (2.7 - 9.2)* NB post-ictal confusion: Sheldon LR 3.0 (2.5-3.7)* **very low** [1, 4, 7] • Long history of TLoC (**low** [1, 7]) median 186 mo (IQR 67 - 352) vs 24 mo (0.33 - 169); p < 0.001 • Large number of previous episodes (**low** [1, 7]): median 168 (IQR 20 -450) vs 3 (IQR 2 to 8); p < 0.001	**very low** [1,3,4,7] Hoefnagels LR 0.09 (0.01-0.63)** Sheldon 0.21 (0.07-0.65) • Remembered loss of consciousness **very low** [1,4,7] LR 0.20 (0.10 - 0.44)*

Additional significant weak univariate predictors for and against epileptic seizures are listed below, together with signs and symptoms with relatively narrow confidence intervals that are neither for nor against seizures. All were of low evidence quality unless otherwise stated.

- **Weak significant univariate predictors for epileptic seizures**: age less than 45 years; TLoC associated with stress; prodromal déjà vu; prodromal trembling; prodromal hallucinations (very low); prodromal preoccupation (very low); observed unresponsiveness; unusual behaviour; cannot remember behaviour; frothing at the mouth; duration of TLoC more than 5 minutes; sleepy post-TLoC; mood changes post-TLoC; muscle pain (2 studies)
- **Weak significant univariate predictors against epileptic seizures**: hypertension; self-reported high blood pressure; chest pain; pre-syncope with hot/warm place; pre-syncope after exercise; pre-syncopal spells; any presyncope; prodromal vertigo pre-TLoC (very low; 2 studies); dimming of vision pre-TLoC (very low); warmth pre-TLoC (very low); pale face during TLoC observed by witness;

- **Non-signficant signs and symptoms, in favour of neither**: concussion in the past; sitting pre-TLoC; standing pre-TLoC; light-headedness pre-TLoC;

Two multivariable analyses were carried out in the Sheldon (2002) study, based on significant univariate predictors at the $p<0.05$ level. Thirty-nine and 37 variables were included, depending on whether symptom burden predictors were included (i.e. the number of spells and the length of the TLoC history); they are listed in Appendix D3. The multivariable analyses were considered to be of low quality, mainly because of the case-control nature of the study, and also because the ratio of patients to covariables was a little low (7). The GDG considered there were no important confounders missing from the variables added to the regression analysis.

Some variables were independent of the model used: loss of consciousness with stress; head turning to one side during TLoC; unresponsiveness during TLoC; any presyncope, LoC with prolonged standing or sitting; diaphoresis before TLoC.

Other variables were sensitive to the model used (with or without symptom burden): waking with a cut tongue; unusual posturing; limb jerking; amnesia for abnormal behaviour; post ictal confusion; prodromal déjà vu (which was also not significant); number of spells more than 30.

Table 2: Multivariable predictors for and against epilepsy

Evidence quality: overall **low** - indirect population (case control, selected patients); limitation – inadequate reference standard (EEG to diagnose epilepsy). Too many variables in the multivariable analysis, but most confounders appear to be taken into consideration.

Predictors for epilepsy (OR > 1) and predictors against epilepsy (OR<1) Model 1 (without symptom burden)	**Predictors for epilepsy (OR > 1) and against epilepsy (OR<1)** Model 2 (with symptom burden)

• Waking with a cut tongue OR 944 [95%CI 18 to 50,400] • Abnormal behaviour noted (one or more of: witnessed amnesia for abnormal behaviour, witnessed unresponsiveness, unusual posturing, limb jerking) OR 45.6 [95%CI 3.1 to 670] • Loss of consciousness with emotional stress OR 53.0 [95%CI 4.2 to 677] • Post-ictal confusion OR 33.8 [95%CI 2.5 to 460] • Head turning to one side during LoC OR 39.3 [95%CI 2.4 to 650] • Prodromal déjà vu or jamais vu OR 15.6 [95%CI 0.95 to 258], i.e. not significant • Any presyncope OR 0.01 [95%CI 0.00 to 0.13] • LoC with prolonged standing or sitting OR 0.00 [95%CI 0.00 to 0.13] • Diaphoresis before TLoC OR 0.00 [95%CI 0.00 to 0.11]	• Unresponsiveness during TLoC OR 48.9 [5.8 to 414] • Loss of consciousness with stress OR 113 [6.9 to1870] • Head turning to one side during LoC OR 95.6 [2.6 to 3520] • Number of spells > 30 OR 36.6 [5.0 to 270] • Any presyncope OR 0.01 [0.00 to 0.10] • LoC with prolonged standing or sitting OR 0.00 [0.00, 0.04] • Diaphoresis before LoC OR 0.07 [0.01 to 0.76]

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A2. Patient history initial evaluation decision rules for diagnosis of epilepsy (Sheldon 2002; van Dijk 2008)

Two studies evaluated decision rules for the diagnosis of epilepsy (Sheldon 2002; van Dijk 2008).

Sheldon (2002) rules

- Population – selected, half the cohort in the study was used for validation of the rules
- 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 multivariable 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; **Rule 2** in the presence of this knowledge.
- 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 (A1) above)

Rule 1 (no knowledge of symptom burden): scores	Rule 2 (knowledge of symptom burden: scores
• waking with a cut tongue (+2)	• head turning to one side during TLoC (+2)
• abnormal behaviour noted (one or more of: witnessed amnesia for abnormal behaviour, witnessed unresponsiveness, unusual posturing or limb jerking) (+1)	• more than 30 episodes of TLoC (+1)
• TLoC with emotional stress (+1)	• unresponsiveness during TLoC (+1)
• postictal confusion (+1)	
• head turning to one side during TLoC (+1)	
• prodromal déjà vu or jamais vu (+1)	
• any presyncope (-2)	• diaphoresis (sweating) before TLoC (-1)
• TLoC with prolonged standing or sitting (-2)	• any presyncope (-2)
• diaphoresis (sweating) before TLoC (-2)	• loss of consciousness with prolonged standing or sitting (-3)
Patients classified as having a seizure if the total points score is 1 or more	Patients are classified as having a seizure if the total points score is 0 or more

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van Dijk (2008)

- Population – unselected (several hospital departments)
- Index test – initial assessment based on ESC guidelines for people predicted to be 'certain' or 'highly likely' to have epilepsy.
  - van Dijk (2008) did not give 'certain' and 'highly likely' definitions of epilepsy, and neither did the ESC guidelines from 2004 (appropriate for this study), but the latter states the following features to distinguish seizures from syncope; these appear to have been derived from the Hoefnagels (1991) study:
    - ◊ tonic-clonic movements usually prolonged and onset coincides with LoC

- ◊ automatism (chewing or lip smacking or frothing at the mouth) during LoC
- ◊ tongue-biting during LoC
- ◊ blue face during LoC
- ◊ epileptic aura pre-event
- ◊ prolonged confusion post-TLoC
- ◊ aching muscles post-TLoC

- Reference standard – two year follow up outcomes, initial evaluation and additional diagnostic tests (e.g. EEG and CT)

The Sheldon (2002) study reported the predictive ability of the two decision rules as ROC curves, giving pairs of sensitivity and specificity at particular 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% (95%CI 89 to 97) 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 92% (95%CI 86 to 96) and a specificity of 83% (95%CI 75 to 89) 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 * indicates imprecision					
Study	**Sens (%)**	**Spec (%)**	**LR+**	**LR-**	**Diag Yield (%)**
Sheldon 2002 Initial symptoms decision rule Rule 1 symptoms only Evidence quality: **low** (case control; inadequate reference standard)	94 (89-97)	94 (89-97)	16 (8-31)	0.06 (0.03-0.12)	50
Sheldon 2002 Initial symptoms decision rule Rule 2 symptoms + TLoC history Test operator: investigator Evidence quality: **low** (case control, inadequate reference standard)	92 (86-96)	83 (75-89)	5.3 (3.6-7.7)	0.09 (0.05-0.17	57
van Dijk 2008 Initial evaluation based on ESC guidelines; certain and highly likely Test operator: attending physician Evidence quality: **low** (index test unclear, but part of reference standard; some imprecision (*))	73* (39 - 94)	100 (99-100)	179 (43-747)	0.27* (0.10-0.72)	2

The evidence quality for the Sheldon (2002) decision rules is low and we note that these rules are likely to overestimate the sensitivity and specificity because they were validated in a case control study. The evidence quality for the van Dijk (2008) study was considered to be moderate.The diagnostic yield is very low in the van Dijk (2008) study.

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

3.3.5.2 *Patient history, physical examination, tests and decision rules for diagnosis of vasovagal syncope*

Patient history for the diagnosis of vasovagal syncope versus other types of syncope (Alboni 2001; Graf 2008; Romme 2009; Sheldon 2006)

One case control study (Sheldon 2006 (n=323)) and three prospective cohort studies (Alboni 2001 (n=337); Graf 2008 (n=212); Romme 2009 (n=380)) reported the value of patient history in distinguishing between vasovagal syncope and other types of syncope in selected patients. All of the studies excluded patients with seizures to some degree: Sheldon (2006) and Romme (2009) excluded those with known epilepsy; Graf (2008) excluded those with seizures and Alboni (2001) excluded those with a neurological or psychiatric cause.

- Population - all the studies had selected patients
  - The Graf (2008) study was in people with unexplained syncope referred to a syncope clinic. It combined the results for people diagnosed with vasovagal syncope (23%) and psychogenic pseudosyncope (17%); the remaining patients had 9% cardiac syncope (7% tachyarrhythmia, 2% AV block); 3% orthostatic hypotension; 2% miscellaneous; 21% unexplained syncope
  - 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. The remaining patients were: 56% tilt positive with no other diagnosis; 23% tilt negative with no other diagnosis and 21% with cardiac syncope or other NM syncope (complete heart block, SVT, idiopathic VT, aortic stenosis, Torsade-de-Pointe, VT, cough syncope, hypertensive carotid sinus syncope)
  - The Alboni (2001) study reported on neurally mediated syncope (58%) - which comprised 10% ‘typical vasovagal’, 47% tilt-induced; 13% situational, 24% carotid sinus; 3% OHT; 3.5% adenosine sensitive syncope - cardiac syncope (23%); unexplained syncope (18%) and neurological / psychiatric syncope (1%).

- The Romme (2009) study sought to investigate the rule derived in the Sheldon (2006) study, and, although Romme (2009) was not a case control study, in order to compare with Sheldon (2006), this study excluded 11% patients with a history of cardiomyopathy or myocardial infarction; 4% with epileptic seizures; and 11% with an unknown cause of syncope after 2 years. This left 55% with vasovagal syncope, 11% with other forms of NM syncope, 12% with orthostatic hypotension; 7% with cardiac syncope, and 6% with psychogenic pseudosyncope.

- 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
- Study design varied:
  - Case control design
    - ◊ Vasovagal syncope (tilt positive) versus 'Secondary causes' (84% cardiac) (Sheldon 2006)
  - Cohort studies
    - ◊ Neurally mediated (NM) syncope versus non-NM syncope in patients referred to a syncope unit (Alboni 2001)
    - ◊ Vasovagal syncope plus psychogenic pseudosyncope (Psy) versus other syncope in patients referred to a syncope clinic for unexplained syncope (Graf 2008)
    - ◊ Vasovagal syncope versus non-vasovagal syncope in a subset (380/503) of patients presenting to neurology, cardiology, internal medicine, cardiac emergency room (up to 100 each) and the ED to (22%). Patients (25%) were excluded if they had a history of

cardiomyopathy or myocardial infarction, epileptic seizures, or no diagnosis after 2 years (Romme 2009)

- Reference standard
  - Diagnosis following secondary tests
    - ◊ Initial evaluation plus other tests (unspecified) (Alboni 2001)
    - ◊ Positive tilt test for vasovagal syncope 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)
    - ◊ Additional tests (echocardiography, 24h Holter monitoring, exercise test, tilt test, carotid sinus massage) or treatment. Final diagnosis using these and ESC criteria plus expert panel if disagreement (Romme 2009)

Signs and symptoms that are considered to be good and strong univariate predictors are shown in Table 4. We also give an evidence quality rating based on:

- Indirectness: Sheldon (2006) was in patients who do not have structural heart disease or unexplained syncope. Graf (2008) and Alboni (2001) had indirect target conditions: respectively, vasovagal syncope or psychogenic pseudosyncope, and neurally mediated syncope.
- Limitations: incorporation bias (index test as part of the reference standard) in Alboni (2001); Graf (2008) and Romme (2009); selection bias (case control) in Sheldon (2006) and to a small extent in Romme (2009)
- Inconsistency between studies is indicated as a footnote with possible explanations.
- Imprecision is defined as described in section 3.3.5.1.

1 Detailed results are reported in Appendix D3.

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

Strength of test	Predictors for vasovagal syncope	Predictors against vasovagal syncope
Strong predictors LR > 10; LR < 0.1	• Mood changes or preoccupation pre-TLoC **very low** [1, 4, 7] LR 10.7 (2.7 - 42.8)** • Paresthesia **very low** [2, 4, 7] LR 13.5 (4.9 - 36.9)*	• Any 1 of bifascicular block, asystole, SVT, diabetes **very low** [1, 6, 7] Sheldon[1, 7] LR 0.05 (0.03 - 0.11)) Romme[7] LR 0.57 (0.36 - 0.88)
Good predictors 5<LR<10 or 0.2>LR>0.1	• Age below 35 years (or low age)* predicted by all 4 studies **very low** [1, 2, 3, 6, 7] Sheldon[1, 7]; LR 8.0 (4.1 - 15.5)) Romme[7] LR 2.7 (1.9 - 3.7). • Longer history of TLoC (Sheldon) **low** [1, 7] • Warm place **very low** [1, 3, 6, 7] Sheldon: LR 6.0 (3.1 to 11.8) Alboni (NM) non-significant LR 1.6 (0.6 - 4.1) • With pain or medical procedure **low** [1, 5, 7] Sheldon[1,7] LR 8.5 (3.6 - 20.0)) Romme[7] LR 2.2 (1.4 - 3.4) • Anxiety pre-TLoC (VV/Psy) **very low** [2, 4, 7] LR 7.5 (2.9 to 19.0)* • Dyspnoea pre-TLoC (VV/Psy) **low** [2,7] LR 7.0 (3.0 to 16.4) • Palpitations pre-TLoC (VVS/Psy and NM syncope) **very low** [2, 3, 6, 7] LR (VV/Psy) 7.1 (3.4 – 14.7) LR (NM) 1.0 (0.6-1.9) not signif • Headaches pre TLoC (Sheldon* and Graf VV/Psy*) **very low** [1, 2, 4, 7] LR (Sheldon) 5.7 (1.8 – 18.0)* LR (Graf) 6.3 (2.4 – 16.2) • Number of prodromes (VV/Psy) **low** [2, 7]	• Syncope during effort (NM syncope) **very low** [3, 4, 7] LR 0.15 (0.04 - 0.51)* • Atrial fibrillation or flutter (Sheldon) **low**[1,7] LR 0.14 (0.04 - 0.42) • P-wave duration (VV/Psy) **low** [2, 7] Mean difference -14ms (-18 to -10) • Cyanotic during syncope **very low** [1, 4, 5, 7] Sheldon LR 0.16 (0.04 - 0.61)* Romme non significant LR 0.43 (0.14 to 1.33)

2 [1] Sheldon 2006 – case control study, patients with structural heart disease excluded
3 [2] Graf – indirect population (vasovagal syncope or psychogenic pseudosyncope)
4 [3] Alboni – indirect population (neurally mediated syncope)
5 [4] Imprecision (one or two asterisks) [5] Inconsistency between studies (minor or same direction)
6 [6] Inconsistency between studies (major) [7]study limitations

Additional significant weak univariate predictors for and against vasovagal syncope are listed below, together with signs and symptoms with relatively narrow confidence intervals that are neither for nor against vasovagal syncope. Only the two vasovagal syncope studies (Romme 2009; Sheldon 2006) are reported, all were of low evidence quality. The Romme (2009) study is indicated with an 'R'.

- **Weak predictors for vasovagal syncope**: age less than 50 years (R); frequency of TLoC - at least 4 in the past year (R); syncope after effort; stress pre-TLoC; auditory distortion pre-TLoC; nausea or vomiting pre-TLoC; diaphoresis pre-TLoC (2 studies); abdominal discomfort pre-TLoC; heart racing pre-TLoC; numbness/tingling pre-TLoC; cannot remember behaviour; unresponsive during TLoC; confusion after a spell; white or pale colour noted by bystander during TLoC; diaphoresis or warm feeling post-TLoC; mood changes post-TLoC; numbness/tingling post-TLoC; nausea or vomiting post-TLoC
- **Weak predictors against vasovagal syncope**: male gender (2 studies); frequency of TLoC - fewer than 1 in the past year (R); valvular heart disease; hypertension; less than 5 seconds warning; no memory about TLoC during syncope (R had no patients with an event); recovery duration of 1 minute or less (R)
- **Not predictors either for or against vasovagal syncope** (R): frequency of TLoC – 2 to 3 in the past year

Three studies carried out multivariable analyses (Alboni 2001; Graf 2008; Sheldon 2006).

The Alboni (2001) study conducted analyses for two groups of patients, those with and without suspected heart disease (following intial evaluation); each analysis was for the diagnosis of neurally mediated syncope (i.e. an indirect target condition for vasovagal syncope). The study included significant univariate predictors in the multivariable analyses: six and two variables were included for the groups, with and without suspected heart disease; they are

listed in Appendix D3. The multivariable analyses were considered to be of low quality, mainly because of the selected population, and also because there were too few variables in the analysis. We considered there were some important confounders missing from the variables added to the regression analysis.

The Sheldon (2006) study carried out two multivariable analyses based on significant univariate predictors at the $p<0.05$ level. Thirty-six and 34 variables were included, depending on whether symptom burden predictors were included (i.e. the number of spells and the length of the TLoC history); they are listed in Appendix D3). The multivariable analyses were considered to be of low quality, mainly because of the case-control nature of the study. We considered there were no important confounders missing from the variables added to the regression analysis.

The Graf (2008) study carried out multivariable analyses based on significant univariate predictors at the $p<0.001$ level; 15 were included in the analysis. The multivariable analyses were considered to be of low quality because of the indirectness of the population (58% vasovagal syncope, 42% psychogenic pseudosyncope for the target condition). The GDG considered there were no important confounders missing from the list of variables in the analysis, and considered that some of the factors largely predicted psychogenic pseudosyncope (e.g. anxiety). The inclusion of these factors might confound the predictors for vasovagal syncope.

Multivariable predictors for and against vasovagal syncope are shown in Table 5. We note that there are no predictors common to more than one study, with the exception of age. Imprecision is indicated by an asterisk.

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Table 5: Multivariable predictors for vasovagal syncope for each study

Study	Predictors for vasovagal syncope	Predictors against vasovagal syncope
Alboni (2001) in patients with suspected or diagnosed heart disease for neurally mediated syncope. Evidence quality: low (indirect population, confounders missing)	• Time between 1st and last TLoC > 4years OR 9.2 (4 to 25) • History of pre-syncope OR 2.7 [1.1 to 7]* • Nausea post TLoC OR 6 (1 to 35)* i.e. borderline significant Not significant in Sheldon analysis (no data; very low)	
Alboni (2001) in patients without suspected or diagnosed heart disease for neurally mediated syncope Evidence quality: **low** (indirect target condition, confounders missing)	• Duration of prodromes > 10s OR 3.5 (1.1 to 11)* < 5s warning was not significant in Sheldon analysis (no data; very low)	
Graf (2008) for vasovagal syncope plus psychogenic pseudosyncope Evidence quality: **low** (indirect population, possible confounders because of psychogenic pseudosyncope)	• Number of prodromes >1 OR 7.1 (3.9 to 13.1)	• Age Category (≤ 45; 46-64; ≥65 y) OR 0.30 (0.20 to 0.47) • P-wave ≥ 120 ms or non-sinus rhythm OR 0.41 [0.20 to 0.87]
Sheldon (2006) for vasovagal syncope in patients without structural heart disease and with known causes of syncope Evidence quality: **low** (case control study)	• Pre-syncope or syncope with prolonged sitting or standing OR 2.6 (1.0 to 6.8)* i.e borderline significant • Sweating or warm feeling pre-TLoC OR 7.0 (2.4 to 21.1) • Pre-syncope or syncope with pain or medical procedure OR 18.2 (3.4 to 96.2)	• Age at first TLoC ≥ 35 y OR 0.07 (0.02 to 0.25) • Any 1 of bifascicular block, asystole, SVT, diabetes OR 0.01 (0.00 to 0.03) • Blue colour noted by bystander OR 0.02 (0.00 to 0.18) • Remembers something about the TLoC OR 0.17 (0.06 to 0.47)

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Patient history initial evaluation score for diagnosis of vasovagal syncope (versus other types of syncope) (Alboni 2001; Graf 2008; Romme 2009; Sheldon 2006; van Dijk 2008)

Four studies evaluated a decision rule for the diagnosis of vasovagal syncope (Romme 2009 (n=380); Sheldon 2006 (n=323), van Dijk 2008 (n=503)) or vasovagal syncope plus psychogenic pseudosyncope (Graf 2008 (n=65)).

- Population – all four studies had selected patients (as above)
- 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 multivariable analyses
  - van Dijk (2008) evaluated an initial assessment scheme, based on the ESC guidelines
    - ◊ A 'certain' diagnosis of vasovagal syncope included: precipitating events such as fear, severe pain, emotional distress, instrumentation, or prolonged standing
    - ◊ A 'highly likely' diagnosis included: absence of cardiac disease; long history of syncope; after unpleasant sight, sound, smell, or pain; prolonged standing or crowded, hot places; nausea/vomiting associated with syncope; during/in the absorptive state after meal; after exertion
  - Sheldon (2006) and Graf (2008) produced decision rules:

Rule 1 (Sheldon 2006 and Romme 2009) - no knowledge of symptom burden: scores	Rule 2 (Graf 2008): scores for prediction of vasovagal syncope or psychogenic pseudosyncope
• any one of: bifascicular block, asystole, supraventricular tachycardia, diabetes (-5)_	• 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
• blue colour noted by bystander (-4)	
• age at first syncope at least 35 years (-3_	• 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
• remembers something about the TLoC episode (-2)	
• presyncope or syncope with prolonged standing or sitting (+1)	• Number of prodromes ('ProdCat'): score 0 for 1 or 0 symptoms, and score 1 for 2 or more symptoms
• sweating or a warm feeling before TLoC (+2_	Apply formula 2 x ProdCat – P-waveCat – AgeCat + 2 Patients are classified as having a vasovagal syncope or psychogenic pseudosyncope if the total points score is 0 or more
• presyncope or syncope with pain or medical procedure (+3)	
Patients classified as having vasovagal syncope if the total points score is -2 or more	

- Study design varied (as above)
- Reference standard
  - Diagnosis following secondary tests (as above)

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.

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 89% (95%CI 85 to 93%) and a specificity of 91% (95%CI 83 to 96) after adjusting

to represent an independent sample. The authors also reported that the score alone was not usually sufficient for a diagnosis of vasovagal syncope, and stated that, for such a diagnosis, the four risk factors of asystole, bifascicular block, SVT and diabetes usually needed 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. The Romme (2009) study validated the Sheldon (2006) rule in a more representative cohort and found a sensitivity of 87% (95%CI 82 to 91) and a low specificity of 31% (95%CI 24 to 40%).

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

The Graf (2008) study reported a sensitivity of 84% (64-95) and a specificity of 50% (34-66) in their validation cohort for the diagnosis of vasovagal syncope or psychogenic pseudosyncope.

The van Dijk (2008) study considered the predictive ability of their ESC guidelines-based initial assessment scheme for people predicted to be 'certain' or 'highly likely' to have vasovagal syncope.

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 vasovagal syncope

Study	Sens (%)	Spec (%)	LR+	LR-	Diag Yield (%)
Graf 2008c Initial symptoms decision rule VV/Psychogenic model; validation cohort. **Low** quality evidence (indirect target condition)	84 (64-95)	50 (34-66)	1.7 (1.2-2.4)	0.32 (0.12-0.83)	63
Sheldon 2006 Initial symptoms decision rule for vasovagal syncope; cut-off above -2. **Low** quality evidence in case control study (no structural heart disease or tilt negative unexplained syncope)	89 (85-93)	91 (83-96)	9.8 (5.1-19.1)	0.12 (0.08-0.17)	67
Romme 2009 Validation of Sheldon 2006 rule in van Dijk 2008 population **Moderate** quality evidence; 25% patients excluded (CMO, MI, epileptic seizures, unknown cause after 2y)	87 (82-91)	31 (24-40)	1.3 (1.1-1.4)	0.42 (0.28-0.62)	80
van Dijk 2008 Initial evaluation based on ESC guidelines certain only moderate quality evidence	97 (91-100)	100 (98-100)	208.3 (52.2-830.6)	0.03 (0.01-0.11)	19
van Dijk 2008 Initial evaluation based on ESC guidelines. Highly likely only moderate quality evidence	98 (93-100)	97 (94-98)	30.4 (17.4-53.2)	0.02 (0.01-0.07)	27
van Dijk 2008 Initial evaluation based on ESC guidelines certain and highly likely moderate quality evidence	98 (94-99)	95 (92-97)	20.8 (12.5-34.8)	0.03 (0.01-0.06)	42

3.3.5.3 Patient history, physical examination, tests and decision rules, for diagnosis of psychogenic pseudosyncope (van Dijk 2008)

One study (van Dijk 2008) investigated the ESC guidelines for the diagnosis of psychogenic pseudosyncope. Details of the study are given in Appendix D1.

The reference standard appeared to be a psychiatric diagnosis, although this was unclear, and it was assumed independent of the index test.

The index test was defined as follows:

Psychogenic pseudosyncope based on ESC guidelines
The definition of psychogenic pseudosyncope was unclear in the van Dijk (2008) paper, simply stating the ESC guidelines were used. The ESC update 2004 (appropriate to this study) identifies the following indicators (Brignole 2004): • young • low prevalence of heart disease • frequent recurrent syncope • fainting in the presence of a witness • may not have injury
The ESC update of 2009 (van Dijk is a member of the Task force for the 2009 edition) states the following indicators (Moya 2009): • Pseudosyncope usually lasts longer than syncope: patients may lie on the floor for many minutes; 15 min is not exceptional. • a high frequency including numerous attacks in a day, • lack of a recognisable trigger • Injury does not exclude functional T-LOC • The eyes are usually closed in functional TLoC

The results are summarised in Table 7: and reported in full in Appendix D3; imprecision is indicated with an asterisk.

Table 7: Diagnostic test accuracy statistics for psychogenic pseudosyncope

Study	Sens (%)	Spec (%)	LR+	LR-	Diag Yield (%)
van Dijk 2008 Initial evaluation based on ESC guidelines; certain and highly likely **Low evidence quality**	86 * (57-98)	100 (99-100)	NA	0.17 * (0.05-0.52)	2

3.3.5.4 *Patient history, physical examination, tests and decision rules, for diagnosis of orthostatic hypotension cause of syncope (van Dijk 2008)*

One study (van Dijk 2008), examined the ESC guidelines for the diagnosis of orthostatic hypotension. Details of the study are given in Appendix D1. Blood pressure was measured in the supine position and after 3 minutes of upright position. The index test was defined as follows:

Orthostatic hypotension based on ESC guidelines
Certain diagnosis: • Documentation of orthostatic hypotension associated with syncope or presyncope • Decrease in systolic bp of 20 mm Hg or a decrease of systolic bp to <90 mm Hg is defined as orthostatic hypotension regardless of whether or not symptoms occur
Highly likely diagnosis: • After standing up • Temporal relationship with start of medication leading to hypotension or changes of dose • Prolonged standing especially in crowded hot places • Presence of autonomic neuropathy or Parkinsonism • After exertion

The GDG regarded the definition of a certain diagnosis as an indirect measure of orthostatic hypotension in that it did not accord with the widely accepted definition from the 1996 Consensus Statement of the American Autonomic Society and the American Academy of Neurology (Consensus 1996): a

decrease in systolic blood pressure of 20 mm Hg or more and/or decrease in diastolic blood pressure of 10 mm Hg or more within 3 minutes of standing.

The study appeared to have included the index test results as part of the reference standard, although this was unclear.

The results are summarised in Table 8 and reported in full in Appendix D3; imprecision is indicated with one or two asterisks.

Table 8: Diagnostic test accuracy statistics for orthostatic hypotension cause of syncope

Study	Sens (%)	Spec (%)	LR+	LR-	Diag Yield (%)
van Dijk 2008 Initial evaluation based on ESC guidelines; certain diagnosis only **very low evidence quality**	100 (63-100) **	99 (98-100)	99	0.00	3
van Dijk 2008 Initial evaluation based on ESC guidelines; Highly likely diagnosis only **very low evidence quality**	80 (44-97) **	99 (97-100)	66	0.20	3
van Dijk 2008 Initial evaluation based on ESC guidelines; certain and highly likely diagnosis **low/very low evidence quality**	89 (65-99) *	98 (96-99)	39	0.11	5

3.3.5.5 Patient history, physical examination, tests and decision rules, for diagnosis of cardiac syncope

Patient history for diagnosis of cardiac causes of syncope

Four prospective cohort studies reported the value of patient history in distinguishing between cardiac causes of syncope and other types of syncope (Alboni 2001 (n=337); del Rosso 2008 (n=260); Graf 2008 (n=317); Sarasin 2003 (n=175)

- Population
  - Three studies were in selected patients: Alboni (2001) – referrals to a syncope unit; Graf (2008) – referred for unexplained syncope; Sarasin (2003) – patients with a definite cause of syncope were excluded (i.e., those with a strongly suspected diagnosis of vasovagal syncope, situational syncope or orthostatic hypotension and people with abnormalities on 12-lead ECG). Del Rosso (2008) was in unselected patients
  - The Sarasin (2003) study recorded results for cardiac *arrhythmic* syncope only
  - The Graf (2008) study recorded results for 'rhythmic syncope', which included 66% cardioinhibitory CSS; the GDG therefore decided not to consider this study further for cardiac syncope
  - del Rosso (2008) excluded non-syncope causes of TLoC and the other two studies had 1% and 13% with neurological or psychiatric causes of syncope (Alboni 2001 and Sarasin 2003 respectively)
- 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.incontinence)

  - Duration of TLoC
  - Recovery after TLoC
  - Prodromal symptoms after TLoC
- Univariate and/or multivariable analyses carried out
- Study design varied:
  - ◊ Unselected patients presenting to ED. Cardiac syncope versus 'other syncope' (70% neurally mediated syncope; 10% orthostatic hypotension; 4% non-syncopal attacks; 3% unexplained) (del Rosso 2008)
  - ◊ Cardiac syncope versus non-cardiac syncope (NM syncope 58%; 1% neurological/psychiatric; 18% unexplained) in patients referred to a syncope unit (Alboni 2001)
  - ◊ Cardiac arrhythmic syncope versus mainly unexplained syncope (organic heart disease 9%; vasovagal syncope 6%; seizures/psychiatric 13%; unknown 50%) (Sarasin 2003)
- 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)
    - ◊ 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)

Signs and symptoms that are considered to be good and strong univariate predictors are shown in Table 9 as likelihood ratios with their 95% confidence intervals; non-significant likelihood ratios are not included. Multivariable predictors for and against cardiac syncope are shown in

Table 10. Detailed results are reported in Appendix D3.

We also give an evidence quality rating based on:

- Indirectness: The GDG originally wished to determine the predictors of cardiac causes of syncope in an unselected population. In practice, the signs and symptoms could be used as predictors, either in the initial stage (unselected) or after referral for cardiological assessment (selected) and we did not downgrade the directness of the population on this basis.
  - The Sarasin (2003) study was restricted to arrhythmic syncope, i.e. a subgroup of the population, and patients were referrals to syncope units for unexplained syncope
- Limitations: more than 20% missing data in del Rosso (2008) for the EGSYS score, and index test part of the reference standard and not blinded in Alboni (2001), and del Rosso (2008)
- Inconsistency between studies is indicated as a footnote
- Imprecision: for likelihood ratios, we defined imprecision as in 3.3.5.1.

Table 9: Univariate predictors for cardiac syncope versus other causes of syncope

Strength of test	Predictors for cardiac syncope ('card') or arrhythmic only ('arrhy')	Predictors against cardiac syncope
Strong predictors LR > 10; LR < 0.1	• Syncope during effort (prodromal symptoms began) **low** [4, 5, 7] **Cardiac** del Rosso: LR* 14.7 (3.1-0.6) Alboni [3]: LR* 4.7 (1.9-12.1)	

Good predictors 5<LR<10 or 0.2>LR>0.1	• Age **low** [3, 7] **Card** - Alboni [3]: MD 13.0 y (8.9-17.1) • Age ≥ 65y (weak predictor) **moderate** [7] **Card** – del Rosso: LR 1.6 (1.3-1.9) **Arrhy** – Sarasin[3] LR 2.3 (1.8-2.8) • Palpitations pre-TLoC (gross heterogeneity) **Cardiac very low** [4, 6, 7] del Rosso: LR* 9.8 (1.9-52.0) Alboni [3]: LR 1.4 (0.7-2.7) not signif • Dyspnoea pre-TLoC **low** [4, 7] **cardiac** del Rosso: LR* 9.8 (1.9-52.0) • Syncope while supine (borderline good) **low** [4, 7] **Cardiac** Alboni [3]: LR* 5.0 (1.8-13.6) del Rosso: LR* 4.9 (1.7-14.5)	• Feeling cold pre-TLoC **low** [4, 7] **Cardiac** Alboni [3]: LR* 0.12 (0.02-0.89) • Nausea or vomiting pre-TLoC **low** [4, 5, 7] **Cardiac** del Rosso: LR* 0.19 (0.06-0.59) **low** [4, 7] • NB nausea – (**low** [4, 7])- Alboni [3]: LR* 0.62 (0.27-1.43) not sig • vomiting - (**very low** [4, 7]) - Alboni [3]: LR** 0.91 (0.26-3.16) not sig • Feeling cold post TLoC **low** [4, 7] **Cardiac** - Alboni [3]: LR* 0.16 (0.04-0.65)

[3] selected population (referred to syncope unit)
[4] Imprecision (one or two asterisks) [5] Inconsistency between studies (minor or same direction)
[6] Inconsistency between studies (major) [7]study limitations

Three studies carried out multivariable analyses (Alboni 2001; del Rosso 2008; Sarasin 2003).

The Alboni (2001) study conducted analyses for all patients and then for two subgroups of patients, those with and without suspected heart disease (following intial evaluation based on history, physical examination or ECG abnormalities); each analysis was for the diagnosis of cardiac syncope. The multivariable analysis of all patients included only the non-syncope variables (age, gender and presence of suspected or certain heart disease), for which the presence of suspected or certain heart disease was the only significant factor. The subgroups' multivariable analyses included significant univariate predictors in the multivariable analyses: six were included for the group with suspected heart disease, but there was only one significant univariate predictor for the group without suspected heart disease; covariables are listed in Appendix D3. The multivariable analyses were considered to be of low

quality, mainly because there were too few variables in the analysis. We considered there were important confounders missing from the variables added to the regression analysis.The del Rosso (2008) study carried out multivariable analyses based on significant univariate predictors at the $p<0.10$ level; 14 were included in the analysis and are listed in Appendix D3. The multivariable analysis was considered to be of moderate quality. We did not think there were important confounders missing from the variables added to the regression analysis.

The Sarasin (2003) study carried out multivariable analysis for arrhythmic syncope based on significant univariate predictors; 5 were included in the analysis. The multivariable analyses were considered to be of moderate quality; the wethought that most important predictors were included.

Multivariable predictors for and against cardiac syncope are shown in Table 10. Imprecision is indicated by an asterisk.

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Table 10: Multivariable predictors for cardiac syncope for each study

Study	Predictors for cardiac or arrhythmic syncope	Predictors against cardiac or arrhythmic syncope
Alboni (2001) all patients Evidence quality: **low** (non-syncope predictors only) **cardiac syncope**	• Suspected or certain heart disease OR 16 (5 to 48)	
Alboni (2001) in patients with suspected or diagnosed heart disease Evidence quality: **low** **Cardiac syncope**	• Time between 1st and last TLoC ≤ 4years OR 55 (6 to 471) • Supine position OR 69 (4 to 1087) • Blurred vision pre-TLoC* OR 4.7 (1.3 to 17)	
Alboni (2001) in people without suspected or diagnosed heart disease Evidence quality: **low** **Cardiac syncope**	• Palpitations (only significant univariate factor) OR 21 (2 to 214)	
Del Rosso (2008) Evidence quality: **moderate** **Cardiac syncope**	• Heart disease or abnormal ECG or both OR 11.8 (7.7 to 42.3) • Syncope during effort OR 17.0 (4.1 to 72.2) - but not significant for cardiac syncope in Alboni study suspected / diagnosed heart disease • Syncope while supine OR 7.6 (1.7 to 33.0) • Palpitations pre TLoC OR 64.8 (8.9 to 469.8)	• Nausea or vomiting or both OR 0.3 (0.1 to 0.8) • Warm crowded place / prolonged orthostasis / fear-pain-emotion OR 0.4 (0.2 to 0.9)*
Sarasin (2003) **arrhythmias** Evidence quality: **moderate**	• Age ≥ 65 years* (**low**) OR 5.4 (1.1 to 26.0) - age not significant for the 2 cardiac syncope studies • Abnormal ECG OR 8.1 (3.0 to 22.7) • History of congestive heart failure OR 5.3 (1.9 to 15.0)	

Patient history initial evaluation score for diagnosis of cardiac syncope or cardiac arrhythmias (del Rosso 2008; Elseber 2005; Sarasin 2003; van Dijk 2008)

Four studies evaluated a decision rule for the diagnosis of cardiac or cardiac arrhythmic causes of syncope (del Rosso 2008 (n=256); Elseber 2005 (n=200); Sarasin 2003 (validation cohort; n=267); van Dijk 2008 (n=503))

- Population
  - Unselected for three studies (del Rosso 2008; Elseber 2005; van Dijk 2008)
  - Selected in the other study: patients with partly unexplained cause after the initial stage (Sarasin 2003)
  - the Elseber (2005) study was a retrospective review of records.

- Index tests

Rule 1 (EGSYS): initial evaluation decision rule based on symptoms and history for prediction of cardiac syncope (del Rosso 2008)	**Rule 2 - Sarasin (2003) for prediction of cardiac arrhythmic syncope**
• Palpitations preceding syncope (+4)	• Age 65 years and older
• Heart disease or abnormal ECG (see Appendix D1) or both (+3)	• Abnormal ECG (conduction disorder; old MI; Rhythm abnormalities (see Appendix D1)
• Syncope during effort (+3)_	
• Syncope while supine (+2)	
• Precipitating or predisposing factors or both (warm, crowded place; prolonged orthostasis; fear/pain/emotion) (-1)	• History of congestive heart failure
• Autonomic prodromes (nausea and/or vomiting) (-1)	
In a referral centre, patients are classified as having cardiac syncope if the total points score is 4 or more	Score one point for each of the above

-

Rule 3 – van Dijk (2008) based on ESC guidelines for cardiac syncope
Certain diagnosis: • abnormal ECG (see Appendix D1)
Highly likely diagnosis: • Presence of severe structural heart disease • Syncope during exertion or supine • Preceded by palpitation or accompanied by chest pain • Family history of sudden death

Rule 4 (ACEP): initial evaluation decision rule based on ACEP guidelines for cardiac syncope (Elseber 2005; retrospective) A cardiac cause of syncope was equated with admission to hospital	
High risk – level B (corresponds to admission criteria); any one of the following:	**Moderate risk – level C (consider admission); any one of the following:**
• History of congestive heart failure or history of ventricular arrhythmias	• Age over 60 years
• TLoC with chest pain or other symptoms of acute coronary syndrome	• History of coronary artery disease or congenital heart disease
• Physical signs of congestive heart failure or significant valve disease	• Family history of sudden death
• Abnormal ECG (see Appendix D1)	• Exertional syncope without an obvious benign cause

- Reference standard
  - Diagnosis following secondary tests (including ECG)
  - Elseber (2005): cardiac tests including initial ECG, plus Holter monitoring or event recording or electrophysiological testing, or cardiac catheterisation or echocardiography

- Follow up at 2 years plus further tests plus expert review leading to final diagnoses (van Dijk 2008)

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. 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 or arrhythmic causes of 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 11, along with values for the other studies. Full results are given in Appendix D3.

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Table 11: 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 **Low** evidence quality (retrospective)	100 (86-100)	81 (75-87)	5.2 (3.8-7.1)	0.02 (0.00-0.38)	29
Elseber 2005 Initial evaluation based on ACEP guidelines; ACEP level B + C **Low** evidence quality (retrospective)	100 (86-100)	33 (26-40)	1.5 (1.3-1.7)	0.06 (0.00-0.95)	71
Sarasin 2003b **Arrhythmic cause** Initial symptoms decision rule >0 risk factors; Validation study **Low** evidence quality (retrospective evaluation)	96 (85-99)	42 (35-49)	1.7 (1.5-1.9)	0.10 (0.03-0.40)	65
Sarasin 2003b **Arrhythmic cause** Initial symptoms decision rule >1 risk factor; Validation study **Low** evidence quality (retrospective evaluation)	66 (51-79)	72 (66-78)	2.4 (1.8-3.2)	0.47 (0.31-0.71)	34
van Dijk 2008 Initial evaluation based on ESC guidelines; certain diagnosis only **Moderate** evidence quality	71* (29-96)	100 (99-100)	NA	0.31 (0.11-0.87)	1
van Dijk 2008 Initial evaluation based on ESC guidelines; highly likely diagnosis only **Moderate** evidence quality	74 (52-90)	99 (97-99)	50.7 (23.4-110.0)	0.26 (0.13-0.53)	5
van Dijk 2008 Initial evaluation based on ESC guidelines; certain and highly likely **Moderate** evidence quality	73 (54-88)	99 (97-99)	49.6 (23.0-106.6)	0.27 (0.15-0.49)	6
del Rosso 2008 EGSYS score >2; **Low** evidence quality (76% follow up)	91 (77-98)	69 (63-75)	3.0 (2.4-3.7)	0.12 (0.04-0.37)	39
del Rosso 2008 EGSYS score >4 **Low** evidence quality (76% follow up)	29 (15-46)	99 (96-100)	21.0 (6.1-72.7)	0.72 (0.61-0.94)	5

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3.3.6 Evidence for predictive factors for serious adverse events

We report the evidence for predictors for adverse events.

3.3.6.1 Patient history, physical examination, tests, decision rules, for predicting death

Patient history for a serious event: death within 12 months (Colivicchi 2003; Quinn 2008)

One study investigated signs and symptoms, physical examination and laboratory tests and ECG for their ability to predict death within 12 months (Colivicchi 2003; n=270), One additional study reported only one predictor, age over 65 years, for death within 30 days, 3 months and 6 months (Quinn 2008; n=1418).

- Population – unselected in both studies
- 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 multivariable analyses carried out
- Reference standard
  - Follow up at 12 months for Colivicchi (2003) and 30 days, 3 and 6 months for Quinn (2008)

Signs and symptoms are reported as the relative risk of death for the symptom present versus not present, with their 95% confidence intervals. The results are given in Appendix D3 and significant risk factors, univariate and multivariable are summarised in Table 12.

We also give an evidence quality rating based on:

- Indirectness: both studies were in unselected patients. However, the time of outcome measure is indirect: the GDG wished to know about death within 1-2 weeks.
- Limitations: Neither study was considered to have limitations
- Inconsistency between studies is indicated as a footnote
- Imprecision: for relative risks for mortality we defined imprecision in terms of a clinical important threshold of 1.25 or 0.75. Imprecision is indicated by one or two asterisks.

Likelihood ratios are also given in Appendix D3, but no symptom alone was a good or strong predictor for death.

The Colivicchi (2003) study carried out multivariable analysis for arrhythmic syncope based on significant univariate predictors; 8 were included in the analysis for 31 events. The multivariable analysis was considered to be of low quality because there were too few events per covariable and only one of the GDG's key risk factors was present (age). The univariate risk factors listed in Table 12 are those entered in the multivariable analysis (i.e. the remainder were not significant independent risk factors).

We note that the multivariable predictors all have fairly small predictive abilities.

Table 12: multivariable and univariate risk factors for death in people who have had a TLoC	
Multivariable risk factors for death at 12 months (low quality evidence)	Univariate risk factors for death at 12 months (low quality evidence because indirect)
• Age > 65 years* RR 1.42 (95%CI 1.24 to 1.62)	• Age > 65 years RR 8.07 (2.90 to 22.43) – 12 months Quinn 2008 results: RR 7.60 (1.77 to 32.63) – 30 days RR 6.23 (2.46 to 15.79) – 3 months RR 6.80 (3.12 to 14.85) – 6 months
• Cardiovascular disease in clinical history* RR 1.34 (95%CI 1.19 to 1.49) • Abnormal ECG findings* RR 1.29 (95%CI 1.16 to 1.43) • Syncope without prodromes (small effect)* RR 1.13 (95%CI 1.06 to 1.21)	• Cardiovascular disease in clinical history RR 5.91 [95%CI 2.85 to 12.26] • Abnormal ECG RR 3.63 [95%CI 1.85 to 7.13] • Absence of prodromes RR 7.80 [95%CI 3.32 to 18.35] • Syncope-related traumatic injuries RR 2.66 [95%CI 1.35 to 5.23] • Hypertension RR 2.68 [95%CI 1.37 to 5.22] • Diabetes mellitus RR 2.59 [95%CI 1.27 to 5.29]

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

Four studies examined different risk stratification rules for death (Colivicchi 2003 (n=270); Crane 2002 (retrospective; n=208); del Rosso 2008 (n=256); Quinn 2008 (n=1418)).

- Population
  - Unselected for all studies
  - the Crane (2002) study was a retrospective review of records.

- Index tests

Rule 1 (EGSYS): initial evaluation decision rule for prediction of death (del Rosso 2008)	Rule 2 (OESIL ‡ score): for prediction of death (Colivicchi 2003)
• Palpitations preceding syncope (+4)	• Age 65 years and older
• Heart disease or abnormal ECG or both (see Appendix D1) (+3)	• Abnormal ECG (see Appendix D1)
• Syncope during effort (+3)	• Clinical history of cardiovascular disease
• 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)	• Syncope without prodromal symptoms
In the ED, patients are classified as being at risk of death if the total points score is 4 or more.	Score one point for each of the above. Patients with more than 1 risk factor are considered at risk of death.

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Rule 3 (San Francisco Syncope Rule) for prediction of death (Quinn 2008):	Rule 4 (based on ACP guidelines): for prediction of all-cause mortality (Crane 2002)
• history of congestive heart failure	**High risk** (admission indicated) – any one of: • history of coronary artery disease or congestive heart failure (CHF) or ventricular tachycardia (VT) • abnormal ECG (see Appendix D1) • TLoC with symptoms of chest pain • physical signs of CHF, significant valve disease, stroke or focal neurology
• abnormal ECG (see Appendix D1)	
• haematocrit below 30%	
• patient complaint of shortness of breath	
• triage systolic blood pressure less than 90 mm Hg	**Moderate risk** (admission often indicated) – 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
Any one of the above risk factors	

2

- Reference standard
  - Follow up at 12 months in Colivicchi (2003) and Crane (2002)
  - Follow up at 21-24 months in del Rosso (2008)
  - Follow up: Quinn (2008) 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 and all cause death also at 30 days and 3 months.
- Target condition
  - The GDG wished to determine which patients were at risk of a serious adverse event in the next 1-2 weeks, so they could identify people at higher risk who needed urgent referral. Therefore, the target condition for the studies was considered indirect

Colivicchi (2003) reported the percentage of patients who died as a function of the number of risk factors the 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 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.

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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 13.

Table 13: 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 **Very low quality evidence** (retrospective, indirect time, imprecision)	67 (45-84)*	83 (76-88)	3.9 (2.5-6.1)	0.40 (0.23-0.71)	23
Crane 2002 Initial evaluation based on ACP guidelines; moderate risk; death 12 months **Low quality evidence** (retrospective, indirect time)	33 (16-55)	70 (63-77)	1.1 (0.6-2.1)	0.95 (0.70-1.28)	30
Crane 2002 Initial evaluation based on ACP guidelines, high + moderate risk; 12 months **Low quality evidence** (retrospective, indirect time)	100 (86-100)	53 (45-61)	2.1 (1.8-2.5)	0.04 (0.00-0.59)	53
San Francisco Syncope Rule					
Quinn 2008 San Francisco Syncope Rule all-cause deaths at 30 days **Moderate quality evidence** (indirect time)	100 (84-100)	52 (52-52)	2.1	0.0	49
Quinn 2008 San Francisco Syncope Rule all cause deaths at 3 months **Moderate quality evidence** (indirect time)	86 (74-94)	52 (52-53)	1.8	0.28	49
Quinn 2008 San Francisco Syncope Rule deaths related to syncope at 6 months **Moderate quality evidence** (indirect time)	100 (90-100)	52 (52-53)	2.1 (1.9-2.2)	0.03 (0.00-0.44)	49
Quinn 2008 San Francisco Syncope Rule all cause deaths at 6 months **Moderate quality evidence** (indirect time)	89 (79-95)	53 (52-53)	1.9 (1.7-2.1)	0.22 (0.11-0.44)	49
Quinn 2008 San Francisco Syncope Rule deaths related to syncope at 12 months **Moderate quality evidence** (indirect time)	93 (83-97)	53 (52-53)	2.0 (1.8-2.2)	0.14 (0.05-0.36)	49

Table 13: Diagnostic test accuracy for risk stratification tools for death					
Study	**Sens (%)**	**Spec (%)**	**LR+**	**LR-**	**Diag Yield (%)**
Quinn 2008 San Francisco Syncope Rule all cause deaths at 12 months **Moderate quality evidence** (indirect time)	83 (75-89)	54 (53-55)	1.8 (1.6-2.0)	0.31 (0.20-0.47)	49
OESIL score					
Colivicchi 2003 OESIL score > 1 at 12 months **Moderate quality evidence** (indirect time)	97 (83-100)	73 (67-78)	3.6 (2.9-4.$)	0.04 (0.01-0.31)	35
EGSYS score					
del Rosso 2008 EGSYS score ≥ 3; at 21-24 months **Very low quality evidence** (indirect time; study limitations, imprecise)	82 (57-96)*	82 (76-87)	4.6 (3.1-6.7)	0.22 (0.08-0.60)	24

3.3.6.3 Patient history for a serious adverse event

Eight studies investigated signs and symptoms, physical examination and laboratory tests and ECG for their ability to predict serious adverse events, such as death or myocardial infarction (Birnbaum 2008 (n=743); Costantino 2008 (n=676); Grossman 2007 (n=362); Hing 2005 (n=113); Quinn 2004 (n=684); Reed 2007 (n=99); Reed 2010 (n=548); Sun 2007(n=477)). Hing (2005) was primarily a retrospective study.

- Populations – unselected for all studies except Costantino (2008).
  - In Costantino (2008), patients were excluded if:
    - ◊ they presented with conditions, primarily confirmed in the ED, that would have required hospital admission independently of whether they had TLoC, such as: myocardial infarction, acute pulmonary embolism, subarachnoidal haemorrhage, stroke, cardiac arrest, sustained bradycardia (< 35 bpm), complete atrioventricular block, sustained ventricular tachycardia
    - ◊ they had a referred non-spontaneous return to consciousness
- 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 and multivariable analyses carried out
- Reference standard
  - Follow up
    - ◊ At 7 days (Birnbaum 2008; Sun 2007; Quinn 2004)
    - ◊ At 10 days and at 11 days to 1 year (Costantino 2008)
    - ◊ At 30 days (Grossman 2007; Reed 2010)
    - ◊ At 3 months (Reed 2007)
    - ◊ At 3-6 months (Hing 2005)
- Outcome/adverse events: the studies differed in their definitions of serious adverse events:

Birnbaum 2008; Grossman 2007; Quinn 2004; Sun 2007; Reed 2007; Reed 2010	**Hing 2005**	**Costantino 2008**
Death	Death as a result of presumed cardiac causes	All-cause death
Myocardial infarction	Diagnosis or ongoing episodes of ischaemic heart disease requiring further investigation, including medication changes, admission to hospital, angiogram, etc	
Life threatening arrhythmia	Significant arrhythmia requiring treatment such as a pacemaker or medication	Need for pacemaker / ICD insertion or acute antiarrythmia medication
Pulmonary embolism		
Stroke, subarachnoid haemorrhage		
Significant haemorrhage / anaemia needing transfusion		

Any condition likely to cause a return to the ED or which did cause a return to the ED (not Reed 2010)		Readmission to hospital for the same or similar symptoms
Hospitalisation for related event		ICU admittance
Procedural intervention to treat syncope cause (only Reed 2007; Reed 2010; Sun 2007)		Major therapeutic procedures including: • cardiopulmonary resuscitation • pacemaker / ICD insertion
Aortic dissection (only Sun 2007)		
New diagnosis of structural heart disease (only Sun 2007)		
Severe infection / sepsis (only Grossman 2007)		

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 14; also reported are non-significant results where there is agreement between two or more studies. Results are reported as relative risks with their 95% confidence intervals, for the median value (or lowest value or 7 day value) in order to give an indication of the size of effect and precision. Lower quality evidence is reported only if there is no other. Disagreement between studies is indicated in Table 14, but where the disagreement was between 7 and 30 day studies, the former value was taken.

We also give an evidence quality rating based on:

- Indirectness:
  - The GDG wished to determine which patients were at risk of a serious adverse event in the next 1-2 weeks, so they could identify people at higher risk who needed urgent referral. Therefore, the target condition for three studies was considered indirect (Hing 2005 (3-6 months; Reed 2007 (3 months); Grossman 2007 (30 days))

  - We recognised that the Costantino (2008) study reported for a different target condition, excluding people with conditions presenting in ED that would have required admission regardless of whether the person had TLoC. This study was not, however, treated as an indirect population.
- Limitations: the Hing (2005) study was retrospective and only 22% of eligible patients were recruited
- Inconsistency between studies is indicated as a footnote
- Imprecision: for likelihood ratios, we defined imprecision as in 3.3.6.1.

We have not reported the results for the Hing (2005) study in Table 14.

1

Table 14: Significant univariate risk factors for serious events at 1-2 weeks – low quality evidence is indicated, otherwise moderate quality.

Sign / symptom is a risk factor for serious adverse outcomes	Protective factor

• Age over 40 years (2 studies) – 7 days; lowest RR 4.0 (1.3-12.5)
• Age over 60 years (2 studies) - 7 days;
  o Lowest RR 1.8 (1.1-3.0)* **low**
• Age over 65 years (1 study) – 10 days
  o RR 3.8 (1.9 – 7.9) - Costantino
• Age continuous (1 study) – 7 days; MD 6.0 years (1.7-10.3)
• Male gender (3 agreed, 1 disagreed for 7 & 30 days)
  o median RR 2.3 (1.4 – 3.8) – 7 days
• Coronary artery disease (2 studies, 7 & 30 days)
  o RR 1.5 (0.96-2.5)* – 7 days borderline significant **low**
• Congestive heart failure (5 studies; at 7, 10 and 30 days)
  o median RR 2.2 (1.2-4.2)* **low**
• Structural heart disease (Costantino; 10 days) RR 2.9 (1.6–5.3)
• Hypertension (borderline effect - 2 studies, 7 and 10 days);
  o RR 1.5 (0.98 – 2.3)* - 7 days **low**
• Abnormal ECG (4 studies at 7 days) not sig at 30 days
  o median RR 4.1(1.8 – 9.5)
• Arrhythmia (7 days) RR 2.5 (1.5 – 4.1)
• Abnormal rhythm (non sinus) (1 study, 7 days)
  o RR 2.8 (1.8 – 4.1)
• Diabetes (1 study; 7 days) RR 1.9 (1.1 – 3.3)* **low**
• COPD (1 study; 10 days; Costantino) RR 2.4 (1.1 – 5.1)* **low**
• Diuretics (1 study; 7 days) RR 1.8 (1.1 – 3.0)* **low**
• Antiarrhythmic medication (1 study; 7 days) RR 2.5 (1.4-4.6)
• Dyspnoea (4 studies, 7 and 30 days) **low**
  o Median 7d studies: borderline RR 1.8 (0.99–3.3)*
• Chest pain (1 study, 7 days), not sig 30d RR 1.9 (1.1-3.4)* **low**
• Absence of symptoms pre-TLoC (10 days, Costantino)
  o RR 2.2 (1.2 – 3.9)* **low**
• Systolic blood pressure < 90 mm Hg (3 studies (7 days; 1 study 30 days); some heterogeneity; Median RR 3.2 (1.9 – 5.4) **low**
• Oxygen saturation < 95% (1 study, 7 days) RR 1.8 (1.1–3.0)* **low**
• Respiratory rate > 24 / min (1 study, 7 days) RR 3.7 (2.1–6.4)
• Pulse rate < 50bpm or >110 (1 study, 7 days, not sig at 30 days)
  o RR 3.9 (2.5 – 5.9)
• Rales (1 study, 7 days) RR 2.7 (1.7 – 4.4)
• Abnormal heart sounds (1 study, 7 days) RR 3.4 (2.2 – 5.4)
• Heart murmur (systolic or diastolic; 1 study, 7 days),
  o not significant at 30 days RR 3.8 (1.6 – 9.2) diastolic
• Carotid bruits (1 study, 7 days) RR 3.8 (1.6 – 9.2)
• Profound dehydration (1 study, 30 days)
  o RR 2.9 (1.3 – 6.7) – indirect time **low**
• Haematocrit < 30% (3 studies at 7 days)
  o RR median 3.7 (2.4 – 5.7) not sig at 30 days
• GI bleed (1 study at 30 days) borderline significant
  o RR 2.2 (0.96 – 5.1)* **very low**
• Trauma (1 study Costantino at 10 days) not sig at 7 days for face and head trauma; RR 2.2 (1.2 – 4.1)* **low**
	Vagal symptoms (borderline, 1 study at 7 days) RR 0.52 (0.28 – 0.99)* **low**

2

Three studies (Costantino 2008; Quinn 2004; Reed 2010) carried out multivariable analyses to determine the independent risk factors for short term serious adverse events including death. Two studies (Costantino 2008; Reed 2010) reported values for multivariable risk factors (given below). The Quinn (2004) study incorporated the multivariable risk factors in their risk stratification tool developed, but did not give separate results.

The Reed (2010) study carried out a multivariable analysis based on significant univariate predictors at the $p<0.10$ level; at least 8 were included in the analysis for 40 events and are listed in Appendix D3 (the full list was not stated). The multivariable analysis was considered to be of low quality, partly because there were insufficient events per covariable. The GDG noted that the BNP test covered their key risk factor for cardiovascular comorbidities, but noted that the other key risk factors, age and history of a cardiac disease, were not included.

The Costantino (2008) study examined multivariable risk factors for serious adverse events within 10 days, excluding patients with clinical conditions confirmed in ED that would have led to hospital admission independently of TLoC. Eight covariables for 41 events were included and are listed in Appendix D3. The multivariable analysis was considered to be of moderate quality, partly because there were insufficient events per covariable, but the GDG considered that 2/3 of their key risk factors were included.

The longer term analysis included nine covariables for 62 events and these are also listed in Appendix D3. The multivariable analysis was considered to be of moderate quality, partly because there were insufficient events per covariable, but the GDG considered that all of their key risk factors were included.

Multivariable predictors are shown in Table 15.

1

Table 15 Multivariate predictors for serious adverse outcomes Evidence quality moderate unless otherwise stated; asterisk indicates imprecision		
Study	**Predictors for 10 day outcomes**	**Predictors for 11 days – 1 year outcomes**
Costantino 2008 (population excludes people with a serious condition that would have led to hospital admission regardless of TLoC.	• Abnormal ECG on presentation OR 6.9 (3.1 to 15.1) • Trauma OR 2.9 (1.4 to 5.9) • Absence of symptoms preceding syncope OR 2.4 (1.2 to 4.8)* • Male gender **low** (borderline significant) OR 2.2 (1.0 to 4.5)*	• Age above 65 years OR 3.4 (1.6 to 7.4) • Neoplasms OR 3.2 (1. 6 to 6.5) • Cerebrovascular disease OR 2.5 (1.3 to 4.7) • Structural heart disease OR 2.3 (1.3 to 4.2) • Ventricular arrhythmias OR 3.9 (1.0 to 15.3)* (borderline significant) **low**
Reed 2010 Outcomes at 1 month	• B-type natriurectic peptide (BNP – marker for prognosis in heart failure and cardiac disease) concentration ≥ 300pg/ml OR 7.3 (2.8 to 19.4) **low** • Rectal examination showing faecal occult blood; OR 13.2 (3.4 to 52.0) **low** • haemoglobin ≤ 90g/l; OR 6.7 (2.2 to 20.6) **low** • Q-wave (25% R wave) / left bundle branch block OR 4.8 (1.3 to 18.3) **low** • Male gender; OR 2.6 (1.1 to 5.9)* **very low** • Oxygen saturation ≤ 94% on room air OR 3.0 (1.2 to 7.8)* **very low** • albumin <37g/l; OR 3.2 (0.8 to 12.2)* not significant **very low** • white cell count > 14 x 10^9 cells/litre OR 2.4 (0.8 to 7.1)* not significant **very low**	

2

3 Age over 65 years was not a significant risk factor for the short term outcome
4 in the Costantino (2008) study, neither were heart failure; structural heart
5 disease or COPD. However, two of these factors were significant for the
6 longer term outcome. In the longer term analysis, hypertension, heart failure,
7 COPD and abnormal ECG at presentation were not significant risk factors.

8

3.3.6.4 *Decision rules for a serious adverse event (Birnbaum 2008; Grossman 2007; Hing 2005; Quinn 2005; Quinn 2006; Reed 2007; Reed 2010; Schladenhaufen 2008; Sun 2007)*

Ten studies examined four different risk stratification rules for serious adverse events (Birnbaum 2008 (n=738); Cosgriff 2007 (n=113); Grossman 2007 (n=362); Hing 2005 (n=100); Quinn 2005 (n=684); Quinn 2006 (n=767); Reed 2007 (n=99); Reed 2010 (n=549); Schladenhaufen 2008 (retrospective; n=592); Sun 2007 (n=477)).

- Population – unselected for all studies
  - The Schladenhaufen (2008) study retrospectively determined the San Francisco Syncope Rule items and all patients were over 65 years
  - The Quinn (2006) study excluded patients with outcomes diagnosed in the ED; three other studies carried out subgroup analyses excluding patients with outcomes diagnosed in the ED (Birnbaum 2008; Grossman 2007; Sun 2007).
- Index tests

Rule 1 (San Francisco Syncope Rule): for prediction of adverse events (Birnbaum 2008; Cosgriff 2007; Quinn 2005; Quinn 2006; Sun 2007; Reed 2007)	**Rule 2 (OESIL‡ score): for prediction of adverse events (Hing 2005; Reed 2007)**
	• Age 65 years and older
• Abnormal ECG (see Appendix D1)	• Abnormal ECG (see Appendix D1)
• History of congestive heart failure	• Clinical history of cardiovascular disease
• Haematocrit below 30%	
• Patient complaint of shortness of breath	
• Triage systolic blood pressure less than 90 mm Hg	• Syncope without prodromal symptoms
Any one of the above.	Score one point for each of the above. Patients with more than 1 risk factor are considered at risk of adverse events.

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Rule 3 (Boston Syncope Rule) – ESC guideline + San Francisco Syncope Rule + expert advice: for prediction of adverse events (Grossman 2007) see Appendix D1 for more details	Rule 4 (ROSE rule): for prediction of adverse events (Reed 2010)
• Signs/symptoms of acute coronary syndrome, including chest pain and complaint of shortness of breath	• Chest pain associated with syncope
• Worrying cardiac history, including coronary artery disease, heart failure, ventricular tachycardia etc	• B-type natriuretic peptide (BNP) level at least 300 pg/ml (marker for heart failure and cardiac disease)
• Family history of sudden death, HOCM, Brugada's, or long QT	• Bradycardia 50 bpm or less in ED or pre-hospital
• Valvular heart disease (including heart murmur in history or on examination)	
• Signs of conduction disease, including syncope during exercise	• ECG showing Q-waves (25% R wave) / left bundle branch block
• Volume depletion, including GI bleed by haemoccult or history and haematocrit < 30%	• rectal examination showing faecal occult blood (if suspicion of gastrointestinal bleed)
• Persistent (more than 15min) abnormal vital signs, including bp < 90 mm Hg	• Oxygen saturation 94% or less on room air
• Primary CNS event	• Anaemia – haemoglobin level 90 g/l or less
Any one of the above.	Any one of the above

- 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
  - **Rose Rule**: follow up events (See Appendix D1)
    - ◊ 1 month (Reed 2010)
    - ◊ Identification of high risk group; equated with the need for admission to hospital / discharge

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

Hing (2005) and Reed (2007) each reported the number of patients who had an adverse event as a function of 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.

We also examined the evidence quality, based on:

- Indirectness:
  - The GDG wished to determine which patients were at risk of a serious adverse event in the next 1-2 weeks. Therefore, the target condition for three studies was considered indirect (Hing 2005 (3-6 months; Reed 2007 (3 months); Grossman 2007 (30 days); Quinn 2006 and Reed 2010 (1 month))
- Limitations: the Schladenhaufen (2008) study was retrospective; the Cosgriff (2007) study had an unacceptable follow up rate of 79%; the Reed (2007) study had a population skewed towards more serious risk patients and the Hing (2005) study had a retrospective reference standard and only 22% of those eligible were recruited.
- Inconsistency between studies is indicated as a footnote

- We considered imprecision around the diagnostic test accuracy statistics.

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

There is clearly heterogeneity among the SFSR studies. In the absence of the studies with limitations, a slightly improved result was found (Figure 3.6), but overall the evidence for this rule is of low quality.

Figure 3.6: sensitivity analysis for San Francisco Syncope Rule

The diagnostic test accuracy statistics for each of the risk stratification rules are given in Appendix D3 and summarised in Table 16. A range of values is reported for the SFSR studies (based on the studies without limitations) and the optimum OESIL score from the ROC curve (a score of more than 1) is used.

1

Table 16: Decision rules for adverse outcomes

Study	Sens (%)	Spec (%)	LR+	LR-	Diag Yield (%)
OESIL score, 2 or more of: age > 65y; history of cardiovascular disease; syncope without prodromal symptoms; abnormal ECG					
Hing 2005 and Reed 2007 OESIL score >1 3 months follow up **Very low** quality evidence (indirect time, study limitations, imprecision)	Range 78 (56-93)* to 91(59-100)*	Range 64 (52-74) to 49 (38-60)*	Range 1.8 to 2.2	Range 0.19 to 0.34	Range 46 to 56
San Francisco Syncope Rule = any 1 of: history of congestive heart failure; abnormal ECG; haematocrit below 30%; patient complaint of shortness of breath; triage systolic bp < 90 mm Hg					
Range for studies without limitations (Birnbaum 2008; Quinn 2005; Sun 2007) 7 day outcomes only **low** quality evidence (inconsistency, imprecision)	Range 74 (61-84)* to 96 (89-99)	Range 57 (53-61) to 62 (58-66)	Range 1.7 to 2.5	Range 0.06 to 0.46	Range 45-48
Boston Syncope Rule = any 1 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 (> 15 min) abnormal vital signs; primary CNS event					
Grossman 2007 30 days **Moderate** quality evidence (indirect time)	97 (90 to 100)	62 (56 to 69)	2.6 (2.2 to 3.1)	0.05 (0.01 to 0.19)	52
ROSE Rule = any 1 of: BNP concentration ≥ 300 pg/ml; rectal examination showing faecal occult blood; haemoglobin ≤ 90 g/l; chest pain; bradycardia ≤ 50 bpm; ECG showing Q waves (25% R wave) / left bundle branch block; O_2 sats ≤ 94%					
Reed 2010 1 month **Moderate** quality evidence (indirect time)	87 (73-96)	66 (61-70)	2.5	0.20	38

2

3 *Risk stratification tools for recurrence of syncope*

4 One study (Hing 2005; n=100) also reported the number of patients with
5 recurrence of syncope after 3 to 6 months follow up. The diagnostic test
6 accuracy of the OESIL score for this outcome was reported, by the risk points
7 score, and the ROC curve is given in Figure 3.7. The summary curve is very
8 close to the diagonal, indicating that this is not a good test for recurrence of
9 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. None of the clinical questions relating to the initial assessment were prioritised for further economic analysis, and therefore 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. These considerations are discussed in the evidence to recommendations sections below. (3.6.1 & 3.6.2).

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- and very low- quality evidence from three studies for univariate and multivariable predictors for epilepsy in selected patients.

Signs and symptoms that are predictors <u>for</u> epilepsy: Multivariable predictors are indicated by M1 and M2 for the two Sheldon (2006) models; strong and good univariate predictors by SU and GU (and weak significant univariate predictors by U, where appropriate); and the evidence quality is given
• Cut tongue (M1 (low) & SU – low (3 studies agreed)) • Cut tongue lateral (SU – very low)
• Head-turning to one side during TLoC (M1 (low), M2 (low) & SU (low); all same study)
• Unusual posturing during TLoC (SU – low)
• Limb jerking noted by others during TLoC (GU - low)
• Unresponsiveness during TLoC (M2 – low)
• Abnormal behaviour noted [i.e. one or more of: witnessed amnesia for abnormal behaviour,(also GU – converse; same study) witnessed unresponsiveness (also M2; same study), unusual posturing during TLoC (also SU; same study), limb-jerking (also GU; same study)] (M1 - low)
• Post-ictal confusion (M1 – low; U – very low; same study) • Disoriented post TLoC (separately patient and witness reported) (GU – both very low)
• TLoC with emotional stress (M1 & M2 – both low; same study)
• Prodromal déjà-vu or jamais-vu (M1 but not significant – very low)
• Younger age (GU - low, 2 studies agreed)
• Blue colour observed by bystander (GU - very low, 2 studies agreed)
• Bedwetting during TLoC (GU - very low; inconsistency[‡] with second study – not significant for urinary incontinence (U – very low)
• long history of TLoC (GU - low)
• large number of episodes (GU - low) • Number of spells > 30 (M2 – low; same study)

[‡] The cause of the inconsistency may have been differences in methodological quality between the two studies or possibly different definitions of the predictor ('bedwetting' versus 'urinary incontinence')

[A 'strong' univariate predictor is a likelihood ratio of more than 10 and a 'good' predictor is more than 5. Multivariable predictors are independent risk factors.]

Signs and symptoms that are predictors <u>against</u> epilepsy being the cause of the TLoC:
• Any pre-syncope (M1 & M2 – both low; same study)
• TLoC with prolonged standing or sitting (M1, M2 (both low; same study) & SU (very low; same study); second study – sitting and standing before TLoC not significant (U - very low))
• Pre-syncope with prolonged sitting or standing (GU – very low; study 1)
• Sweating before TLoC (GU – very low (2 studies agreed); M1 & M2 – low; same as one of the GU studies)
• Coronary heart disease (SU - very low)
• Breathlessness preceding TLoC (SU - very low)
• Palpitations before TLoC (GU – very low)
• Nausea before TLoC (GU – 2 studies partly agreed (one LR 0.21) – very low)
• Remembered loss of consciousness (GU – very low)

3.5.1.2 Decision rules for Epilepsy

There was low quality evidence from one case control study with two decision rules, and from one cohort study of initial evaluation based on the ESC guidelines (2001):

Rule 1: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: 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:
• tonic-clonic movements usually prolonged and onset coincides with LoC
• automatism (chewing or lip smacking or frothing at the mouth) during LoC
• tongue-biting during LoC
• blue face during LoC
• epileptic aura pre-event
• prolonged confusion post-TLoC
• aching muscles post-TLoC

The sensitivity and specificity of rule 1 were high (94% each, with little uncertainty) and were high (92%) and moderately high (83%) for rule 2, with little uncertainty. The sensitivity was moderate (73%) with much uncertainty, and the specificity (100%, with little uncertainty) for the ESC initial assessment.

3.5.2 Diagnosis of vasovagal syncope versus other forms of syncope

3.5.2.1 Signs and symptoms of vasovagal syncope

There was low- and very low- quality evidence from four studies investigating vasovagal syncope in selected patients; two studies had indirect target conditions of vasovagal syncope or psychogenic pseudosyncope (Graf 2008) and neurally mediated syncope (Alboni 2001), which showed the following:

Signs and symptoms that are predictors *for* vasovagal syncope
Multivariable predictors are indicated by:
M1 for Sheldon (2006) without structural heart disease or unknown causes
M2 for Alboni (2001) heart disease patients; M3 for Alboni (2001) without heart disease
M4 for Graf (2008) in unexplained syncope; Strong & good univariate predictors by SU & GU
Predictors for VVS / Psychogenic pseudosyncope by V/P & neurally mediated syncope by NM
• Time between the first and last TLoC more than 4 years (M2 – low; NM)
• Longer history of TLoC (GU – low)
• History of pre-syncope (M2 – low; NM)
• Duration of prodromes longer than 10 seconds (M3 – low; NM) • Second study disagreed: less than 5 seonds warning was not significant, but no data were given (M1 – very low)
• More than one prodrome (M4 for V/P – low; GU – low for V/P (same study))
• Age below 35 years or low age (GU – very low (all 4 studies including V/P and NM); different magnitude of effect between VVS studies (Sheldon larger))
• Pre-syncope or syncope with prolonged sitting or standing (M1 – very low; borderline significant; GU – low (same study); different magnitude of effect between VVS studies (Sheldon larger))
• Pre-syncope or syncope with pain or medical procedure (M1 – low; GU - low (same study); different magnitude of effect between VVS studies (Sheldon larger))
• Warm place (GU – very low; 2 studies disagreed - VVS (Sheldon) significant; NM (Alboni) not significant)
• Mood changes or preoccupation before TLoC (SU – very low)
• Paresthesia (SU – very low)
• Anxiety before TLoC (GU – very low; V/P)
• Dypsnoea pre-TLoC (GU – low; V/P)
• Palpitations pre-TLoC (GU – very low; 2 studies disagreed very much (V/P significant and NM not significant))
• Sweating or warm feeling before TLoC (M1 - low)
• Headaches pre TLoC (GU - very low; 2 studies agreed: VV (Sheldon) & V/P
• Nausea after TLoC (2 studies disagreed: M2 – low for NM syncope, borderline significant and M1 – very low for VV, not significant but no data)

Signs and symptoms that are predictors ***against*** vasovagal syncope
• Age at first TLoC 35 years and older (M1 – low) • age as continuous variable (M4 - low; V/P)
• Any one of bifascicular block, asystole, SVT, diabetes (SU – very low; 2 studies, very different magnitude of effect between VVS studies (Sheldon larger); M1 - low)
• Blue colour noted by bystander (M1 - low)
• Cyanotic during syncope (GU – very low; 2 VVS studies disagreed (Sheldon significant; Romme not significant)
• Remembers something about the TLoC (M1 - low)
• P-wave at least 120 ms or non-sinus rhythm (M4 – low; V/P) • P-wave duration (GU – low; V/P)
• Syncope during effort (GU – very low; NM)
• Atrial fibrillation or flutter (GU – low)

3.5.2.2 Decision rules

There was low- and moderate-quality evidence from four studies investigating three decision rules for vasovagal syncope; one study had an indirect target condition of vasovagal syncope or psychogenic pseudosyncope (Graf 2008); two studies validated the Sheldon (2006) rule in a selected (Sheldon 2006) and a relatively unselected (Romme 2008) population; one study investigated an initial evaluation scheme based on the ESC guidelines (2001):

Rule 1 (Sheldon 2006): 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. People with epilepsy were excluded.

ESC guidelines – presence of:
• precipitating events (such as fear, severe pain, emotional distress, instrumentation, or prolonged standing) which are associated with typical prodromal symptoms – '**certain diagnosis'**
• absence of cardiac disease; long history syncope; after unpleasant sight, sound, smell, or pain; prolonged standing or crowded, hot places; nausea/vomiting associated with syncope; during/in the absorptive state after meal; after exertion (extracted from list for neurally mediated syncope) – '**highly likely diagnosis'**

We note that this study included patients with epilepsy (2%).

Rule 2 (classified as VVS or psychogenic pseudosyncope if score is 0 or above), TLoC is classified as a vasovagal syncope or psychogenic pseudosyncope 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.

The sensitivity and specificity of the Sheldon (2006) rule differed across the two populations: being moderately high (89% and 91%), with little uncertainty in the selected population (low quality evidence), and moderately high (87%) and low (31%) in the relatively unselected population (moderate quality evidence).

The sensitivity and specificity were high (98% and 100%; moderate quality evidence) with little uncertainty for the 'certain diagnosis' of the ESC guidelines initial assessment scheme. When a 'highly likely' diagnosis was also included, the sensitivity and specificity remained high (98 and 95% respectively, with little uncertainty).

The sensitivity was moderate (84%), and the specificity moderately low (50%), with some uncertainty, for the Graf (2008) rule for vasovagal syncope or psychogenic pseudosyncope (low quality evidence).

3.5.3 Decision rules for a diagnosis of psychogenic pseudosyncope versus other forms of syncope

There was low-quality evidence from one study of the ESC guidelines for the diagnosis of psychogenic pseudosyncope. The paper was unclear on the definition of psychogenic pseudosyncope and it was assumed that the guidance in the ESC guidelines should be used (Moya 2009; Brignole 2004).

Factors contributing to a diagnosis of psychogenic pseudosyncope included a high frequency of attacks (many in a day); lack of a recognisable trigger; eyes usually closed; long period of lying on the floor, young age.

The sensitivity was 86% with much uncertainty around the estimate and the specificity was 100% with very little uncertainty.

3.5.4 Decision rules for a diagnosis of orthostatic hypotension cause of syncope versus other forms of syncope

There was very low quality evidence from one study investigating the ESC guidelines for the diagnosis of orthostatic hypotension as the cause of syncope. The ESC guideline definition reported in the paper for a ‘certain diagnosis’ was: a decrease in systolic blood pressure of 20 mm Hg or a decrease of systolic blood pressure to below 90 mm Hg, following supine and three minute upright blood pressure measurements. The GDG regarded this as an indirect measure of orthostatic hypotension in that it did not accord with the widely accepted definition of the Consensus Statement of 1996.

The ‘certain’ diagnosis category gave very high sensitivity (100%), but with much uncertainty and very high specificity (99%), with little uncertainty. The addition of patients with a highly likely diagnosis decreased the sensitivity to 89%, with only minor improvements in precision, and the specificity remained at 98%.

3.5.5 Diagnosis of cardiac or arrhythmic causes of syncope versus other forms of syncope

3.5.5.1 Signs and symptoms of cardiac or arrhythmic causes of syncope

There was mainly low- and very low- quality evidence from univariate analyses in two studies investigating cardiac causes of syncope (Alboni 2001; del Rosso 2008) and in one study investigating cardiac arrhythmic causes of syncope (Sarasin 2008); the del Rosso (2008) study was in unselected patients and the other studies had selected populations. Multivariable predictors were mainly moderate- and low- quality evidence.

Signs and symptoms that are predictors <u>for</u> a cardiac cause of syncope or a cardiac arrhythmic cause:
M1: multivariable for del Rosso (2006)
M2: multivariable for Alboni (2001) heart disease patients
M3: multivariable for Alboni (2001) without heart disease
M4: multivariable for Alboni (2001) all patients excluding non-syncope risk factors
M5: multivariable for Sarasin (2003) in patients with unexplained syncope
SU and GU: strong and good univariate predictors
Card and cardiac: predictors for cardiac cause ; Arr_C: arrhythmic causes
• Age 65 years and older, but some heterogeneity o Arrhymic syncope (M5 – low and U moderate; same study) o Cardiac syncope - age as a continuous variable (GU – low) o Cardiac syncope - age 65 years and older (U (weak) – moderate quality; same study as M1 below) o But, cardiac syncope - age 65 years and older (2 studies: M4 and M1, not significant, but no results – very low/low)
• Suspected or certain heart disease or abnormal ECG – cardiac syncope or cardiac arrhythmic syncope - moderate / low o Suspected or certain heart disease (Cardiac - M4 – low) o Heart disease or abnormal ECG or both (Cardiac - M1 – moderate) o Abnormal ECG (Arrhythmia – M5 – low) o History of congestive heart failure (Arrhythmia – M5 – low)
• Time between first and last TLoC less than 4 years (in subgroup with suspected/diagnosed heart disease – cardiac; M2 - low)
• Syncope while supine; Cardiac syncope (borderline GU; 2 studies – low; M1 – moderate (same study as one of GU studies)) o Also significant in multivariable analysis in subgroup of people with suspected/diagnosed heart disease (M2 – low)

• Syncope during effort, but some heterogeneity – Cardiac syncope
  ○ Significant in two studies (SU – low; M1 – moderate (same study as one of SU studies),
  ○ Not significant in multivariable analysis in people with suspected/diagnosed heart disease in a third study (M2 - no results reported – very low)

• Dyspnoea pre-TLoC; Cardiac syncope (GU; low)
• Blurred vision pre-TLoC; Cardiac syncope in subgroup of people with suspected/diagnosed heart disease (M2 – very low)

• Palpitations pre-TLoC, gross heterogeneity; Cardiac syncope – very low
  ○ 2 studies, both univariate; one not significant (same study as M4), one GU
  ○ only significant predictor for cardiac syncope in people without suspected/diagnosed heart disease (M2 – subgroup of M4)

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Signs and symptoms that are predictors <u>against</u> cardiac or cardiac arrhythmic syncope:
• Warm crowded place / prolonged orthostasis (standing upright) / fear-pain-emotion - cardiac (M1 - low)
• Nausea or vomiting before TLoC, heterogeneity – Cardiac, low • Nausea or vomiting or both (M1 – moderate; GU – low; same study) • Nausea and vomiting as separate items – neither significant (U – low and very low)
• Feeling cold before TLoC – cardiac (GU – low)
• Feeling cold after TLoC - cardiac (GU – low)

2 *3.5.5.2 Decision rules for cardiac syncope*

3 There was low- and moderate- quality evidence from four studies investigating
4 decision rules for cardiac syncope or cardiac arrhythmic syncope, three
5 studies in selected patients. Two of the studies investigated an initial
6 evaluation scheme based on syncope guidelines (ESC in one study and
7 ACEP in another retrospective study):

Rule 1 (del Rosso 2008; EGSYS score): TLoC is classified as a 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 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)

1

Rule 2 (Sarasin 2003): TloC is classified as cardiac arrhythmic syncope 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)

2

Rule 3: ESC guidelines (certain and highly-likely diagnoses): TloC is classified as cardiac syncope if the patient has any of the following:
• ECG abnormalities (certain diagnosis)
• Presence of severe structural heart disease (highly likely diagnosis)
• Syncope during exertion or when supine (highly likely diagnosis)
• TLoC preceded by palpitation or accompanied by chest pain (highly likely diagnosis)
• Family history of sudden death (highly likely diagnosis).

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Rule 4: ACEP recommendations: TLoC is classified as cardiac syncope, which is equated with admission to hospital, if the patient has any one of the following:
ACEP level B (high risk, admit to hospital):
• 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
ACEP level C (moderate risk; consider admission to hospital)
• 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

For cardiac syncope:

- EGSYS (low quality evidence): sensitivity high (91%), with some uncertainty; specificity moderate (69%), with little uncertainty
- ESC guidelines: sensitivity moderate (71%), with large uncertainty, specificity high (100%), with little uncertainty for the 'certain diagnosis' (low quality evidence). Inclusion of a 'highly likely' diagnosis gave similar sensitivity and specificity and the uncertainty was reduced (moderate quality).
- ACEP guidelines: sensitivity high (100%) and the specificity moderately high (81%), with little uncertainty, for level B in a retrospective study (low quality evidence). When level C patients were also included, the sensitivity was unchanged but the specificity reduced (33%).

For cardiac arrhythmic syncope:

- Sarasin score: sensitivity high (96%), with little uncertainty, and specificity moderately low (42%) (low quality evidence).

ROC curves comparing the EGSYS score and the Sarasin rule suggested that the most reliable test of these two was the EGSYS score.

3.5.6 Risk factors and decision rules for death within 12 months

3.5.6.1 Features that are risk factors for death

There was low-quality evidence from two studies recording death at an indirect time (12 months and limited evidence for 30 days).

Signs and symptoms that are predictors for a risk of death within 12 months: Multivariable predictors are indicated by M; significant univariate risk factors by SigU
• Age 65 years and older (2 studies; M (12 months), SigU (30 days, 3, 6 months) – low, indirect)
• Cardiovascular disease in clinical history (M – low; SigU – low, indirect; same study)
• Abnormal ECG findings (M – very low; SigU – low, indirect; same study)
• Syncope without prodromes (M – small effect, very low; SigU – low indirect; same study)
• Hypertension (SigU – low indirect)
• Diabetes mellitus (SigU – low indirect)
• Syncope-related traumatic injuries (SigU – low indirect)

3.5.6.2 Decision rules for death within 12 months

There was low- , very low- and moderate-quality evidence from four studies examining different risk stratification rules for death in an unselected population; one study was retrospective:

OESIL score (Colivicchi 2003); 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 (Quinn 2008); the score was predictive of death at 30 days, 3, 6 and 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.

ACP guidelines (Crane 2002, retrospective) – the group at high risk of death was identified with admission criteria:
• 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 – the moderate risk group was identified with considering admission
• 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

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 moderate quality evidence, although at an indirect time (mainly 6 and 12 months), high sensitivity (97 and 93% respectively), but only moderate specificity (73 and 53%). There was low-quality evidence at an indirect time from one UK study, which evaluated the American College of Physicians (**ACP**) **guidelines**. The high- and moderate-risk groups combined had a sensitivity of 100% and a specificity of 53%.

3.5.7 Risk factors and decision rules for a serious adverse event within 7-14 days

A 'serious event' is defined in most of the studies in this section 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.

The Costantino (2008) study excluded patients with conditions primarily confirmed in the ED, that would have required hospital admission independently of whether they had TLoC, such as: myocardial infarction, acute pulmonary embolism, subarachnoidal haemorrhage, stroke, cardiac arrest, sustained bradycardia (< 35 bpm), complete atrioventricular block, sustained ventricular tachycardia. The events recorded in this study were death and major therapeutic procedures or early re-admission.

3.5.7.1 Risk factors for a serious adverse event

There was low- and moderate-quality evidence from six studies in unselected patients showing that the following features were statistically significant risk factors for a serious event within 7-14 days;

Univariate and multivariable risk factors for a serious event 7-14 days
2 studies investigated multivariable predictors, indicated by: M1 (Costantino 2008 – different adverse events) and M2 (Reed 2010); Ssignificant univariate risk factors are indicated by SigU. We state when the confidence interval for the RR (or OR) lies wholly or almost wholly > 2.
• Age over 40 years (SigU, moderate quality evidence, RR > 2) in two studies • Age over 60 years in 2 studies (SigU, low) • Age over 65 years in 1 study (SigU, moderate, RR > 2) • Age not significant for multivariable analyses in the short term: M1 (moderate) and M2 (low), but significant in the longer term (11 days to 1 year, moderate, OR>2)
• Male gender (SigU, moderate; multivariable M1 (low, borderline significant) and M2 (very low))
• Coronary artery disease (1 study, SigU, borderline, low)
• Congestive heart failure (5 studies, SigU, low; M1 (low, not significant)); but BNP ≥ 300pg/ml (marker for CHF) is significant in M2 (low, OR >> 2)
• Structural heart disease (1 study, SigU, moderate, RR > 2; M1 not significant - same study)
• Hypertension (borderline, 2 studies, SigU, low)
• Abnormal ECG (4 studies, SigU, moderate, RR > 2; M1, moderate, OR >>2)
• Arrhythmia (2 studies, SigU, moderate, RR > 2); M2 abnormal Q wave/left bundle branch block (low, OR > 2)
• Diabetes (1 study, SigU, low)
• COPD (1 study, SigU, low; M1 not significant same study, low)
• Diuretics (1 study, SigU, low)
• Antiarrhythmic medication (1 study, SigU, moderate)
• Breathlessness (4 studies, SigU, borderline significant, low)
• Systolic blood pressure < 90 mm Hg (3 studies, SigU, low, RR > 2)
• Oxygen saturation < 95% (1 study, SigU, low; M2 not significant, very low)
• Respiratory rate >24 breaths per minute (1 study, SigU, moderate, RR > 2)
• Pulse rate < 50 bpm or > 110 bpm (1 study, SigU, low, RR > 2)
• Chest pain (1 study, SigU, low)
• Any one of: râles; abnormal heart sounds; carotid bruits; heart murmur (systolic or diastolic) (1 study, SigU, moderate, RR > 2)
• Haematocrit less than 30% (3 studies, SigU, moderate, RR > 2)
• Haemoglobin ≤ 90g/l (1 study, M2 low, OR >>2)
• Rectal examination showing faecal occult blood (1 study, M2, low, OR >>2)
• GI bleed (1 study, SigU, borderline significant, very low)
• Absence of symptoms pre-TLoC (1 study (Costantino), SigU, low; M1 (Costantino) low – same study)
• Trauma (1 study (Costantino), SigU, low; M1 (Costantino), moderate – same study) but another study not significant for face and head trauma

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There was moderate quality evidence in one study (Costantino 2008) for multivariable analyses comparing short term events (up to 10 days) and longer term (11 days to 1 year).

The short term events predictors included: • abnormal ECG (OR>>2) • trauma • absence of symptoms preceding syncope (low quality evidence) • male gender (borderline significant – low). Not significant were age over 65 years, heart failure; structural heart disease and COPD.
The longer term events predictors included: • age above 65 years • neoplasms • cerebrovascular disease • structural heart disease • and ventricular arrhythmias (borderline significant) as low quality evidence. Not significant were: hypertension, heart failure, COPD and abnormal ECG at presentation.

3.5.7.2 Decision rules for a serious adverse event

Ten studies reported four decision rules for serious adverse events at 1-2 weeks. The evidence was very low quality for the OESIL score (2 studies at 3 months); low quality for the San Franciso Syncope Rule (6 studies, 3 without limitations); moderate quality for the Boston Syncope Rule (1 study at 30 days) and moderate quality for the ROSE Rule (1 study at 1 month).

San Francisco Syncope Rule (6 studies) for predicting adverse events. 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 (1 study) at **30 days**. 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 > 500 ms
• Gastrointestinal bleed by haemoccult or history
• Haematocrit < 30%
• Dehydration not corrected in the ED
• Persistent (> 15 min) abnormal vital signs: o respiratory rate > 24 / min o oxygen saturation < 90% o sinus rate < 50 bpm or >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**: 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

For the San Francisco Syncope Rule at 7 days, the sensitivity ranged from 74-96% across the studies, with little uncertainty in the point estimates and the specificity ranged from 57 to 62%, with little uncertainty.

For the Boston Sycope Rule at 30 days for a single study, the sensitivity was 97% and the specificity 62%, both had little uncertainty around the estimates.

For the OESIL Rule at 3 months, the sensitivity was 78 or 91%, with some uncertainty, and the specificity was 64 or 49%, with little uncertainty.

For the ROSE Rule at 1 month for a single study, the sensitivity was 87%, with some uncertainty, and the specificity was 66%, with little uncertainty.

3.6 Evidence to Recommendations

3.6.1 Information-gathering and initial decision making (recommendations 1.1.1.1 - 1.1.3)

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.

The GDG were mindful that information obtained at the initial assessment is critical in establishing whether a TLoC has occurred, making an initial diagnosis and directing patients along the correct care pathway. The GDG considered it likely that recommendations to improve the quality of information available to clinicians would be highly cost-effective, given that a lack of good quality information could result in patients receiving inappropriate subsequent care which may be costly, ineffective and possibly harmful.

The GDG recognised at the outset that people who had a serious injury as a result of a suspected TLoC could be in need of urgent treatment. They noted that injury was fairly common in people having TLoC, and drew on additional information (Bartoletti 2008) that recorded 29% of patients with TLoC presenting to a general hospital ED had physical injury secondary to TLoC and 5% had severe trauma (causing skull or other major bone segments fracture; intracranial haemorrhage; internal organ lesions requiring urgent, specific treatment; retrograde amnesia or focal neurologic defect).

The GDG were also aware that TLoC can, rarely, be caused by acute hydrocephalus, such as in tumours of the third ventricle (colloid cysts) and in patients with cerebrospinal fluid shunts who develop blocking of the shunt. These patients may have dilated unreactive pupils and respiratory arrest or impairment during an attack, and such episodes constitute a neurological emergency. The GDG therefore decided to make a recommendation covering both of these issues (recommendation 1.1.1.1). Health care professionals should use clinical judgement to determine appropriate management and the urgency of treatment for people with suspected TLoC who had an injury or who had not made a full recovery of consciousness. This ‘appropriate management’ could equally include further investigation of the TLoC (all subsequent recommendations).

The GDG determined that the next stage in the patient pathway was to find out as much information as possible about the TLoC event. Recommendation 1.1.1.2 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. Part of recommendation 1.1.4.1 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 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, therefore in order to exclude someone from the guideline, it is necessary to be definite that the person did not have TLoC; people in whom there is uncertainty should be assumed to have had TLoC. Recommendation 1.1.1.4 describes the steps that should be taken.

3.6.2 Obtaining patient history, clinical examination, and initial tests (recommendations 1.1.2.1 and 1.1.2.2)

The GDG described in recommendation 1.1.2.1 items of patient history that should be obtained, features that should be determined by clinical examination and general tests that should be carried out to aid diagnosis. The GDG also recognised that some people would have underlying conditions that might have caused TLoC, such as hypoglycaemia, and recommended that the health care professional carry out relevant additional tests (recommendation 1.1.2.2). A 12-lead ECG should also be obtained (see section 4.8).

3.6.3 Making a judgement based on initial assessment

Decision-making based on evidence was on the following:

- people at increased risk of death or serious adverse events in the immediate future (and who require urgent referral to specialist departments)
- 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 vasovagal syncope, orthostatic hypotension, epileptic seizures and cardiac syncope.

3.6.3.1 Red flag recommendations (1.1.5.1 and 1.1.5.2)

Quality of the evidence

There was moderate- and low-quality evidence from the review on risk factors and decision rules for serious adverse events; mainly low-quality evidence from the review on risk factors and decision rules for death; and moderate- and low-quality evidence on univariate and multivariable predictors and decision rules for a cardiac cause of syncope.

GDG discussion

The GDG wished to determine who was at high risk of a serious event and who should be referred for urgent assessment (that is, within 24 hours). This is how 'red flags' are defined in the guideline. Serious events could be death, cardiovascular, or cerebrovascular.

In considering red flags, the GDG focussed on the evidence for short term adverse outcomes (up to 2 weeks). They also noted that a diagnosis of a cardiac cause of syncope has been identified with higher risk and admission to hospital. Although several of the studies aligned high risk with hospital admission, the GDG concluded that a decision to admit the patient should be left to clinical judgement, but that the recommendations should indicate the urgency of the need for further investigation or treatment. The GDG were mindful of the costs of urgent hospital admission and of other urgent referral, and the potential impact of hospitalisation on the individual's quality of life. They therefore felt that it was important to target urgent referral to those people who were most likely to experience a serious adverse event in the days following TLoC.

The GDG considered the decision rules for a diagnosis of cardiac syncope or cardiac arrhythmic syncope, preferring to use the predictors for the former.

The GDG identified that it was important to minimise the number of false negatives (i.e. requiring a test of high sensitivity), because failing to identify people who had a cardiac cause of syncope could have serious consequences. Preferably, the test should have high specificity to avoid over-referral.

For a diagnosis of a cardiac cause of syncope, the GDG considered the Sarasin (2003) rule and the ACEP guidelines (level B) study (Elseber 2005). However, both of these studies were retrospective and the GDG had some concerns about the evidence quality. The GDG also took into account the consistent univariate and multivariate signs and symptoms predicting cardiac syncope, namely: suspected heart disease, history of congestive heart disease, abnormal ECG, syncope while supine, syncope during effort and dyspnoea pre-TLoC. The GDG did not feel confident in the risk factors, palpitations pre-TLoC and blurred vision or the time between first and last TLoCs. The GDG was also concerned to include a family history of sudden death as an important risk factor: they recognised this as a relatively rare, though serious, occurrence that might not be sufficiently prevalent to be detected in an multivariable analysis – family history of sudden death appeared in the two guidelines tested as 'moderate risk'. The GDG noted that there was heterogeneity across the multivariable analyses for the risk factor, age over 65 years, and identified that even when this risk factor was significant, there was uncertainty around the estimate.

The GDG then considered the reviews of predictors and decision rules for death and for serious adverse events. The GDG emphasised that the most relevant target condition was serious adverse events within 7-14 days. They took into consideration the Costantino (2008) study which showed that multivariable predictors for death, major therapeutic procedures or early re-admission were very different for longer term follow up (11 days to one year), compared to short term events (up to 10 days). As a result, the GDG decided to regard as indirect evidence the review for risk factors for death at up to 12 months and the studies reporting risk factors or decision rules for serious events at three months and, to a lesser extent, at one month. This meant that

the OESIL and San Francisco Syncope Rules for death and the OESIL score for serious adverse events were treated with caution.

The GDG decided not to recommend using the San Francisco Syncope Rule because it only had moderate-high sensitivity (74 - 96%) and moderate specificity (57 – 62%). The ROSE rule for serious events at one month was regarded as slightly indirect evidence and had only moderately high sensitivity (87%) and specificity (66%). The remaining rule, the Boston Syncope Rule was regarded as slightly indirect at one month, and the GDG noted this was validated in only one study, however, the sensitivity was high (97%) and the specificity moderate (62%).

The GDG therefore decided to also take into account the significant univariate and multivariable predictors about which they were confident. These included: congestive heart failure, abnormal ECG, breathlessness, systolic blood pressure below 90 mm Hg, respiratory rate more than 24 breaths per minute, pulse rate less than 50 bpm or more than 110 bpm, chest pain, any one of râles; abnormal heart sounds; carotid bruits and heart murmur; haematocrit less than 30%, a rectal examination showing faecal occult blood, a GI bleed; haemoglobin 90 g/l or less; the absence of symptoms pre-TLoC and trauma.

The GDG noted that age over 65 years was a significant univariate predictor, but did not feature in the short term multivariable analyses, and concluded that it could be a confounder for other factors. Nevertheless the GDG were concerned, from their clinical experience, about the risks of adverse events in people over 65 years who had no warning before TLoC.

The GDG took into account the Costantino (2008) study which separated out (and excluded) the patients who had conditions confirmed in ED that would have led to hospital admission independently of TLoC. These conditions included myocardial infarction, acute pulmonary embolism, subarachnoidal haemorrhage, stroke, cardiac arrest, sustained bradycardia (< 35 bpm), complete atrioventricular block, and sustained ventricular tachycardia.

In a similar way, the GDG decided to separate the predictors for short term adverse events and those for a diagnosis of a cardiac cause of syncope into two main groups: (1) those identifying people for whom TLoC is secondary to a condition that requires immediate treatment, and (2) those for people who had TLoC and also have other signs and symptoms, that together mean that the patient requires urgent attention.

For the latter category, the GDG noted that, although the absence of prodromal symptoms was a multivariable independent predictor for short term adverse events in one study (Costantino), the odds ratio was relatively small with some uncertainty, and did not appear to be supported by other studies. The GDG also noted that, although most people with cardiac syncope and potential high risk of death will have no prodromes and that people with vasovagal syncope are most likely to have prodromes, older people with vasovagal syncope do not always have prodromes. The GDG decided that the risk factor, absence of prodromal symptoms, although an indicator of a high risk category, was not sufficiently strong to use independently to determine people in need of urgent referral, and decided to add a weak recommendation combining age with no prodromal symptoms (recommendation 1.1.5.2).

The GDG also noted that some of the predictors in the other studies fell into this category of conditions independently requiring urgent attention, for example, a GI bleed, chest pain and abnormal vital signs. If people who had TLoC did have conditions that required immediate treatment, they should be managed according to the needs for that condition, with the appropriate degree of urgency (recommendation 1.1.5.1).

The GDG concentrated on defining the risk factors that, together with TLoC, made the person at high risk of an adverse event (recommendation 1.1.5.2). In doing so, 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.

3.6.3.2 Recommendations for an uncomplicated faint (recommendation 1.1.5.3)

Quality of the evidence

There was low- and very-low quality evidence from the review on univariate and multivariable predictors and low- and moderate- quality evidence for decision rules for vasovagal syncope.

GDG discussion

The GDG considered it important to identify those people who have experienced an uncomplicated faint, which is not associated with any increased risk of serious adverse events, in order to prevent further unnecessary investigations which would be inconvenient for the person, costly and unlikely to result in any change in clinical management.

The GDG considered the evidence for decision rules and noted that the Sheldon (2006) rule did not perform well in a population representative of the guideline, having low specificity, which would result in people being incorrectly assessed to have had vasovagal syncope, when they might have more serious causes of TLoC. The GDG decided to focus on the evidence for the population with pure vasovagal syncope, and based their recommendations on the univariate and multivariable predictors of vasovagal syncope, together with the factors included in the ESC guidelines study. The GDG noted that the evidence also required cardiac syncope predictors to be absent and made this clear in their recommendation.

The multivariable evidence showed the vasovagal predictors were independent so only one was necessary for a diagnosis of uncomplicated faint. Based on their consensus experience, the GDG expanded the posture factor to cover any previous similar episodes in which TLoC has been prevented by lying down. Although the multivariable predictor for prodromes was specifically ‘sweating and feeling warm pre-TLoC’, the GDG also took account of the weak univariate evidence for other prodromal factors and

decided to recommend prodromal symptoms more generally. After the DVLA, the GDG adopted the mnemonic, 'the 3Ps' 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 1.1.5.4.

3.6.3.3 Recommendations for orthostatic hypotension (recommendation 1.2.1.1)

Quality of the evidence

There was low to very low-quality evidence from one study on the predictors for orthostatic hypotension based on the ESC guidelines. There was much uncertainty in the estimates of diagnostic test accuracy and the GDG regarded the definition of orthostatic hypotension as being indirect because it differed from the 1996 Consensus Statement.

GDG discussion

The study reported indicators for both 'certain' and 'highly likely' diagnoses of orthostatic hypotension, following supine and three-minute upright blood pressure measurements. The GDG noted the very high point estimate for the sensitivity (100%) and very high specificity (99%) for the certain diagnosis, but also took into account the high degree of uncertainty surrounding the sensitivity. The GDG therefore lacked confidence in the evidence.

The GDG also drew on their experience and noted that there are different definitions of orthostatic hypotension, with a range of definitions used in the recent literature. In the absence of a full literature review of orthostatic hypotension, including in people who have not necessarily had TLoC, the GDG decided to state in their recommendation the basic method of measuring orthostatic hypotension (supine followed by three minutes of repeated measurements in an upright position). This approach should be taken only for people who are suspected, on the basis of history, to have orthostatic hypotension, and who do not have features suggesting an alternative diagnosis.

The GDG did not consider it desirable to routinely carry out supine and standing blood pressure measurements, which could be time consuming. The GDG recognised that some people who had a suggestive history of orthostatic hypotension would not necessarily have positive results on this simple test, but rather than recommendating alternative approaches that they had not reviewed, preferred to refer the person with suspected orthostatic hypotension for further specialist cardiovascular assessment. [Alternative approaches might involve tilt testing with beat-to beat blood pressure monitoring in order to detect transient initial orthostatic hypotension or delayed orthostatic hypotension].

The GDG noted that orthostatic hypotension can be caused by some medications, and indicated in their recommendation that if the condition is diagnosed, causes including drug therapy should be investigated. When describing further management following a diagnosis, the GDG 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.

3.6.4 Recording information and transfer of patients and records

The GDG noted from their discussions that different clinicians may be involved; for example, there may be initial contact with the ambulance service, but then the person is transferred to the Emergency Department or discharged home. 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 1.1.4.1).

If the person with TLoC had a clear diagnosis of uncomplicated faint or situational syncope, they should be discharged home, provided there were no other social or clinical causes for concern. The GDG wished to encourage people to see their GP if they had called an ambulance or attended the ED

and were later discharged. The health care professional should give a copy of the patient record and ECG report to the patient (recommendation 1.1.5.5).

The GDG made one recommendation specific to the ambulance service (recommendation 1.1.5.6), namely that all people who had TLoC should be taken to the ED unless they clearly had a diagnosis of an uncomplicated faint or situational syncope. This recommendation did not discrimate the degree of urgency.

3.6.4.1 Recommendation for a diagnosis of psychogenic pseudosyncope

Quality of the evidence

There was low-quality evidence from one study on indicators for psychogenic pseudosyncope, based on the ESC guidelines. There was much uncertainty in the estimates of diagnostic test accuracy.

GDG discussion

The GDG did not carry out a full review of the literature on psychogenic pseudosyncope or psychogenic non-epileptic seizures (PNES), outside diagnostic test accuracy studies. They considered that this topic should be dealt with as a separate guideline and were aware that this may be taken up by NICE at a later date. Meanwhile, the GDG recognised that some guidance in the TLoC guideline was needed for people with suspected psychogenic pseudosyncope or PNES and made a recommendation accordingly (recommendation 1.4.1.2).

The GDG did not feel sufficiently confident in the evidence from the review of a single study to use signs and symptoms to make a differential diagnosis of psychogenic pseudosyncope or PNES at the initial stage, preferring to carry out other investigations first, and then consider the possibility of psychogenic pseudosyncope or PNES later in the diagnostic pathway. The GDG gave some indications for suspecting psychogenic forms of TLoC, noting that the distinction between epilepsy and non-epileptic seizures is complex and requires specialist assessment, usually neurological.

The GDG noted that there is some evidence on the use of tilt testing for the diagnosis of psychogenic pseudosyncope, but had not reviewed the evidence for this topic.

Recommendation 1.4.1.2 is based on the GDG's experience, with limited supporting evidence from the van Dijk (2008) study.

3.6.4.2 Recommendation for referral to a specialist in epilepsy (recommendation 1.2.2.1)

Quality of the evidence

There was low-quality evidence for three decision rules for predicting epilepsy: One of the decision rules had high sensitivity (94%) and specificity (94%), but was validated in a selected population. The other study in an unselected population had only moderate sensitivity (73%) with uncertainty around this estimate; the specificity was 100%. Three studies reported data on signs and symptoms as univariate predictors of epilepsy as the cause of the TLoC: one study also gave multivariable predictors. The evidence quality for each of these predictors was low or very low, reflecting study limitations, a lack of representativeness of the population, inconsistency between studies and imprecision.

GDG discussion

The GDG considered the benefits of referring people with features that are suggestive of epilepsy to an epilepsy specialist in order to obtain an accurate diagnosis and appropriate treatment. Given the much lower prevalence of epilepsy in comparison to syncope, they were also mindful of the likely costs and possible harms that could result from directing patients with syncope along the wrong diagnostic pathway. They were therefore keen to ensure that referrals to an epilepsy specialist are targeted at those patients with features that are suggestive of epilepsy and without features suggestive of syncope.

The GDG did not feel confident to recommend either of the Sheldon (2002) decision rules because the study excluded people with an unexplained cause of TLoC. In the study examining the ESC guidelines, the GDG considered that there was too much uncertainty around the estimates to recommend the ESC guidlelines. The GDG therefore examined individual predictors from the univariate and multivariable analyses to help them make recommendations.

Usually it would be desirable to base judgements on independent multivariable predictors for risk factors, but these varied with the model used and the GDG considered that, for signs and symptoms, strong or good univariate predictors would be equally useful. The GDG interpreted the low- and very low quality evidence 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, and they were not very confident in the results from the case-control studies.

The GDG also noted that, although the main study stated that it excluded people with psychogenic non-epileptic seizures, it did not say how this was diagnosed. The GDG considered that the multivariable risk factor, TLoC with emotional stress, was more likely to be a predictor for psychogenic non-epileptic seizures, and therefore decided not to include this factor in their recommendation for epileptic seizures.

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.

Regarding tongue biting, the GDG considered the very low quality evidence from a case control study in a highly selected population in addition to the main study. The former study suggested lateral tongue biting was an even stronger predictor than tongue biting generally, but there was much imprecision, and the GDG were more confident to use the non-specific ‘tongue biting’ symptom as an indicator of epilepsy.

Regarding the often cited ‘urinary incontinence’ as an indicator of epilepsy, the GDG noted the difference between univariate predictors in two of the studies, one significant for ‘bedwetting’ and one not significant for ‘urinary incontinence’. The absence of either term in multivariable analysis and the very low quality of the evidence reinforced the GDG’s lack of confidence in this indicator for epilepsy.

The GDG also decided to give an indication of features that health care professionals should consider more likely to be caused by syncope than epileptic seizures, and based their recommendation on the very low quality evidence and their consensus discussion. The GDG’s consensus, based on the evidence, is given in recommendation 1.2.2.1.

Finally, the GDG wished to reinforce the recommendation from the NICE guideline on epilepsy on not using an electroencephalogram routinely in the investigation of TLoC.

3.7 Recommendations

1.1 Initial assessment

1.1.1 Gathering information about the event and initial decision making

1.1.1.1 If the person with suspected transient loss of consciousness (TLoC) has sustained an injury or they have not made a full recovery of consciousness, use clinical judgement to determine appropriate management and the urgency of treatment.

1.1.1.2 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 by telephone witnesses who are not present. Record details about:

- circumstances of the event
- person’s posture immediately before loss of consciousness
- prodromal symptoms (such as sweating or feeling warm/hot)
- appearance (for example, whether eyes were open or shut) and colour of the person during the event

- presence or absence of movement during the event (for example, limb-jerking and its duration)
- any tongue-biting (record whether the side or the tip of the tongue was bitten)
- injury occurring during the event (record site and severity)
- duration of the event (onset to regaining consciousness)
- presence or absence of confusion during the recovery period.

1.1.1.3 When recording a description of the suspected TLoC from the patient or 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.

Determining whether the person had TLoC

1.1.1.4 Use information gathered from all accounts of the suspected TLoC (see recommendation 1.1.1.2) to confirm whether or not TLoC has occurred. If this is uncertain it should be assumed that they had TLoC until proven otherwise. But, if the person did not have TLoC, instigate suitable management (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 Obtaining patient history, physical examination and tests

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 that may have contributed to TLoC (for example, diuretics)
- vital signs (for example, pulse rate, respiratory rate and temperature) – repeat if clinically indicated

- lying and standing blood pressure if clinically appropriate
- other cardiovascular and neurological signs.

1.1.2.2 If during the initial assessment, there is suspicion of an underlying problem causing TLoC, or additional to TLoC, carry out relevant examinations and investigations (for example, check blood glucose levels if hypoglycaemia is suspected, or haemoglobin levels if anaemia or bleeding is suspected).

1.1.5 Making a judgement based on initial assessment

Red flags: people requiring urgent assessment and treatment

1.1.5.1 If TLoC is secondary to a condition that requires immediate action, use clinical judgement to determine appropriate management and the urgency of treatment.

1.1.5.2 Refer within 24 hours for specialist cardiovascular assessment by the most appropriate local service, anyone with TLoC who also has any of the following.

- An ECG abnormality (see recommendation 1.1.3.1).
- Heart failure (history or physical signs).
- TLoC during exertion.
- Family history of sudden cardiac death in people aged younger than 40 years and/or an inherited cardiac condition.
- New or unexplained breathlessness.
- A heart murmur.

Consider referring within 24 hours for cardiovascular assessment, as above, anyone aged older than 65 years who has experienced TLoC without prodromal symptoms.

No further immediate management required

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

- there are no features 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 suggestive of uncomplicated faint (the 3 'P's) such as:
  - **P**osture – prolonged standing or similar episodes that have been prevented by lying down
  - **P**rovoking factors (such as pain or a medical procedure)
  - **P**rodromal symptoms (such as sweating or feeling warm/hot before TLoC).

1.1.5.4 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 straining during micturition (usually while standing) or by coughing or swallowing.

1.1.5.5 If a diagnosis of uncomplicated faint or situational syncope is made, and there is nothing in the initial assessment to raise clinical or social concern, no further immediate management is required. If the presentation is not to the GP, the healthcare professional should:

- advise the person to take a copy of the patient report form and the ECG record to their GP
- inform the GP about the diagnosis, directly if possible; if an ECG has not been recorded, the GP should arrange an ECG (and its interpretation as described in recommendation 1.1.3.2) within 3 days.

Further immediate management required

1.1.5.6 If the person presents to the ambulance service, take them to the Emergency Department unless a diagnosis of an uncomplicated faint or situational syncope is clear.

1.2 Further assessment and referral

1.2.1 Suspected orthostatic hypotension

1.2.1.1 Suspect orthostatic hypotension on the basis of the initial assessment when:

- there are no features suggesting an alternative diagnosis **and**
- the history is typical.

If these criteria are met, measure lying and standing blood pressure (with repeated measurements while standing for 3 minutes). If clinical measurements do not confirm orthostatic hypotension despite a suggestive history, refer the person for further specialist cardiovascular assessment.

If orthostatic hypotension is confirmed, consider likely causes, including drug therapy, and 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]).

1.2.2 Suspected epilepsy

1.2.2.1 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 2 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.
- Head-turning to one side during TLoC.
- No memory of abnormal behaviour witnessed by someone else.
- Unusual posturing.
- Prolonged limb-jerking (note that brief seizure-like activity can often occur during uncomplicated faints).
- Confusion following the event.
- Prodromal déjà vu, or jamais vu (see glossary).

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

- Prodromal symptoms that on other occasions have been abolished by sitting or lying down.
- Sweating.
- Prolonged standing that appeared to precipitate the TLoC.
- Pallor during the episode.

Do not routinely use electroencephalogram (EEG) in the investigation of TLoC (see 'The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care' [NICE clinical guideline 20]).

4 12-lead ECG

4.1 Clinical Questions

Q8) In people who have experienced 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, Brignole 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 had 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 had 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 had TLoC

4.3.1 Methods of the review – selection criteria

4.3.1.1 Types of participants

Adult patients who had 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 17:

Table 17: 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

4.3.2.2 Target condition

The target conditions for the six studies were:

- Death only, at 12 months (Colivicchi 2003)
- Death and cardiac outcomes only: sudden death, myocardial infarction, arrhythmias (VT>3, sick sinus disease, etc) structural heart disease (aortic 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

Six studies (Colivicchi 2003; Grossman 2007; Hing 2004; Quinn 2004; Reed 2007; Sun 2008) 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 18 and Table 19, with imprecision indicated by one or two asterisks.

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 18: 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 **moderate quality evidence**	66 (54-76)	73 (69-76)	2.4 (2.0-2.9)	0.47 (0.35-0.64)	12	24	32
Reed 2007 3 months follow up **very low**	82 * (48-98)	45 (35-56)	1.5 (1.1-2.1)	0.40 (0.11-1.43)	11	16	58
Death and Cardiac outcomes only							
Sun 2008 **moderate** 14 days follow up	76 (60-87)	76 (71-80)	3.1 (2.5-4.0)	0.32 (0.19-0.54)	10	26	30
Hing 2004 3 to 6 months follow up **very low**	74 * (52-90)	69 (57-79)	2.4 (1.6-3.6)	0.38 (0.19-0.77)	23	42	41
Death only							
Colivicchi 2003 death 12 months **low**	61* (42-78)	74 (68-79)	2.3 (1.6-3.3)	0.53 (0.34-0.82)	12	23	30

Table 19: 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 **moderate quality evidence**	1 (0-8)	98 (95-99)	0.7 (0.1-5.6)	1.01 (0.97-1.04)	2
Grossman 2007 QT interval > 500ms; all adverse events; 30 days **moderate quality evidence**	0 (0-5)	100 (98-100)	NA	1.00	0
Grossman 2007 heart block; all adverse events; 30 days **moderate quality evidence**	1 (0-8)	98 (95-99)	0.7 (0.1-5.6)	1.01 (0.97-1.04)	2
Grossman 2007 abnormal sinus rate; 30 days **moderate quality evidence**	6 (2-14)	95 (91-98)	1.2 (0.4-3.7)	0.99 (0.93-1.06)	5
Quinn 2004 Abnormal rhythm (non sinus); 7 days **moderate**	43 (32-55)	81 (78-84)	2.3 (1.7-3.1)	0.70 (0.58-0.85)	21
Quinn 2004 abnormal ECG, new changes **moderate quality evidence**	56 (44-67)	82 (79-85)	3.2 (2.5-4.1)	0.54 (0.42-0.69)	22

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

One study in 477 patients (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 20; imprecision is indicated by one or two asterisks.

Table 20: 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 **very low**	50 ** (1-99)	88 (80-93)	4.1 (0.9-17.9)	0.57 (0.14-2.28)	2.0	8.0	1.1	13
age 40-59y **low**	90 * (55-100)	88 (79-94)	7.3 (4.0-13.1)	0.11 (0.02-0.73)	10.0	45.0	1.3	20
age 60-79y **low**	71 * (42-92)	67 (57-76)	2.2 (1.4-3.3)	0.43 (0.18-0.99)	12.0	23.0	5.5	38
age 80 and above **low**	72 * (47-90)	60 (50-71)	1.8 (1.2-2.7)	0.46 (0.21-0.99)	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 study in 477 patients (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 21; imprecision is indicated by one or two asterisks. 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. This reduced the evidence quality to low or very low as indicated.

Figure 4.1: Effect of operator

Table 21: 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 (53-87) *	74 (67-80)	2.8 (2.0-3.8)	0.37 (0.21-0.68)	32
all ages Test operator: attending physician	59 (39-76) *	72 (65-78)	2.1 (1.4-3.1)	0.57 (0.37-0.89)	32
age 18-39y (very low) Test operator: resident physician	0 ** (0-98)	82 (70-91)	1.4 (0.1-15.9)	0.92 (0.41-2.07)	18
age 18-39y (very low) Test operator: attending physician	0 ** (0-98)	88 (76-95)	1.9 (0.1-23.0)	0.86 (0.39-1.93)	12
age 40-59y (very low) Test operator: resident physician	100 ** (40-100)	85 (71-94)	5.6 (2.8-11.6)	0.12 (0.01-1.65)	22
age 40-59y (very low) Test operator: attending physician	50 ** (7-93)	80 (66-91)	2.6 (0.8-8.0)	0.62 (0.23-1.67)	22
age 60-79y (very low) Test operator: resident physician	67 * (35-90)	67 (40-69) *	2.0 (1.1-3.5)	0.48 (0.21-1.10)	39
age 60-79y (very low) Test operator: attending physician	67 * (35-90)	55 (40-69) *	1.5 (0.9-2.5)	0.60 (0.26-1.40)	49
age over 80y (very low) Test operator: resident physician	75 * (43-95)	61 (46-74) *	1.9 (1.2-3.1)	0.41 (0.15-1.12)	46
age over 80y (very low) Test operator: attending physician	58.* (28-85)	65 (50-78) *	1.7 (0.9-3.0)	0.64 (0.32-1.30)	40

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

A summary of study design features across studies is given in the table and further details of individual studies are given in Appendix D1.

Characteristics	Details
Design	• 2 studies were prospective cross sectional (Charbit 2006, Fatemi 2008); • 2 were retrospective (Christov 2001, Denny 2007 and Taha 2000) • 1 was unclear (Kaneko 2005).
Sample size	• The number of patients in the prospective studies varied from 108 to 440, while the database population in the retrospective studies varied from 329 to 44,808.

4.4.2.2 Population

A summary of population characteristics across studies is given in the table below and further details of individual studies are given in Appendix D1.

Characteristics	Details

Setting	• 3 studies examined a 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).
	• 1 examined patient database records from a cardiology department (Christov 2001)
	• 1 assessed patients admitted to a Coronary Care Unit (CCU) or a Cardiac Emergency Ward (Fatemi 2008)
	• 1 assessed patients in a recovery room after anaesthesia (mainly general anaesthesia); those with known cardiac arrhythmias or bundle branch block were excluded (Charbit 2006)

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

Studies of diagnostic test accuracy were assessed using QUADAS criteria (see Appendix D2).

The overall QUADAS assessment of all the studies was "-" due to patients potentially not being representative of an unselected TLoC population..The following studies were considered to be more at risk of bias than others:

- Charbit 2006 (patients in the recovery room following anaesthesia more unrepresentative; also did not have an adequate reference standard as did not have a cardiologist as the assessor for clinician-read ECGs)
- 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)

- Fatemi 2008 (patients in a CCU more unrepresentative)

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 studies looked for a prolonged QT interval (Charbit 2006 (n=108), Denny 2007 (n=44,808). 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.

Figure 4.2: 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 in 200 patients. This study included in the definition of arrhythmia the following conditions: premature atrial or ventricular contractions, atrial fibrillation, paroxysmal supraventricular tachycardia. Figure 4.3 shows the forest plot for sensitivity and specificity.

Figure 4.3: 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) (n=329) and Taha (2000) (n=4172). Figure 4.4 shows the forest plot for sensitivity and specificity.

Figure 4.4: 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; n=21,621). Figure 4.5 shows the forest plot for sensitivity and specificity.

Figure 4.5: specific arrhythmias as target condition: Brugada syndrome

4.4.4.5 Myocardial infarction or ischaemia

One study carried out in a CCU (Fatemi 2008; n=200) assessed ischaemic patterns to the ECGs (acute myocardial infarction or ischaemic heart disease). Figure 4.6 shows the forest plot for sensitivity and specificity.

Figure 4.6: myocardial infarction or ischaemia as the target condition

4.4.4.6 Structural disorders

One study carried out in a CCU (Fatemi 2008; n=200) assessed structural disorders (enlarged atrium, ventricular hypertrophy). Figure 4.7 shows the forest plot for sensitivity and specificity.

Figure 4.7: Structural disorders as target condition

4.4.4.7 Conduction disorders as the target condition

One study carried out in CCU (Fatemi 2008; n=200) assessed conduction disorders (atrioventricular block, bundle branch block, sinoatrial block). Figure 4.8 shows the forest plot for sensitivity and specificity.

Figure 4.8: 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 22 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.

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Table 22: 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 **very low** Fridericia formula long QT	44 * (20-70)	96 (89-99)	10.1	0.59	14.8	63.6	9.3
Charbit 2006 **very low** Bazett formula long QT	54 * (37-70)	90 (80-96)	5.3	0.51	36.1	75.0	22.5
Denny 2007; long QT **very low**	98 (97-99)	78 (77-78)	4.4	0.03	5.3	19.6	0.1
Target condition: arrhythmias							
Fatemi 2008 **very low**	68 (49-83) *	76 (69-82)	2.8	0.43	15.5	33.9	7.2
Target condition: atrial flutter/fibrillation							
Christov 2001 **low**	93 (85-98)	91 (87-94)	10.8	0.07	22.8	76.1	2.1
Taha 2000 **low**	83 (79-87)	98 (98-99)	47.3	0.17	8.7	81.9	1.6
Target condition: Brugada syndrome							
Kaneko 2005 Brugada type 1 **low**	93 (88-97)	100 (100-100)	329	0.07	0.70	69.7	0.00
Kaneko 2005 Brugada type 2 **low**	88 (82-93)	100 (100-100)	950	0.12	0.60	85.9	0.1
Kaneko 2005 Brugada type 3 **low**	92 (87-96)	100 (100-100)	991	0.08	0.70	86.8	0.1
Target condition: cardiac abnormalities							
Fatemi 2008 **very low** conductive disorders	70 (46-88) *	97 (93-99)	21	0.31	10.0	70.00	3.3
Fatemi 2008 **very low** structural disorders	93 (66-100) *	83 (77-88)	5.6	0.09	7.0	29.50	0.6
Fatemi 2008 **very low** acute MI or IHD	90 (83-95)	99 (93-100)	73.7	0.10	59.0	99.10	12.9

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4.5 Clinical evidence review: 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 difficulties to control epilepsy and learning disabilities. It is noted that, in the Long QT Registry, 6% of patients with 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 automatic and manual determination of heart rate, PR interval, QT and QTc intervals on an ECG. Manual reading of ECGs was undertaken by cardiologists from a tertiary care centre in the UK.

4.5.2 Methodological quality

The study was in a highly selected population. It was unclear if the reference standard assessors were blinded to the index test results.

4.5.3 Results:

A 12 lead ECG was taken 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 ECGs showed some abnormality.

4.5.3.1 *Automatic versus Manual Interpretation of ECGs:*

(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 (see Figure 4.9). The two tests varied in their results by -6.4 to +7.5 beats/minute by the Bland-Altman test.

Figure 4.9: Automatic versus manual interpretation of ECGs

(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 (Figure 4.9 – we note that this analysis does not take account of the paired nature of the data). There was 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 (Figure 4.9). The values between the two methods varyied 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) (Figure 4.9). The variation in the calculation of the QTc between the two methods was -52.1 to +48.2 ms (Bland-Altman Method).

Other observations

The study noted that automatic calculation of QT/QTc uses various linear methods while manual calculation was done using the Bazett's formula. Usually, automatically calculated QT/QTc's are longer, though their accuracy in the face of abnormal T waves was uncertain.

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: Direct Access ECG 12 lead]. 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 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 [6]The relevant HRG code for an A&E attendance in which there is no investigation and no significant treatment is VB11Z. If there is a category 1 investigation with a category 1 or 2 treatment then the relevant HRG code is VB09Z. 12-lead ECG is considered to be a category 1 investigation. Therefore, if the treatment consists of nothing more complicated that verbal/written advice, then a category 1 investigation, such as ECG, would push the spell out of the VB11Z category into the VB09Z category increasing the cost of the spell by £20 (see table 21). However, simple measures such as vital sign recording are regarded as a category 1 treatment

[6] Full details of which ED investigations are covered in each category can be found in "HRG4 Chapter Summaries, Feb 2007" available from www.ic.nhs.uk

and therefore if these are already being used the attendance would already be categorized as VB09Z and 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.

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.

Table 23: NHS reference costs* for 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;category 1 invest with category 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 significant treatment or investigation e.g no ECG, guidance/advice is only treatment	58 (39 – 71)	3,122,898
Cost attributable to ECG if no other category	VB09Z- VB11Z = 20	

1 investigation or treatment is used		

. *NHS reference costs 07/08

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%), with a little uncertainty, for 12-lead ECG as a predictor for all adverse events at 7 days
- Moderate values (72 and 74%, respectively) for death and cardiac outcomes at 14 days, with a little uncertainty

There was very low quality evidence for death at 12 months and the sensitivity and specificity were moderate (61 and 74% respectively), with some uncertainty around the estimate for sensitivity.

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

There was low- and very low-quality evidence (because of imprecision) for the diagnostic test accuracy at different ages. There was a suggestion that there was a peak in the sensitivity with age for the group 40 - 59 years, but this was very uncertain 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 very low quality 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 in a non-TLoC population

There was very-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 (44 to 98 %), with some uncertainty and specificity (78 to 96%), with little uncertainty.

There was very low-quality evidence in a non-TLoC population that showed moderate sensitivity (68%), with some uncertainty 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- and very-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) (low)
- Brugada Syndrome (88-93% and 100%), depending on Brugada type (low)
- Myocardial infarction or ischaemia (90 and 99%) (very low)
- Structural disorders (enlarged atrium, ventricular hypertrophy); 93 (with some uncertainty) and 83% (very low)

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

4.7.1.5 Automated ECG interpretation versus clinician-read ECG in a selected TLoC population

There was unpublished evidence, of unclear quality, from one study in epilepsy patients, comparing automated versus clinician-read ECGs, showing no significant difference between the two modes of measurement for heart

rate, QT interval and QTc interval. There was a small significant difference in PR interval.

4.7.1.6 Cost-effectiveness of 12-lead ECG

No evidence was identified on the cost-effectiveness of 12-lead ECG. The cost of obtaining a 12-lead ECG is likely to be £33 (IQR £19 to £43) when a patient presents to primary care and they are referred for a 12-lead ECG through direct access diagnostic testing. It is likely to be lower (£20 or less) when an ECG is obtained during assessment in the emergency department or during an outpatient appointment.

4.8 Evidence to recommendations

4.8.1 12-lead ECG – items to be assessed and recorded (recommendation 1.1.3.2)

All of the items in the list for Recommendation 1.1.3.2 came from the evidence, mainly from the studies described in chapter 3 (Appendix D1), and these features were examined carefully by the GDG. For recommendations 1.1.3.1 and 1.1.3.2, the GDG focussed on the review evidence for 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 moderately sensitive single test to predict serious adverse events
- The very low-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 very low quality evidence, for the TLoC population, for the effect on diagnostic test accuracy of the clinician reading the 12-lead ECG

- The low- and very-low quality evidence, in an indirect population (no TLoC), comparing automated ECG reports and clinician-read ECGs
- The unclear-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, and for cardiac syncope decision rules of 71-100% and 69-100%.

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 TLoC should have a 12-lead ECG, in order, both to help make an early diagnosis, and to determine whether a person could be discharged home. In addition, the GDG was concerned that conditions predisposing to life-threatening arrhythmias could be missed in young people if the test was not carried out for them.

The published evidence for automated interpretation versus clinician-read ECGs was low- and very-low quality, and was in a non-TLoC (indirect) population. The GDG was not confident in this evidence, but took into consideration the results, together with the evidence from the unpublished study in an epilepsy population, which suggested that an automated ECG performed adequately compared with clinician-read ECGs. 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 can be uncertain. They noted that different ECG recorders used different algorithms for automated interpretation, so the accuracy of interpretation may vary according to the manufacturer. The GDG also recognised 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 made a research recommendation to compare automated and expert ECG interpretation in the TLoC population.

The GDG also took into consideration the very low quality evidence that clinicans who were not regularly intepreting ECG traces were likely to be 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. The GDG recommended that the automatic printout was inspected for particular abnormalities, all of which could be noted by a non-specialist health care professional (recommendation 1.1.3.1). The presence of any abnormality would trigger urgent referral for a specialist cardiovascular assessment. The GDG noted that some automatic ECGs detect abnormalities but sometimes label the condition inaccurately; however, they did not regard

this inaccuracy to be highly important – the patient would be referred to a specialist service, where a correct ECG reading would be taken. The GDG regarded it as more important to find all the people at risk and concluded that an automatic machine would not miss many cases. The use of an automatic machine was preferable to having all ECGs read by a health care professional skilled in interpreting ECGs, a requirement that would be unlikely to be cost effective or practicable.

Consequently, the GDG recommended the following: (1) that everyone should have an ECG (2) that an automated interpretation of the ECG should be used where available and (3) that any abnormality identified should be treated as a red flag (recommendation 1.1.3.1). 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 (recommendation 1.1.3.2).

The GDG recommended that if an ECG was not available (for example, out of hours GP call out) and the person was discharged home with a diagnosis of an uncomplicated faint or situational syncope, the GP should be contacted and a 12-lead ECG arranged within three days of the TLoC, so that important information was not missed.

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 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 long QT syndrome and Brugada syndrome), in which the GDG was aware that a single ECG may give false negative evidence. 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 list of abnormalities (recommendation 1.1.3.2) was produced by the cardiology specialists on the GDG, drawing on their experience and 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 and 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

1.1.3 Recording a 12-lead electrocardiogram (ECG)

1.1.3.1 Record a 12-lead electrocardiogram (ECG) using automated interpretation. Treat as a red flag (see recommendation 1.1.5.2) if any of the following abnormalities are reported on the ECG printout:

- conduction abnormality (for example, complete right or left bundle branch block or any degree of heart block)
- evidence of delayed atrio-ventricular conduction, including bundle branch block
- evidence of a long or short QT interval, **or**
- any ST segment or T wave abnormalities.

1.1.3.2 If a 12-lead ECG with automated interpretation is not available, take a manual 12-lead ECG reading and have this reviewed by a healthcare professional trained and competent in identifying the following abnormalities.

- Inappropriate persistent bradycardia.
- Any ventricular arrhythmia (including ventricular ectopic beats).

- Long QT (corrected QT > 450 ms) and short QT (corrected 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.

1.1.4 Recording the event information and transfer of records

1.1.4.1 Record carefully the information obtained from all accounts of the TLoC. Include paramedic records with this information. Give copies of the ECG record and the patient report form to the receiving clinician when care is transferred, and to the person who had the 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 epileptic 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) and suspected carotid sinus syncope
- 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. In chapter 6, we 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.

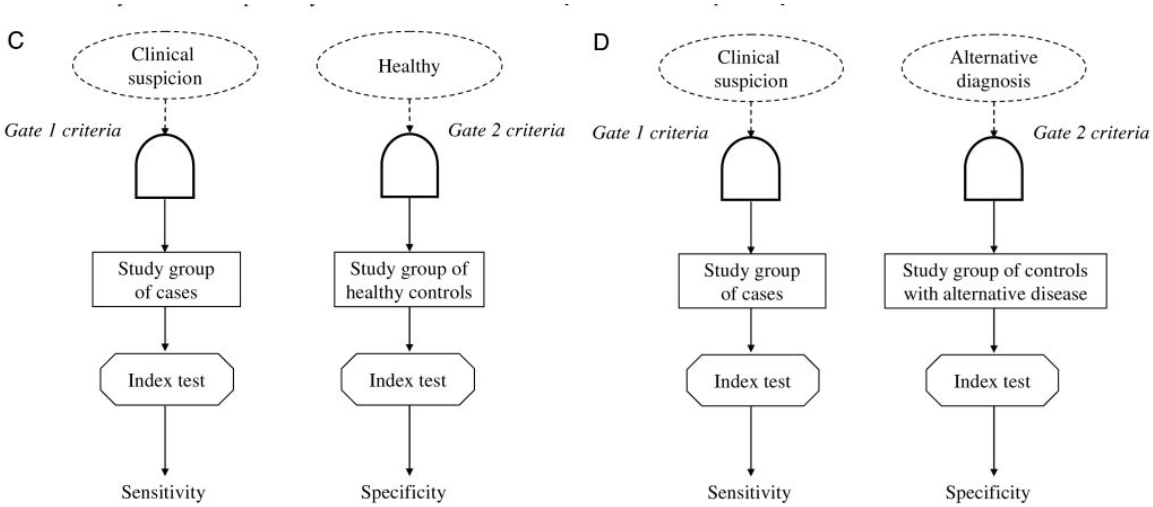
The role of any diagnostic test is to establish the cause of a person's spontaneous episodes, and the choice of the test should reflect this: clinicians should appreciate that if an episode is provoked by, for instance a tilt test, this does not neccessarily indicate that the individual's habitual TLoC has the same cause. Wherever possible, an investigation should be chosen which establishes the cardiac rhythm at the time of a spontaneous attack ("electro-clinical correlation"), because this correlation provides the most secure diagnostic information, to accurately guide treatment.

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 a particular type of syncope on the basis of prior tests, history and examination, and ‘controls’ are those who are not suspected of having that form of 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 case-control 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 Background

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 had TLoC are likely to have arrhythmias that are related to cardiac conditions or 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 type of 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:

- Bradyarrhythmias
  - 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, unless the appropriate arrhythmias were reported separately.

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 among 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

A summary of study design features across studies is given in the table and further details of individual studies in Appendix D1.

Characteristics	Details
Design	• 3 RCTs (Farwell 2003; Krahn 2001; Rockx 2005) • 1 non-randomised comparative study (Krahn 2000) • 1 prospective comparative study of tilt test versus Holter monitoring in the same patients (Fitchet 2003) • The rest of the studies were case series
Prospective / retrospective	• 11 retrospective (Ashby 2002; Cumbee 1990; Gibson 1984; Kabra 2009; Krahn 2000; Kuhne 2007; Mason 2003; Morrison 1997; Porterfield 1999; Schernthaner 2008; Zeldis 1980) • The rest were prospective
Country of study	• 2 in the UK (Farwell 2006; Fitchet 2003) • 15 in 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 in other countries
Funding and possible conflicts of interest	• 4 studies received some funding from Medtronic, the manufacturers of the Reveal Plus implantable event recorder (Brignole 2006b; Farwell 2006; Mason 2003; Pierre 2008) • 1 had funding from Cardionet, the manufacturers of the mobile cardiac outpatient telemetry system (Rothman 2007) • 11 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) • The rest did not state a funding source.
Sample size	• 13 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. • Overall the study size ranged from 25 to 1512 patients

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2 *5.3.3.2 Population*

3 A summary of population characteristics across studies is given in the table
4 below and further details of individual studies in Appendix D1.

Characteristics	Details
Setting	• 29 in hospital cardiology departments (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 in emergency department (Morrison 1997; Sarasin 2001a; Sarasin 2001b). NB The GDG regarded the emergency department patients as possibly representing a different population so that these studies were to be considered in sensitivity analyses. • 19 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 in a blackout clinic or syncope unit (Ashby 2002) • 1 did not state the setting (Porterfield 1999).

5

Prior tests	• 42 studies performed an extensive set of prior tests (including 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) • 5 performed basic prior tests (history and 12-lead ECG only: Arya 2005, Comolli 1993, Ringqvist 1989, Sarasin 2005, Saxon 1990) • 7 did not mention prior tests (Boudoulas 1979, Ermis 2003; Fitchet 2003; Gibson 1984; Krahn 2000; Kuhne 2007; Porterfield 1999).
Age and gender	• 21 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 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). • The proportion of male patients ranged from 30% to 89%.
Ethnicity	• Ethnicity was not reported in any study.
.History of heart disease	• 5 had 100% patients with heart disease (Boudoulas 1979; Brembilla-Perrot 2001; Brembilla-Perrot 2004a; Brembilla-Perrot 2004b; Menozzi 2002) • 39 had some patients with heart disease (proportion 14–92%: 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). This includes 15 with over 50% 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: • 1 had a positive test result on tilt table test (Deharo 2006) • 2 reported the cause was unexplained by initial tests and further ambulatory ECG tests (Comolli 1993; Kapoor 1991) • 2 reported the cause was unexplained by a range of initial and second stage tests, including carotid sinus massage and tilt table tests (Cumbee 1990; Schuchert 2003) • 4 did not give any information (Gibson 1984; Krahn 2000; Morrison 1997; Porterfield 1999).

Type of TLoC

A summary of TLoC details across studies is given in the table and further details of individual studies in Appendix D1.

Characteristics	Details
Definition	• 11 '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 'syncope' without definition (Donateo 2003; Kabra 2009; Krahn 2001; Lombardi 2005; Pezawas 2007) • 6 syncope or near syncope (counted as a single category: Ashby 2002; Boudoulas 1979; Fogel 1997; Krahn 2000; Rothman 2007; Rockx 2005). • 2 'a short loss of consciousness' (Brembilla-Perrot 2004a; Brembilla-Perrot 2004b) • 1 'temporary and reversible loss of consciousness' (Nierop 2000) • 1 'blackouts suggestive of vasovagal syncope' (Fitchet 2003) • 1 'cerebral symptoms possibly due to cardiac arrhythmias (includes dizziness)' (Saxon 1990). NB 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. • The rest stated that patients had had a TLoC but did not define it.
Previous episodes of TLoC	• The mean number of episodes ranged from 2.4 to 50 (range 1–100) • The median duration of TLoC, where reported, varied from 6.5 to 18 months (range 0.02–60 years). • 36 studies 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) • 1 had 58% patients with multiple episodes, suggesting that the rest may have had single or 2 episodes (Kapoor 1991) • 1 had 52% patients with single episodes (Sarasin 2005); • 1 had 35% patients with single episodes (Ringqvist 1989) • 1 had 13% single episodes (Krahn 2001); • 17 did not say if TLoC 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). • • 5-10 TLOC 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)

5.3.3.3 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 assumed to be 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 having 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 ambulatory ECG test), while 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 reported in forest plots, with these single episode studies being treated in sensitivity analyses.

5.3.3.4 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 up 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.

5.3.3.5 Comparative studies

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; RCT)

- The Farwell (2006) study did not give details of what tests the control group received, but stated in 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 non-randomised 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).

5.3.3.6 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 among 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).

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

- 12 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).
- Selection bias: Brignole (2005) reported that only one-third of patients with unexplained syncope were given an IER.

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, we estimated heterogeneity by inspecting overlap of the confidence intervals; we did not carry out a meta-analysis for observational studies.

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 in section 5.3.2.6, 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 data on the 'good' arrhythmias only, and these studies were acceptable. 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)
- Three studies reported separately the 'good' and 'bad' arrhythmias, therefore, the 'good' arrhythmias were used in the analyses, and the studies considered unbiased (Brignole 2006; Fitchet 2003; Kapoor 1991)
- Four were unclear on what was recorded (Arya 2005, Boudoulas 1979, Boudoulas 1983, Lacroix 1981)
- And the rest were 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 the 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 the 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).

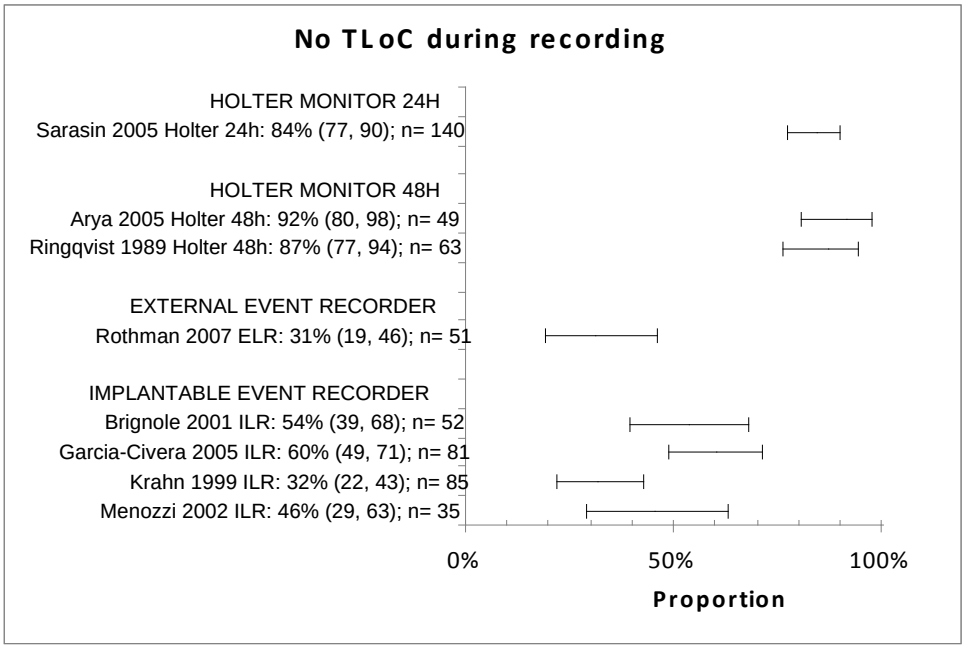
A1. No TLoC during recording period

Seven studies reported the outcome of no TLoC during the recording period in 508 patients; all patients in these studies had recurrent TLoC except the Sarasin (2005) study, which had 52% of patients with a single episode.

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.

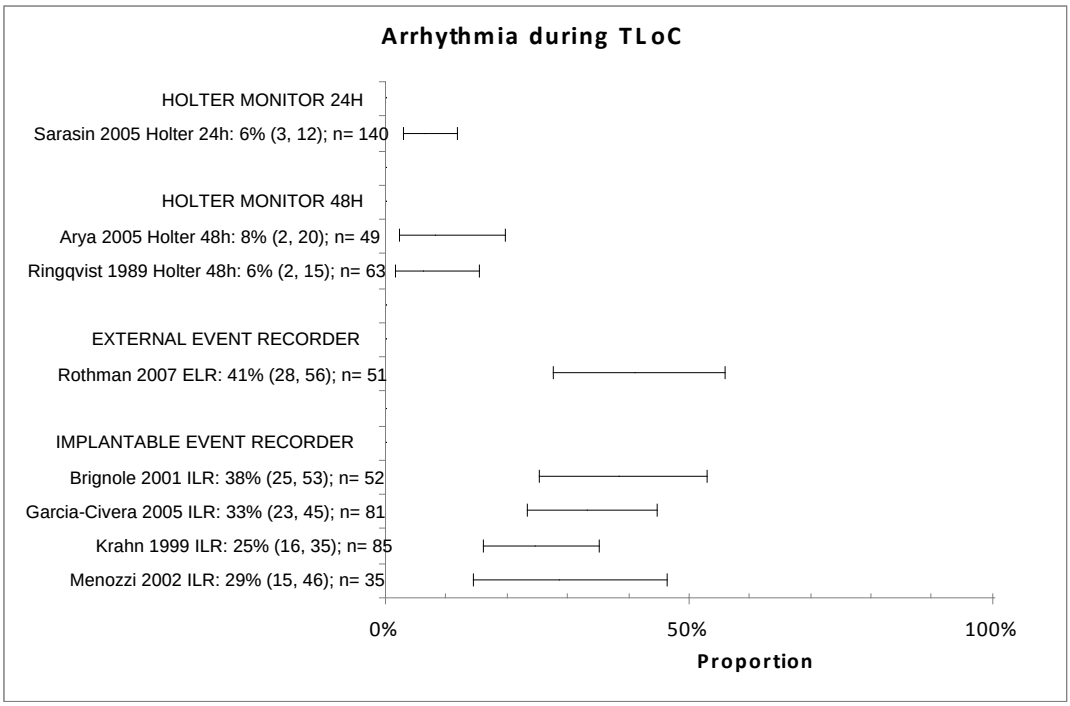
A2. Normal rhythm during TLoC

Seven studies reported this outcome (see Appendix D4 for graph).

A3. Arrhythmia recorded during TLoC

Eight studies reported this outcome: one (Sarasin 2005) 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. We note that the Arya (2005) and Ringqvist (1989) studies were not self consistent.

Figure 5-2: Arrhythmia during TLoC; subgroup by type of device



The diagnostic yield for capturing an arrhythmia during TLoC is higher for IER (ca. 30%) and EER (41%) than Holter monitoring (7%), and there was no heterogeneity among the IER studies.

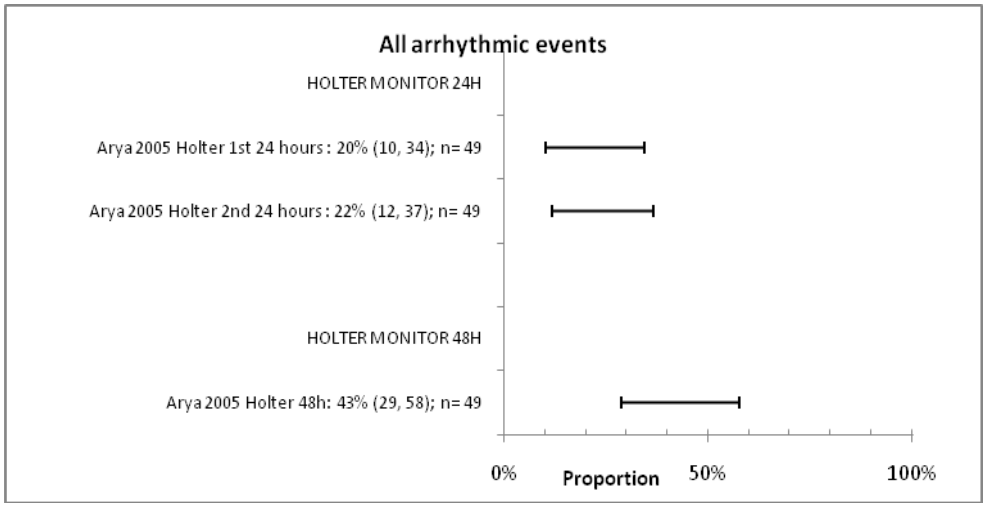
A4. Other outcomes

The forest plots for the outcomes: arrhythmia recorded not during TLoC; no ECG recorded; number of patients started on therapy; adverse events and death are reported in Appendix D4.

A5. 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 5-3: 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; two of these only included patients with vasovagal syncope (Deharo 2006; Fitchet 2003), one included people who were tilt positive and had negative results on carotid sinus massage (Moya 2001b) and the other study included patients with NM syncope with a severe presentation, and excluded people with carotid sinus syncope. All reported recurrent TLoC.

We note that the Brignole (2006) study was funded by Medtronic Inc, who also provided a study manager.

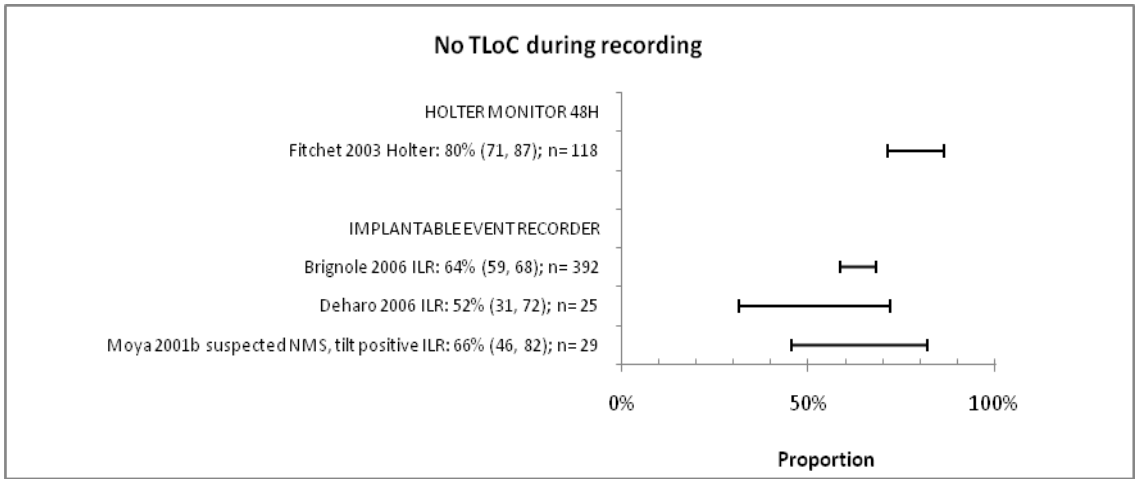
The following devices were investigated for this patient group:

- 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 5-4. No TLoC during recording period. Subgroups by type of device



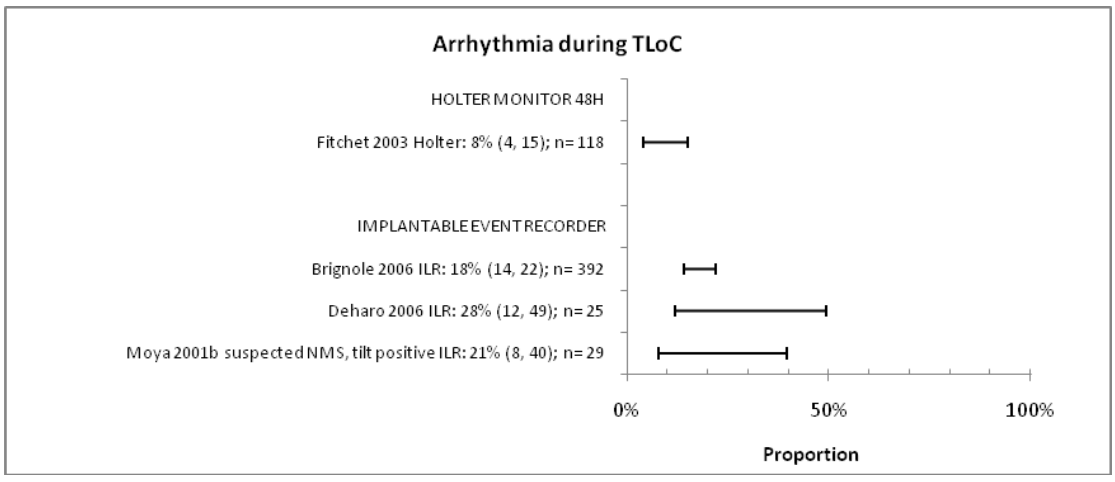
B2. Normal rhythm during TLoC

Four studies reported this outcome (Brignole 2006, Deharo 2003, Fitchet 2003, Moya 2001). See Appendix D4 for graph

B3. Arrhythmia during TLoC

Four studies assessed this outcome (Brignole 2006, Deharo 2006, Fitchet 2003, Moya 2001).

Figure 5-5. Arrhythmia during TLoC by type of device in patients with suspected NM syncope



B4. Other outcomes

The forest plots for the outcomes: arrhythmia recorded not during TLoC; no ECG recorded; number of patients started on therapy; adverse events and death are reported in Appendix D4.

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.

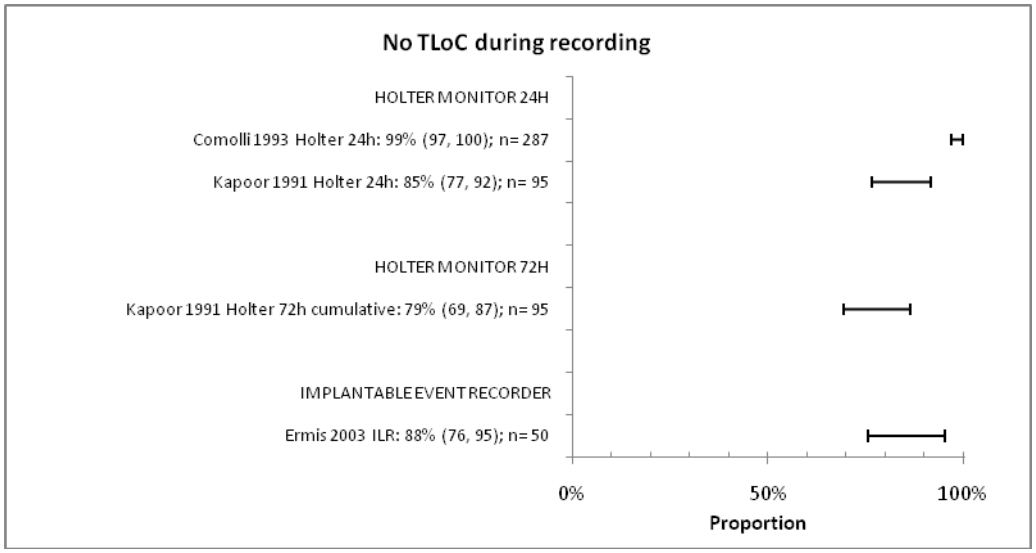
The following devices were investigated for this patient group:

- 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 5-6. No TLoC during recording period in patients with syncope unexplained after initial tests; subgroup by type of device



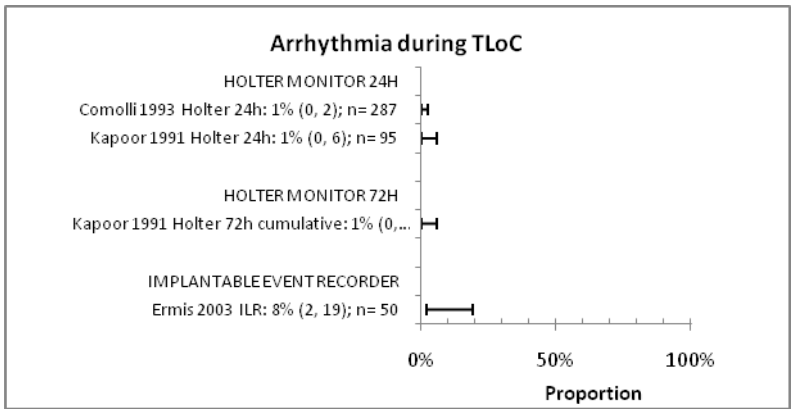
C2 Normal rhythm during TLoC

Three studies reported this outcome (Comolli 1993, Ermis 2003, Kapoor 1991). See Appendix D4 for graph

C3 Arrhythmia during TLoC

Three studies reported this outcome (Comolli 1993, Ermis 2003, Kapoor 1991).

Figure 5-7. Arrhythmia during TLoC in patients with syncope unexplained after initial tests; subgroup by type of device



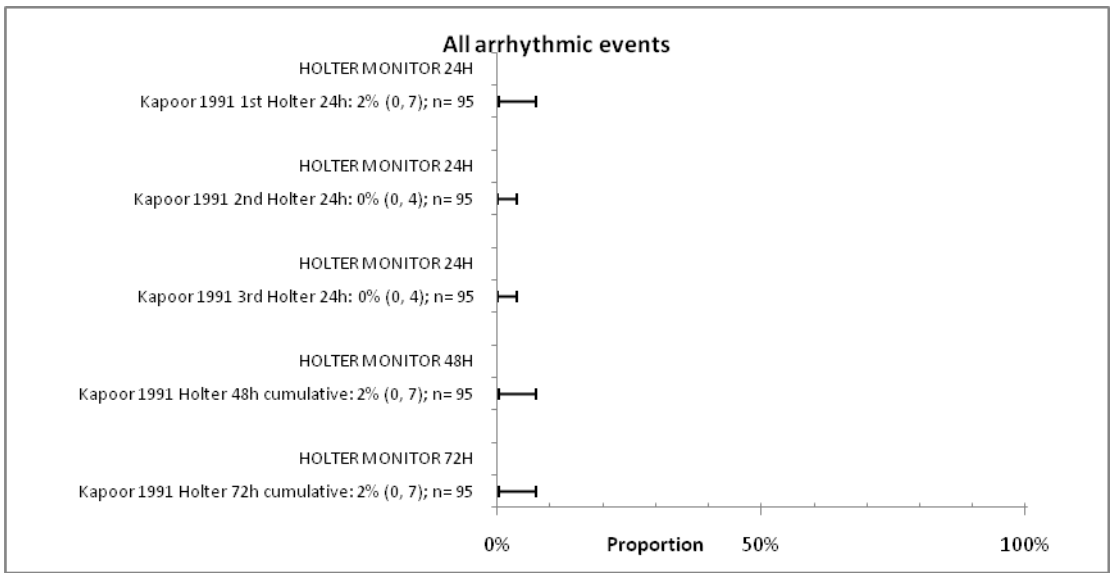
C4. Other outcomes

The forest plots for the outcomes: arrhythmia recorded not during TLoC; no ECG recorded; number of patients started on therapy; adverse events and death are reported in Appendix D4.

C5. Patients with 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 5-8.

Figure 5-8: Holter monitoring for 24h versus 48h 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.

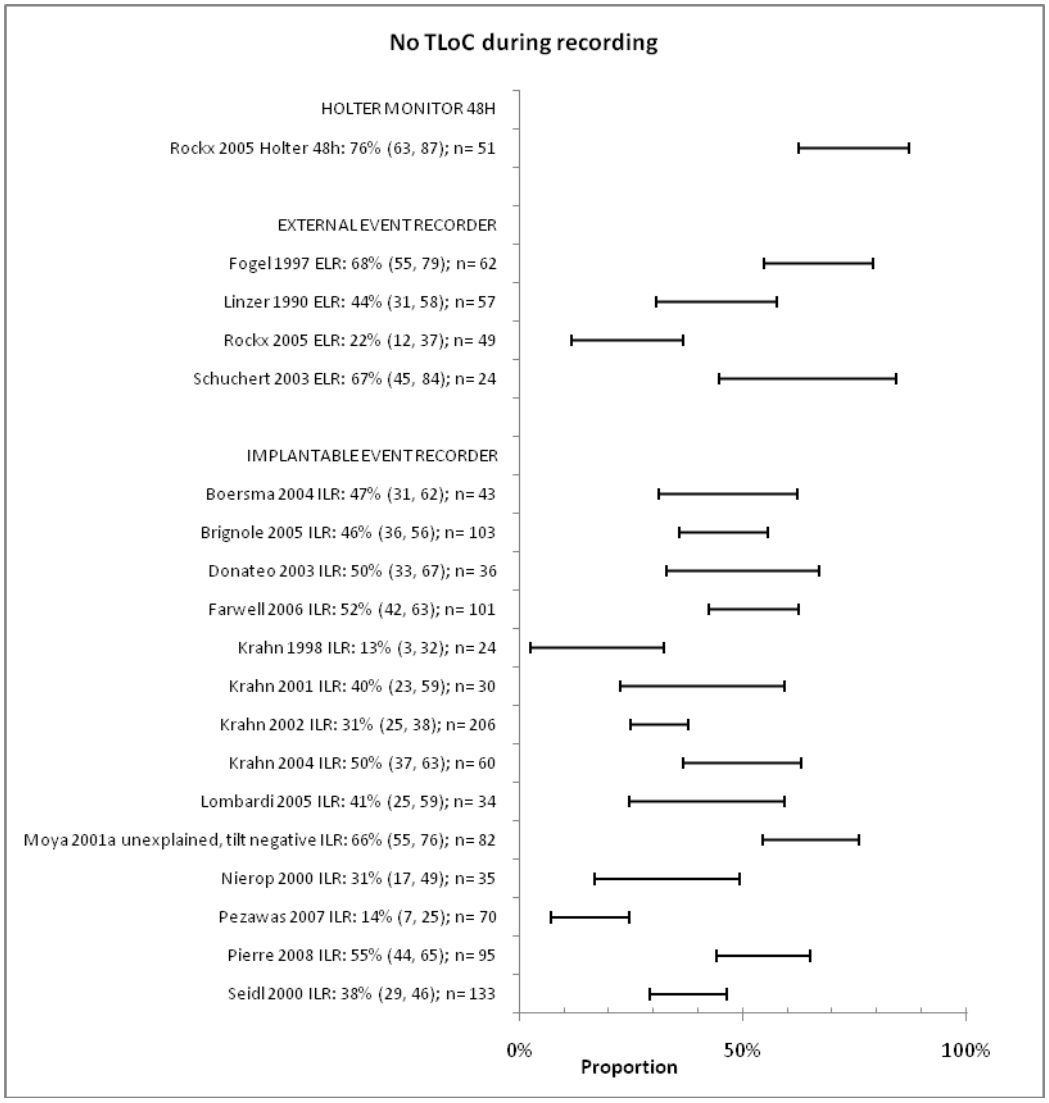
D1. No TLoC during recording period

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 5-9. No TLoC during recording period (unexplained after secondary tests); subgroup by type of device; recurrent only.



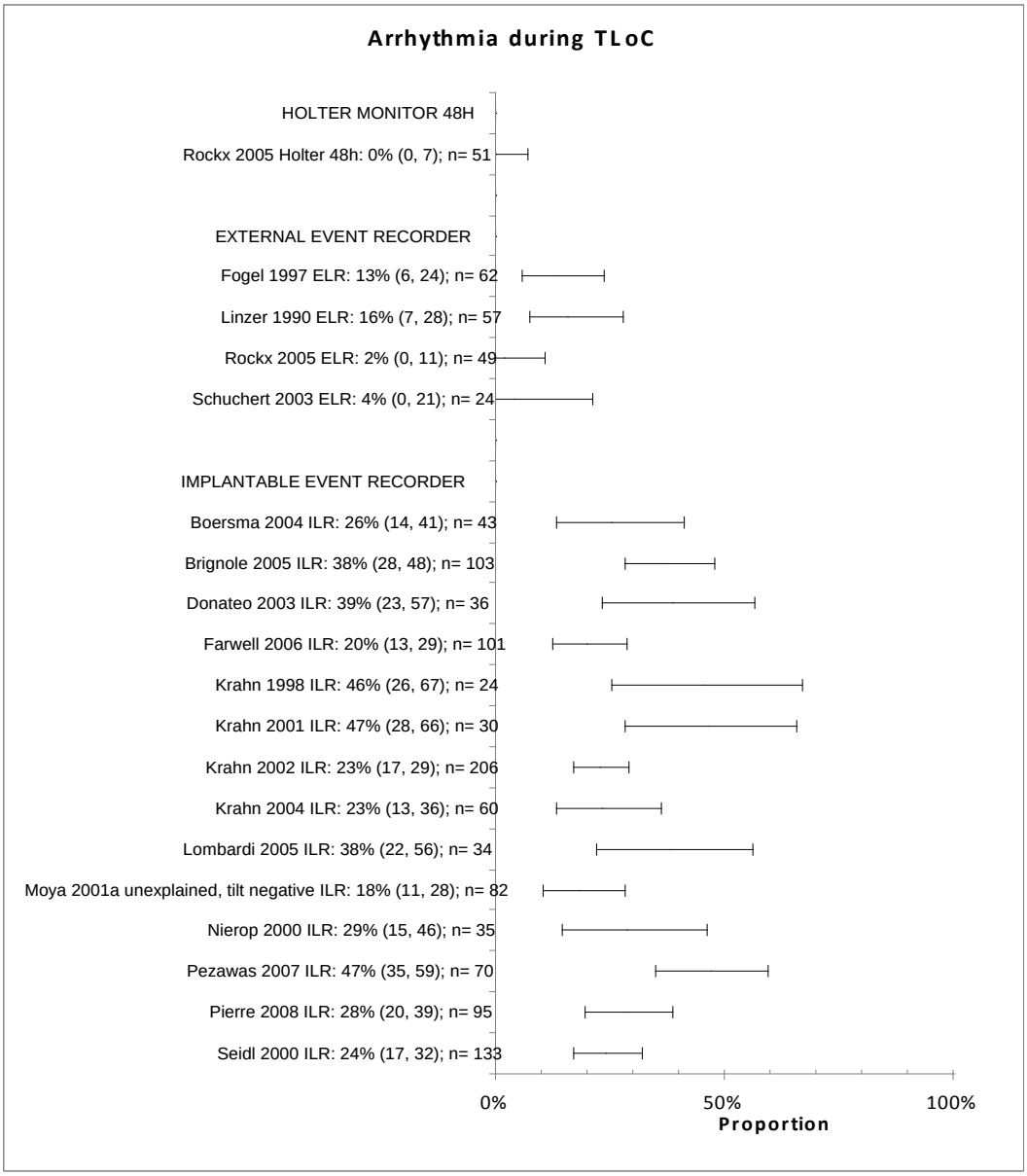
D2 Normal rhythm during TLoC

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. See Appendix D4 for graph

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 5-10. Arrhythmia during TLoC (unexplained after secondary tests); subgroup by type of device; recurrent TLoC only



D4. Other outcomes

The forest plots for the outcomes: arrhythmia recorded not during TLoC; no ECG recorded; number of patients started on therapy; adverse events and death are reported in Appendix D4.

1 Summary

2 The results from these tests are summarised in Table 24. A high level of
3 heterogeneity is indicated by (blue) shading.

Table 24: Summary of results: reported as the median for the proportion (range); number of studies (N); number of patients (n)

	Holter 24h	Holter 48h	External ER	Implantable ER
No TLoC during recording				
Suspected arrhythmia (>50% single episode)	84% N=1; n=140	none	none	none
Suspected arrhythmia	none	89.5 (87-92); N=2; n=112	31%; N=1; n=51	50% (32 to 60); N=4; n=253
Suspected NM syncope	none	80%; N=1; n=118	none	64% (52 to 66); N=3; n=446
Unexplained after initial	92% (85-99); N=2; n=382	72h Holter 79%; N=1; n=95	none	88%; N=1; n=50
Unexplained after secondary tests	none	76%; N=1; n=51	55.5% (22 to 68); N=4; n=192	43.5% (13 to 66); N=14; n=1052
Normal rhythm during TLoC				
Suspected arrhythmia (>50% single episode)	9%; N=1; n=140	none	none	none
Suspected arrhythmia	none	6%; N=1; n=63	27%; N=1; n=51	8.5% (2 to 34); N=4; n=253
Suspected NM syncope	none	12% ; N=1; n=11	none	9% (7 to 20); N=3; n=446
Unexplained after initial	7% (0 to 14); N=2; n=382	72h Holter: 20% N=1; n=95	none	4%; N=1; n=50
Unexplained after secondary tests	0%; N=1; n=100	24%; N=1; n=51	14% (0 to 61%); N=4; n=192	24% (6 to 42); N=14; n=1052
Arrhythmia during TLoC				
Suspected arrhythmia (>50% single episode)	6%; N=1; n=140	none	none	none
Suspected arrhythmia	none	7% (6 to 8); N=2; n=112	41%; N=1; n=51	31% (25 to 38); N=4; n=253
Suspected NM syncope	none	8%; N=1; n=118	none	21% (18 to 28); N=3; n=446
Unexplained after initial	1% (1 to 1); N=2; n=382	72h Holter: 1%; N=1; n=95	none	8%; N=1; n=50
Unexplained after secondary tests	none	0%; N=1; n=51	8.5% (2 to 16); N=4; n=192	28.5% (18 to 47); N=14; n=1052
Arrhythmia recorded, not during TLoC				
Suspected arrhythmia (>50% single episode)	0%; N=1; n=140	none	none	none
Suspected arrhythmia	none	21.5% (8-35); N=2; n=112	0%; N=1; n=51	0% (0-8%); N=3; n=168
Suspected NM syncope	none	0%; N=1; n=118	none	3%; N=1; n=392
Unexplained after initial tests	10% (1-19); N=2; n=382	48h Holter 23% N=1; 95 72 hour Holter 26%; N=; n=95	none	26%; N=1; n=50
Unexplained after secondary tests	none	0%; N=1; n=51	0% (0-0%); N=3; n=130	0% (0 to 15); N=8; n=566

Table 24: Summary of results: reported as the median for the proportion (range); number of studies (N); number of patients (n)				
	Holter 24h	Holter 48h	External ER	Implantable ER
No ECG recorded				
Suspected arrhythmia (>50% single episode)	none	none	none	none
Suspected arrhythmia	0%; N=1; n=140	0%; N=1; n=63	0%; N=1; n=51	7.5% (0 to 14); N=4; n=253
Suspected NM syncope	none	none	none	8% (7 to 9); N=2; n=421
Unexplained after initial	0%; N=1; n=287	none	none	0% (0 to 0); N=2; n=145
Unexplained after secondary tests	none	0%; N=1; n=51	21.5% (0 to 32%); N=4; n=192	5% (0 to 11%); N=11; n=844
Number of patients started on therapy				
Suspected arrhythmia (>50% single episode)	none	none	none	none
Suspected arrhythmia	none	13%; N=1; n=63	none	26% (22 to 44); N=3; n=168
Suspected NM syncope	none	3%; N=1; n=118	none	14% (14 to 28); N=3; n=446
Unexplained after initial	none	none	none	32%; N=1; 50
Unexplained after secondary tests	43%; N=1; n=148	none	18%; N=1; n=57	28% (12 to 49%); N=13; n=1022
Number of patients who died				
Suspected arrhythmia (>50% single episode)	none	none	none	none
Suspected arrhythmia	18% (16 to 29); N=3; n=310	none	none	2% (2 to 2); N=3; n=133
Suspected NM syncope	none	none	none	0%; N=1; 29
Unexplained after initial	none	none	none	6%; N=1; 50
Unexplained after secondary tests	13%; N=1; n=100	none	none	1.5% (0 to 11); N=6; n=516

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 11% with a TLoC, the EER was 69% and the IER was 50%.

The same trends are found for arrhythmia during TLoC, with the yield for this outcome, ranging from 7 (Holter 48h) to 31% (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

The IER reported a failure to record an ECG during TLoC for a number of studies, ranging from 7 to 11% (where non-zero). Three studies in EERs for patients with unexplained syncope after secondary tests reported a range of 14 to 32% for this outcome.

The IER had a higher proportion of people started on therapy as directed by the monitoring device.

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 proportion of patients with arrhythmia 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.

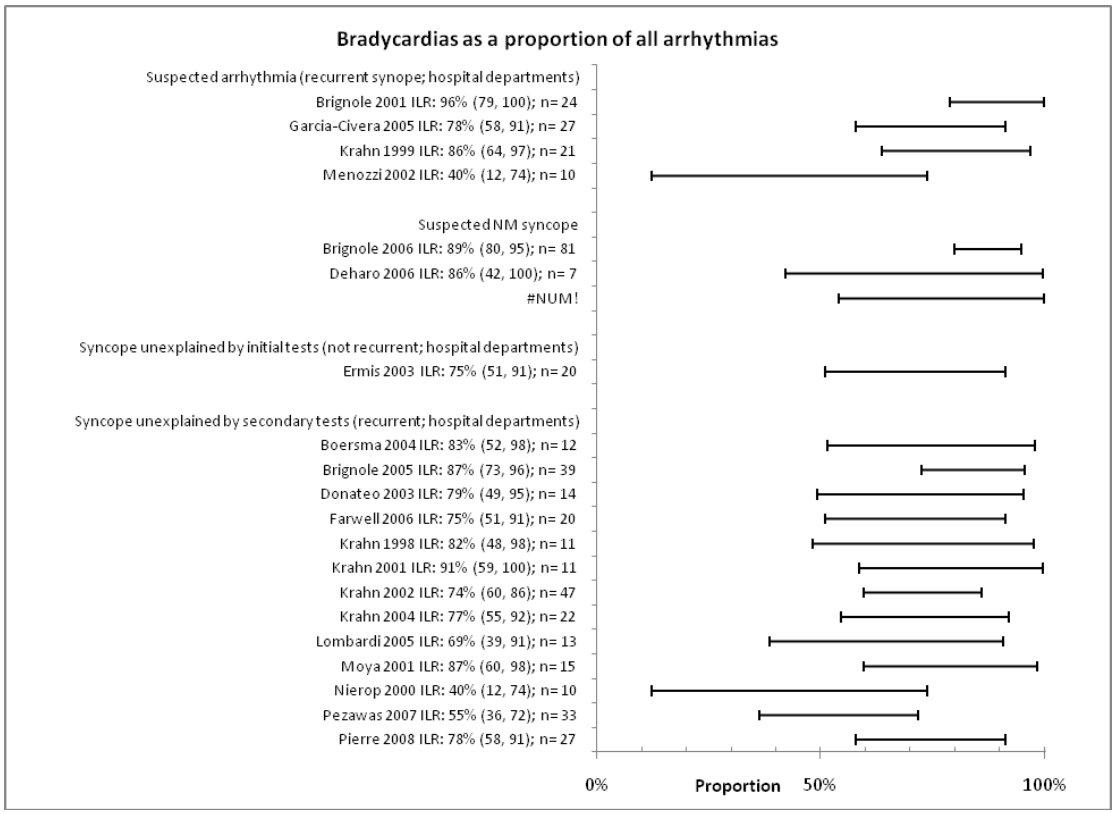
- For the proportion of patients with a TLoC during monitoring; there appeared to be a lower incidence in the group with suspected neurally mediated syncope (36%) versus suspected arrhythmia (40-68%) and versus unexplained syncope following secondary tests (34-87%). There was only one study for unexplained 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 (6-42%) 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 (18-28%) 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 5-11). 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 5-11 Proportion of bradycardias (of all arrhythmias)



5.3.5.8 Results: subgroup analyses to investigate heterogeneity in IER studies

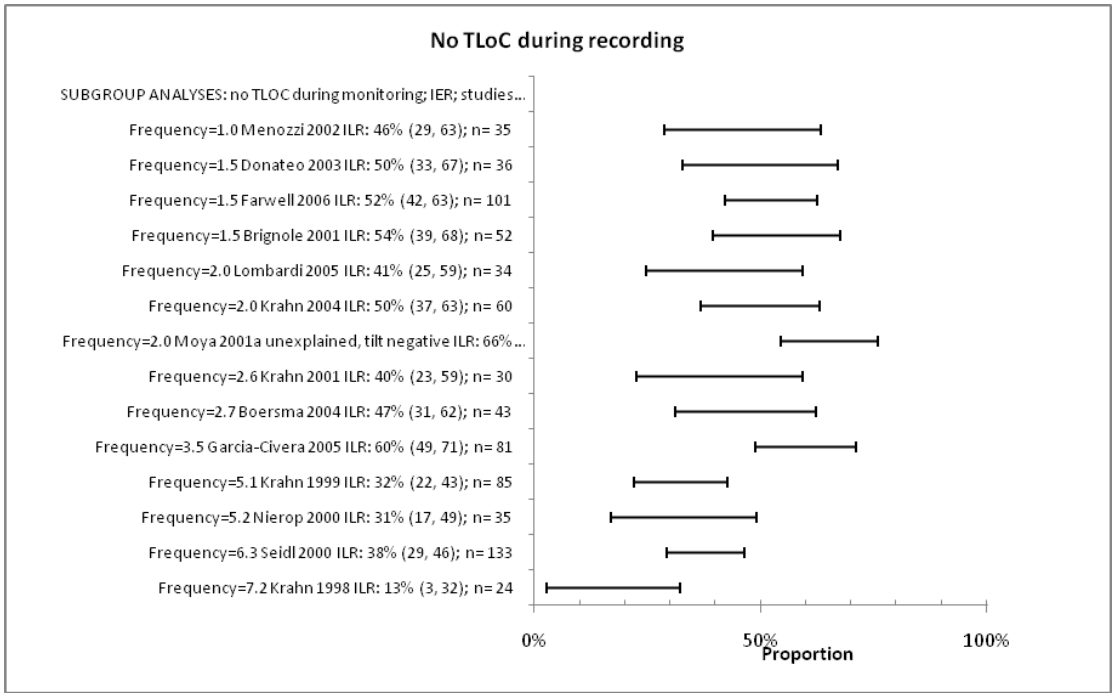
We carried out three subgroup analyses for the IER studies: by duration of monitoring; by frequency of previous TLoC and according to the product, duration of monitoring x frequency of TLoC. These analyses were peformed for the outcome, no TLoC during monitoring. Since there was little difference in 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 5-12 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 5-12: 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 5-13. 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 5-13: 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 5-14).

Figure 5-14: 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 5-15, 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 5-15, together with the comparison of EER alone versus EER then Holter.

Figure 5-15: 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 5-16 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 5-16. 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 64 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 5-17 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 5-17: Sensitivity and specificity of exercise testing

This study showed moderate sensitivity with some uncertainty (78% (52-94%)) for the group with a history of exercise-induced syncope, with high specificity and some uncertainty for the non-syncope controls (95% (75-100)) (very low quality evidence); 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% (12-48) and the pre- and post-test probabilities were 57 and 88% respectively; the likelihood ratio was 5.4 (very low quality evidence).

Comparing people with a history of exercise-induced syncope with those with non-exercise-induced syncope, the sensitivity and specificity were 78% (52-94) and 73% (52-88) respectively, with pre- and post-test probabilities of 41 and 67%, and a likelihood ratio of 2.9 (very low quality evidence).

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. The study is has a case-control design and there is uncertainty around the estimates.

5.4.4.2 Exercise testing versus ambulatory ECG in people with a suspected arrhythmic cause of syncope

One study (Boudoulas 1979) in 119 people compared exercise testing with 24-hour Holter monitoring 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 5-18 but this study should be treated with caution because we are unclear what was being reported for Holter monitoring (very low quality evidence).

The exercise test had low sensitivity (14% (7-24)) in this population, although the specificity was high (93% (82-99)) (Figure 5-18); the pre- and post-test probabilities were 61 and 77% respectively and the likelihood ratio was 2.1.

Figure 5-18 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% (3-35), with some uncertainty in the estimate, with a specificity of 91% (59-100), also imprecise. Exercise testing showed the presence of sinus tachycardia, while 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 (very low quality evidence).

Figure 5-19: 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 5-20).

Figure 5-20: 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

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) were 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 Evidence

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 5-21a, 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 5-21a: Forest plot of all tilt test types.

The ROC curve is shown in Figure 5-21b. 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 5-21b: 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 5-22a. Forest plot of studies remaining after excluding studies in sensitivity analysis

Figure 5-22b. 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 5-23a to 5-23f (below and Appendix D4).

Figure 5-23a. Forest plot subgroup analysis by type of tilt test (passive or GTN or IPN)

Figure 5-24b. 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 5-24c. ROC curve for passive test and ISDN test

Figure 5-24d. Forest plot of IPN, ISDN and IPN followed by ISDN)

Figure 5-24e. Forest plot of adenosine, clomipramine, bromocriptine.

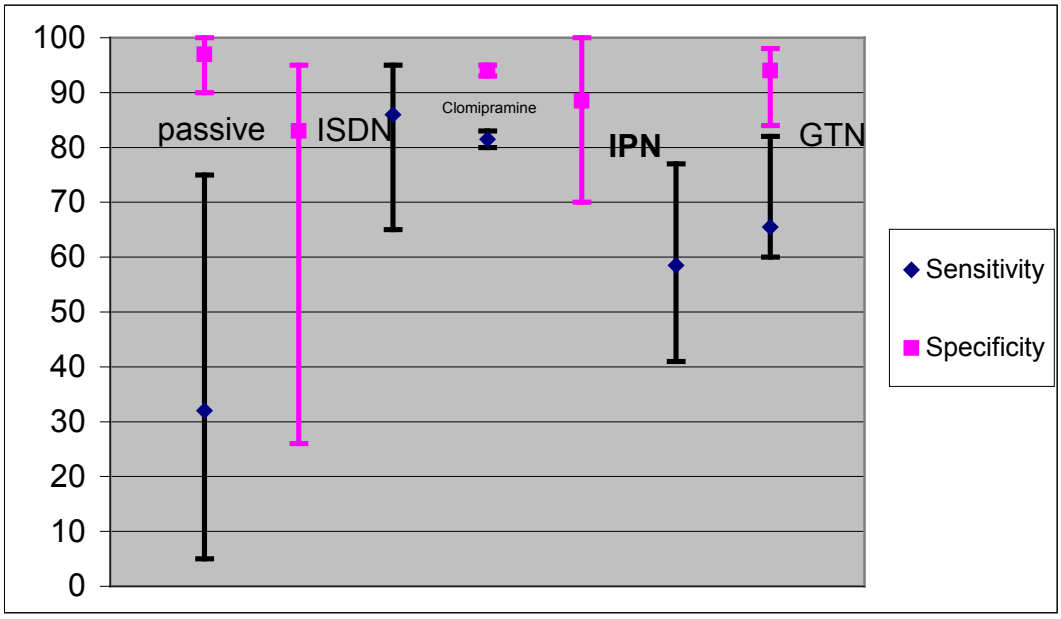
Figure 5-24f. ROC curves for main drug-stimulated tests (GTN, IPN, ISDN)

The median and interquartile range were calculated for the sensitivity and specificity for each test and are shown in Table 25, and the median and range are plotted in Figure5-24g. 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 25:

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 5-24g: 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 5-25a. Forest plot of all studies assessing HUT-passive (sorted by author)

Figure 5-25b. 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 5-26a. Forest plot of standard HUT-GTN versus accelerated HUT-GTN

b) HUT-IPN versus HUT-GTN

Figure 5-26b. Forest plot of HUT-IPN versus HUT-GTN

c) HUT-IPN versus HUT-clomipramine

Figure 5-26c. 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 5.21a and 5.21b 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 (* means imprecision)

Test	Sensitivity	Specificity	LR	Pre-test prob	Post test prob
HUT (Parry 2008)	11 (7 – 18)	89 (80 – 95)	1.05	64.2	65.3
GTN HUT (Parry 2008)	36 (29 – 46)	72 (61 – 82)	1.31	64.2	70.1
Cf GTN HUT Oraii 1999	69 (57 – 80)	90 (68 – 99)	6.92	76.4	95.7
GTN HUT Zeng 2001	62 * (45 – 78)	90 * (68 – 99)	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 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, but directly addressed people with unexplained syncope.

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 Evidence

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 5-27, with the Parry (2000) study reported separately because this defined a positive response to be cardioinhibitory only (see also section 5.6.5.4). There is consistency in both sensitivity and specificity, with the former ranging from 9 to 11% and the latter ranging from 93 to 99%. We note that the Benchimol (2008) study is not consistent with this range for sensitivity.

Figure 5-27. 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 5-28).

Figure 5-28. Forest plot of diagnostic test accuracy following full protocol for patients with a positive response defined by cardioinhibitory or vasodepressor or mixed: 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 unexplained syncope, who had a positive result on CSM: this ranged from 11 to 60%. This is the diagnostic yield for this patient group.

Figure 5-29 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 5-29. 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 5-30 to 5-33.

a) Excluding the retrospective study (Kumar 2003)

Figure 5-30. Forest plot excluding the retrospective study (Kumar 2003)

Figure 5-31. 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 5-32. Forest plot excluding the study in which patients were not stated to have syncope (Benchimol 2008).

Thus, for these studies the sensitivity ranged from 22 to 60% and the specificity from 93 to 100%.

Figure 5-33. 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 only

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 5-34. Forest plot for a positive response with a cardioinhibitory or mixed component

Figure 5-35. 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% (4 studies) 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.

The quality of these published economic evaluations, and their applicability to the guideline and to NICE's reference case for economic evaluations, has been evaluated against an economic checklist. The detailed assessment for each study can be found in Appendix E.

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.

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). Given that none of the papers met all of NICE's reference case criteria, they

were all considered to be partially rather than directly applicable to the guideline. All of the studies were considered to have potentially serious limitations.

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. This study was considered to have potentially serious limitations as it did not include the impact of post diagnostic outcomes, such as treatment, on costs and benefits.

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. For this reason it was considered to have potentially serious limitations as a source of cost-effectiveness evidence, but it was considered to have reasonable methodological quality as a source of comparative data on resource use and NHS costs during follow-up.

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, while 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. This study was considered to have potentially serious limitations as it did not include the impact of post diagnostic outcomes, such as treatment, on costs and benefits.

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. This model based evaluation was considered to have potentially serious limations due to a lack of information regarding the cohorts from which the estimates of diagnostic yield have been derived and whether the tests are being used in similar populations within the model. In addition it did not include the impact of post diagnostic outcomes, such as treatment, on costs and benefits. 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: Pace 1 - Single chamber or

Implantable Diagnostic Device]. 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: Electrocardiogram Monitoring and stress testing]. 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 for 24hour ECG / BP monitoring which has an NHS reference cost of £54 (IQR 37 – 63) [DA09: 24 Hour ECG / BP Monitoring], 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 26 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 26			
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)

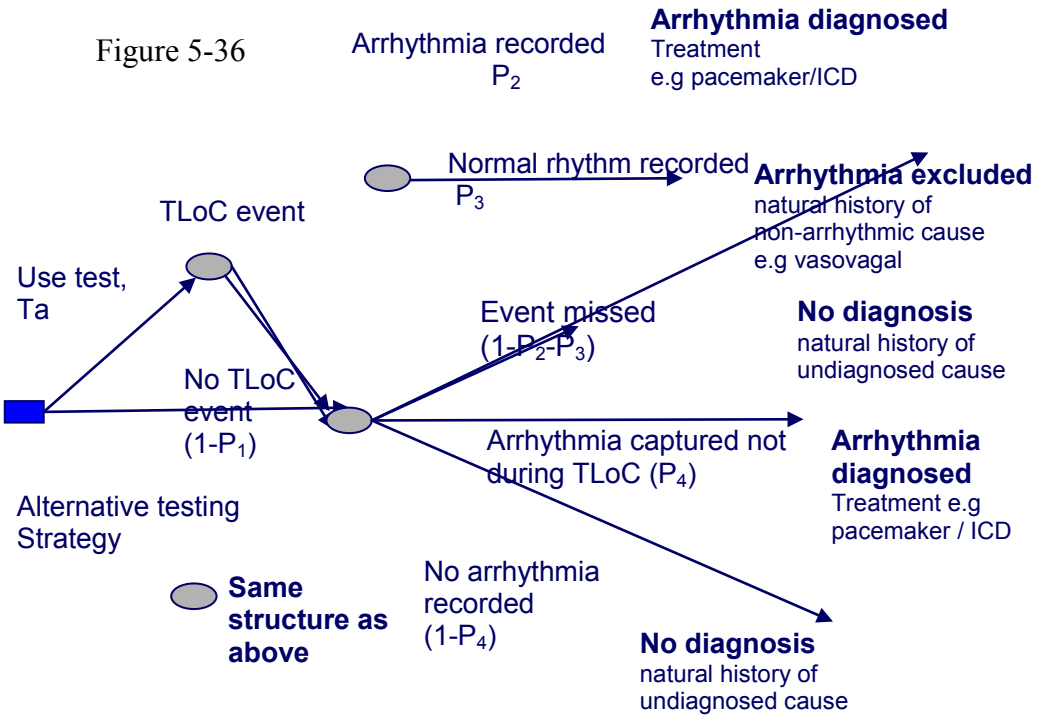
5.8.2 Diagnostic outcomes

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 5-36;

- 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 5-36



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 27 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 27: 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	4[a]	133/253 =0.53	78/133 =0.59	39/133 =0.29	16/133 =0.12	4/44* (3 studies)[d] =0.09
Unexplained after secondary tests	15[b]	616/1102 =0.56	300/616 =0.49	276/616 =0.45	40/616 =0.06	23/175* (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
[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, Krahn 1998
[c] Rockx 2005, Fogel 1997, Linzer 1990, Schuchert 2003
[d] Brignole 2001, Menozzi 2002
[e] Ermis 2003, Krahn 2001, Boersma 2004, Krahn 2004, Pezawas 2007, Pierre 2008. Krahn 1998
[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 28. 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 28: 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 29: Event rates used to describe 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; AV block Sick sinus syndrome Other brady	 106/279 = 0.38 157/279 = 0.56 16/279 = 0.06	20[b]
Proportion of tachyarrhtymias during TLoC that are; VT during syncope Other tachy	 38/141=0.27 103/141 = 0.73	27[c]
Proportion of arrhythmias not during TLoC that are bradyarrhythmias	63/129 =0.49	8[d]
Proportion of bradyarrhythmias not during TLoC that are; Complete AV block Asystole >3s Other brady	 16/63 = 0.23 44/63 = 0.64 9/63 = 0.13	8[d]
Proportion of tachyarrhythmias not during TLoC that are; Sustained VT Other Tachy	 25/66 =0.38 41/66 = 0.62	8[d]

[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: Pace 2 - Dual Chamber]. 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 with category 1 being used for activity with the lowest resource use and category 5 being used for activity with the highest resource use. 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, while 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 consultation which includes category 2 investigations and treatments, and has a reference cost of £134 (IQR £111 to £161) [NHS reference cost 2007/08 for VB07Z: Category 2 investigation with category 2 treatment].

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).” Different reference costs are provided according to the category of call-out. Category A is immediately life-threatening, while category B is serious but not immediately life-threatening and category C is non-serious of life-threatening. The NHS reference cost for this HRG code are £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.

‡ Full details of which A&E investigations are covered in categories 1 & 2 can be found in “HRG4 Chapter Summaries, Feb 2007” available from www.ic.nhs.uk

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.

It is not certain whether patients who have a normal 12-lead ECG during the initial assessment, but who are then found to have AV block during their TLoC through ambulatory ECG monitoring, have the same mortality risk as those recruited to the Devon Heart Block and Bradycardia Survey, as the patients in the study had AV block that was visible on a normal 12-lead ECG. It is therefore possible that the survival benefits of pacing are overestimated in the model. In order to examine this uncertainty, we have conducted a sensitivity analysis in which we assume that there is no survival gain from pacing patients with AV block identified through ambulatory ECG.

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 27, Table 28 and Table 29. 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, we used the interquartile range reported in the reference costs as our 95% confidence interval 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. The details of the distributions used for each parameter can be found in Appendix I.

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 survival gain associated with pacing in AV block, 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 30 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 15 patients having TLoC, and 1 asymptomatic arrhythmia being detected in 41 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 30: 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	91 (91)	143 (141)	31 (30)	91 (88)	155 (154)	£6,522 (£6,460)	0.398 (0.394)	£16,370 (£16,390)	93.9%	100.0%
Unexplained after secondary tests	83 (83)	132 (131)	31 (30)	86 (86)	250 (250)	£6,410 (£6,380)	0.369 (0.366)	£17,390 (£17,450)	88.3%	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 31 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 and survival 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. Similarly, assuming no survival gain from pacing in patients with AV block during TLoC increased the ICER to £24,510.. However, 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. So while the ICER was sensitive to the assumptions regarding the post-diagnostic costs and benefits, the ICER was below £30,000 in all the scenarios considered.

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 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 31: 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	£6,410	0.369	£17,390
No survival gain from pacing after AV block observed during syncope	£6,400	0.261	£24,510
Recurrences continue beyond 2 years in unpaced patients with AV block or SSS	£6,340	0.367	£17,310
Recurrences results in short stay admission in addition to ambulance call-out and A&E assessment	£6,380	0.367	£17,370
Continued recurrences beyond 2 years in unpaced patients and recurrences result in admission	£6,290	0.367	£17,140
Unpaced patients with AV block or SSS experience an average of one admission per annum	£5,620	0.367	£15,320
Lower limit for utility gain after pacing and no utility gain after ICD therapy	£6,400	0.284	£22,520
No uplift in IER device cost since 2004 (£1,400 instead of £1,600)	£6,200	0.367	£16.890
Costs and benefits of pacing estimated over 6 year horizon	£6,360	0.261	£24.350
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 among 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)

The cost-effectiveness of ambulatory ECG monitoring (IER, EER and 24hr & 48hr Holter) was assessed using an economic model which considered both the diagnostic outcomes and the main costs and benefits of treatment following diagnosis. Ambulatory ECG monitoring (IER, EER and 24hr & 48hr Holter) compared to no further testing in patients with suspected arrhythmic syncope had an ICER which was under £20,000 per QALY. The sensitivity analyses conducted suggest that the ICER is unlikely to be greater than £30,000 per QALY even when less favourable model assumptions are applied.

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 among 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).

The cost-effectiveness of ambulatory ECG monitoring (24hr and 48hr Holter) compared to no further testing was assessed using an economic model which considered both the diagnostic outcomes and the main costs and benefits of treatment following diagnosis. Ambulatory ECG monitoring (24hr and 48hr Holter) compared to no further testing in patients with suspected unexplained recurrent syncope after initial tests had an ICER which was under £20,000 per QALY. The sensitivity analyses conducted suggest that the ICER is unlikely to be greater than £30,000 per QALY even when less favourable model assumptions are applied.

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.

The cost-effectiveness of ambulatory ECG monitoring (IER, EER and 48hr Holter) was assessed using an economic model which considered both the diagnostic outcomes and the main costs and benefits of treatment following diagnosis. Ambulatory ECG monitoring (IER, EER) compared to no further testing in patients with suspected arrhythmic TLoC had an ICER which was under £20,000 per QALY. The sensitivity analyses conducted suggest that the ICER is unlikely to be greater than £30,000 per QALY even when less favourable model assumptions are applied. The cost-effectiveness of 48hr Holter monitoring in this population is uncertain as the modeled estimate is based on a single small study (n=51) in which no arrhythmias were detected.

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 among 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%), with some uncertainty, but in people with exercise-

unrelated syncope it is low (27%), also uncertain; the specificity of the test in controls who did not have TLoC is high (95%), with some uncertainty, but the test has only moderately high specificity (73%), also uncertain, 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%; little uncertainty) and high specificity (93%; little uncertainty) for exercise testing versus 24-hour Holter monitoring as a reference standard in the same patients. This is not an appropriate reference standard.

There is very low quality evidence in one small study in young people with exercise-induced TLoC to show a low sensitivity (14%), with some uncertainty and fairly high specificity (91%), also uncertain 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

1.2.3 Referral for specialist cardiovascular assessment

1.2.3.1 Refer all people with TLoC (apart from the exceptions below) for a specialist cardiovascular assessment by the most appropriate local service. Exceptions are:

- people with a firm diagnosis, after the initial assessment, of:
  - uncomplicated faint
  - situational syncope
  - orthostatic hypotension
- people whose presentation is strongly suggestive of epileptic seizures.

1.3 Specialist cardiovascular assessment and diagnosis

1.3.1 Assessment and assignment to type of syncope

1.3.1.1 Carry out a specialist cardiovascular assessment as follows.

- Reassess the person's:
  - detailed history of TLoC including any previous events
  - medical history and any family history of cardiac disease or an inherited cardiac condition
  - drug therapy at the time of TLoC and any subsequent changes.
- Conduct a clinical examination, including full cardiovascular examination and, if clinically appropriate, measurement of lying and standing blood pressure.
- Repeat 12-lead ECG and obtain and examine previous ECG recordings.

On the basis of this assessment, assign the person to one of the following causes of syncope.

- Suspected structural heart disease.
- Suspected cardiac arrhythmic.
- Suspected neurally mediated.
- Unexplained.

Offer further testing as directed by recommendations 1.3.2.1 to 1.3.2.10 or other tests as clinically appropriate.

1.3.1.2 For people with suspected structural heart disease, investigate appropriately (for example, cardiac imaging). Because other mechanisms for syncope are possible in this group, investigate also for a cardiac arrhythmic cause (as described in recommendation 1.3.2.4), and consider investigating

for orthostatic hypotension (often caused/exacerbated by drug therapy – see recommendation 1.2.1.1) or for neurally mediated syncope (see recommendations 1.3.2.5 and 1.3.2.6).

6 Diagnostic tests to direct pacing therapy

6.1 Clinical Questions

In people who have experienced 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.

This question presupposes that there is a population in which pacemakers are differentially effective and assumes that this population includes people with a cardioinhibitory form of either neurally mediated syncope or carotid sinus syncope. A pacemaker is not expected to prevent recurrence of TLoC if it derives from vasodepression. Having said this, we note that the degree of cardioinhibitory behaviour may vary from episode to episode within the same person.

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.

So, firstly, we carried out two systematic reviews of interventions to examine the assumption that pacemakers are clinically effective compared with no pacemaker therapy in two populations: cardioinhibitory neurally mediated syncope (as manifested during tilt testing), and cardioinhibitory carotid sinus syncope (during carotid sinus massage).

Secondly , 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.

The results from the first two reviews were expected to inform our certainty surrounding the diagnostic test accuracy review.

6.3 Clinical Evidence Review: efficacy of pacemakers in people with suspected neurally mediated syncope with a cardioinhibitory response identified during tilt testing

This review seeks to determine whether pacemakers are effective in preventing recurrence of TLoC in people with neurally mediated syncope with a cardioinhibitory response manifested during tilt testing.

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 and other factors 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.

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.

6.3.2.1 Study design

A summary of study design features across studies is given in the table and further details of individual studies in Appendix D1.

Characteristics	Details
Design	• 3 studies had randomised designs (Ammirati 2001 (SYDIT); Connolly 1999 (VPS); Connolly 2003 (VPS II)).
Country of study	• None of the studies were conducted in the UK. • 1 was carried out in North America (Connolly 1999) • 1 in Italy (Ammirati 2001) • 1 was a multicentre study carried out in Canada, Australia, USA and Colombia (Connolly 2003).
Funding and possible conflicts of interest	• 1 study received some funding from Medtronic Inc (pacemaker manufacturer) and the lead author also had an honorarium from them (Connolly 2003) • The other 2 studies did not state a funding source.
Sample size	• 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

A summary of population characteristics across studies is given in the table below and further details of individual studies in Appendix D1.

Characteristics	Details
Prior tests	• In 1 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; Ammirati 2001) • 1 study had also excluded patients with other causes of TLoC (arrhythmias, carotid sinus syndrome, seizures), which implies prior tests (Connolly 1999) • In 1 study the patients were not reported to have had extensive prior tests (Connolly 2003).
Age and gender	• 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	• Ethnicity was not reported.

Type of TLoC

A summary of TLoC details across studies is given below and further details of individual studies are given in Appendix D1.

Characteristics	Details
Definition	• All the studies selected patients with NM syncope.
Selection of patients	• Each study required the patients to have had a 'positive' tilt test, but this included vasodepressor and mixed responses too (see definitions below).
Previous episodes of TLoC	• 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). • Both Connolly (1999) and Connolly (2003) included patients with a history of recurrent syncope. 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.

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 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 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)

In 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 over half the patients did have cardioinhibitory NM syncope in the Ammirati (2001) study.

6.3.2.3 Interventions and comparators

The included studies investigated the following interventions and comparators:

Study	Intervention	Comparator
Connolly (2003)	Dual chamber pacemaker with RDR* defined by drop size 20 beats, drop rate of 70 bpm and an intervention rate of 100 bpm for 2 min, duration 6 months (n=48)	Dual chamber pacemaker set to sensing only – ODO mode (i.e. placebo pacemaker), duration 6 months (n=52)
Connolly (1999)	Dual chamber pacemaker with 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). Plus usual care (none required) (n=27)	Usual care, medical or nonmedical, at the discretion of the physician (none required), duration mean 54 days (n=27)
Ammirati (2001)	Dual chamber pacemaker with 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) (n=46)	Atenolol 50 mg once per day, then titrated up to 100 mg/day within 2-3 days, median 135 days (IQR 15-250) (n=47)

* RDR: rate drop response

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%.

6.3.2.4 Comparisons

The following comparisons were carried out:

- Dual chamber pacemaker, with RDR pacing versus placebo pacemaker (Connolly 2003)

- Dual chamber pacemaker with RDR pacing versus no pacemaker (Connolly 1999)
- Dual chamber pacemaker with RDR pacing versus atenolol (Ammirati 2001)

6.3.2.5 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. 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

Overall, two of the studies were considered to be at risk of 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 (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.

6.3.4 Evidence

For this review, we only considered the evidence for 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. One study in 93 patients (Ammirati 2001) compared pacemaker versus atenolol at a mean follow up of 520 days (SD 266).

Figure 6-1: Recurrence of syncope

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.

6.3.4.1 GRADE analysis

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 (Table 32).

Table 32: 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

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). The detailed protocol is described in Brignole (2007) and is summarised here: 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) and is expected to

answer many of the uncertainties around the usefulness of tilt tests in this population.

6.4 Clinical Evidence Review: efficacy of pacemakers in people with suspected carotid sinus syncope with a cardioinhibitory response to carotid sinus massage

6.4.1 Methods of the review: selection criteria

The same selection criteria as in section 6.3 were to be applied, with the following differences:

6.4.1.1 Types of participants

Participants were to be adults (16 years and older) who had carotid sinus syncope (CSS) 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 carotid sinus syncope of any type (cardioinhibitory response not reported or present only for some of the population)..

6.4.1.2 Subgroup analyses

If there was heterogeneity between studies, the following subgroup analyses were proposed:

- 100% cardioinhibitory CSS / 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 Appendix D1. Three RCTs were included (Claesson 2007, Kenny 2001).

6.4.2.1 Study Design

A summary of study design features across studies is given in the table and further details of individual studies in Appendix D1.

Characteristics	Details
Country of study	• One of the studies was conducted in the UK (Kenny 2001). • 1 was carried out in Sweden (Claesson 2007) • 1 in Italy Brignole 1992c)
Funding and possible conflicts of interest	• 1 study received some funding from Medtronic Inc (pacemaker manufacturer) (Kenny 2001) • The other studies had non commercial funding (Claesson 2007) or did not state a funding source (Brignole 1992c).
Sample size	• All the studies had between 60 and 175 patients.

6.4.2.2 Population

A summary of population characteristics across studies is given in the table below and further details of individual studies in Appendix D1.

Characteristics	Details
Prior tests	• In 2 studies the patients had had extensive prior tests to exclude other causes (history, examination, neurological and cardiological tests; Brignole 1992c; Kenny 2001) ○ One of these also used ambulatory ECG for at least 24 hours (Brignole 1992c) • In 1 study the patients had extensive prior tests, but positive results did not lead to their exclusion from the study (history, examination, 12 lead ECG, orthostatic test, HUT and 24-hour ambulatory Holter monitoring; Claesson 2007)
Age and gender	• 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	• Ethnicity was not reported.

Type of TLoC

A summary of TLoC details across studies is given below and further details of individual studies are given in Appendix D1.

Characteristics	Details
Definition	• All studies included patients who had induced cardioinhibitory carotid sinus syndrome, with asystole of more than 3 seconds, in response to CSM. ○ about half the patients in Brignole (1992) had a mixed response
Details about CSM	• In 2 studies, patients had CSM conducted both supine and erect (Brignole 1992c; Kenny 2001) • 1 study simply reported that the patients had CSM (Claesson 2007)
Selection of patients	• 1 study recruited patients from a cohort that had non-accidental falls and were attending the ED, and had not necessarily had TLoC (this may indicate an indirect population) (Kenny 2001). • 1 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) (Brignole 1992)
Previous episodes of TLoC	• The mean number of previous TLoC episodes across studies was around 2-4

6.4.2.3 Interventions and comparators

Study	Intervention	Comparator
Kenny (2001)	Dual chamber pacemaker with rate drop response, defined by drop rate of 50 bpm and an intervention rate of 100 bpm 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, duration 12 months (n=87)	No pacemaker; duration 12 months (n=88)
Brignole 1992c	18 patients received a ventricular inhibited (VVI) pacemaker, while 14 had a dual chamber (DDD) pacemaker; duration mean 34 months (SD 10) (n=32)	No pacemaker, but 19 (68%) received a pacemaker after a mean of 8.2 months (SD 10); in 15 this was because of TLoC recurrence; mean 36 months (SD 10) (n=28)

Claesson (2007)	24 patients had a pacemaker operating in DDDR mode, 5 in VVIR mode and one in AAIR mode; duration 12 months (n=30)	No pacemaker; but patients were allowed to cross over from the no pacemaker group after recurrence of syncope or pre-syncope (1/3rd) (n=30)

6.4.2.4 Outcomes

The primary 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

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 the latter is not considered important). The Brignole (1992c) study is likely to have risk of bias at later times (mean time to crossover 8.2 months) because of crossover from the no pacemaker arm, but this is expected to reduce the effect size.

6.4.4 Evidence

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 (Figure 6-2).

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 (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.

6.4.4.3 GRADE analysis

Table 33: 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 23 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 were prospective case series and each investigated a different index test compared with the reference standard, symptom-free-after-pacing: Tilt test: Gatzoulis (2003); IER: Brignole (2006) – ISSUE 2 and CSM: Lagi (1991).

A summary of study design features across studies is given in the table and further details of individual studies in Appendix D1.

Characteristics	Details
Country of study	• None of the studies were conducted in the UK. • 1 was in Italy (Lagi 1991) • 1 in Greece (Gatzoulis 2003) • 1 was a multinational study (Brignole 2006).
Funding and possible conflicts of interest	• 1 study was funded by Medtronic Inc, who also provided a study manager to supervise its conduct (Brignole 2006) • The other 2 studies did not state a funding source.

Sample size	• Brignole 2006: n=392; Gatzoulis 2003: n=123; Lagi 1991: n=56

6.5.2.1 Population

None of the studies reported whether the patients had received first line therapy for NM syncope before testing, which may have made the population slightly indirect. A summary of population characteristics across studies is given in the table below and further details of individual studies in Appendix D1.

Characteristics	Details
Population	• 1 study had a directly relevant population - suspected NM syncope on initial assessment, with a severe clinical presentation: ≥3 episodes in past 2 years, the frequency of which affected the patient's quality of life or made them at high risk for physical injury due to unpredictable occurrence (Brignole 2006); • 2 studies had an indirect population: o unexplained syncope (Gatzoulis 2003) o suspected cardiac arrhythmia syncope (75%) or unexplained syncope (Lagi 1991); study also explicitly stated that patients were excluded if they had a diagnosis of vasovagal syncope on initial assessment
Prior tests	• All studies had several prior tests • Gatzoulis 2003: 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. Exclusion of patients with sinus bradycardia < 50 bpm, conduction defects and other ECG abnormalities. • Brignole 2006: prior tests to rule out differential diagnoses of suspected or definite heart disease or cardiac syncope; orthostatic hypotension; non-syncopal TLoC (e.g. epilepsy); subclavian steal syndrome; CSS • Lagi 1991: 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. Exclusions: patients with epilepsy or 'vasodepressive' syncope (characteristic precipitating factors and prodromes; short loss of consciousness and complete recovery after lying down for less than 5 minutes, without neurological sequelae) or with carotid artery disease, or a history of cerebrovascular accident.

Characteristics	Details
Age and gender	• Mean age ranged from 41 to 66 years • The proportion of male patients ranged from 45% to 52% and one study (Lagi 1991) did not state the gender distribution
Ethnicity	• Ethnicity was not reported in any study.
Heart disease	• Lagi 1991: 75% with heart disease (including 39% coronary artery disease), but 24-hour Holter monitoring did not demonstrate the need for permanent pacemaker therapy • In 2 studies, no patients had heart disease (Brignole 2006; Gatzoulis 2003)

TLoC history was as follows:

- Gatzoulis 2003: mean number of previous TLoC events per patient was 4 (range 2 to 8), with the most recent episode in the last 6 months
- Brignole 2006: median of 6 previous episodes of TLoC (range 4 to 10) and 4 (range 3 to 5) in the past 2 years; mean age at first TLoC was 54 years (SD 20)
- Lagi 1991: at least one episode of syncope (isolated or recurrent; no further details).

6.5.2.2 Index tests and treatment

Study	Details
Gatzoulis 2003 Tilt test	• 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
Brignole 2006 IER test	• IER; follow up for median time of 9 months (IQR 3 to 17)
Lagi 1991 CSM test	• Massage to each right and left carotid sinus for about 5 seconds with the neck hyperextended and the patient lying supine

6.5.2.3 Assignment to treatment

Study details	Factors determining treatment	Number of CI patients and reason for pacemaker	Number of CI patients and reason for no pacemaker
Gatzoulis 2003 • tilt test • mean follow up 24 mo (SD 7) • CI 3/123	• Symptoms • patients with cardioinhibitory (CI) response (asystole > 3 s or bradycardia < 40 bpm) considered for pacing • Probably biased	n=1 with CI response – patient offered and accepted pacemaker	n=2 with CI response: • 1 given beta-blockers • 1 declined pacemaker
Brignole 2006 • IER test • median follow up 9 mo (IQR 3 to 17) • 103/392 had ECG duringTLoC • CI: 60/392;	• Symptoms • patients with CI response (asystole > 3 s or bradycardia) - symptom correlation with TLoC • May be biased (unclear)	n=47 with CI response – patients offered and accepted pacemaker	• 13 with CI response given counselling / non-specific therapy (unclear why no pacemaker) • 6 with tachycardia given catheter ablation, ICD or anti-arrhythmic therapy • 36 with normal / slight rhythm variations or progressive sinus tachycardia with TLoC given counselling / non-specific therapy • 1 with tachycardia given counselling / non-specific therapy
Lagi 1991 • CSM test • mean follow up 11 mo (SD 8) • CI: 44/56	• Symptoms • patients with CI response (asystole > 3 s or variation in cardiac rhythm), with or without decrease in bp • recurrent symptoms with ECG indication of heart disease • Probably biased	• n=34 with CI response and asystole > 3s offered and accepted pacemaker • n=3 CSM negative, but symptoms & ECG signs of heart disease	• n=7 with CI response and asystole < 3s

6.5.3 Methodological quality of included studies

All the studies were prospective and there was less than 5% missing data in any study..

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 Evidence

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 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).

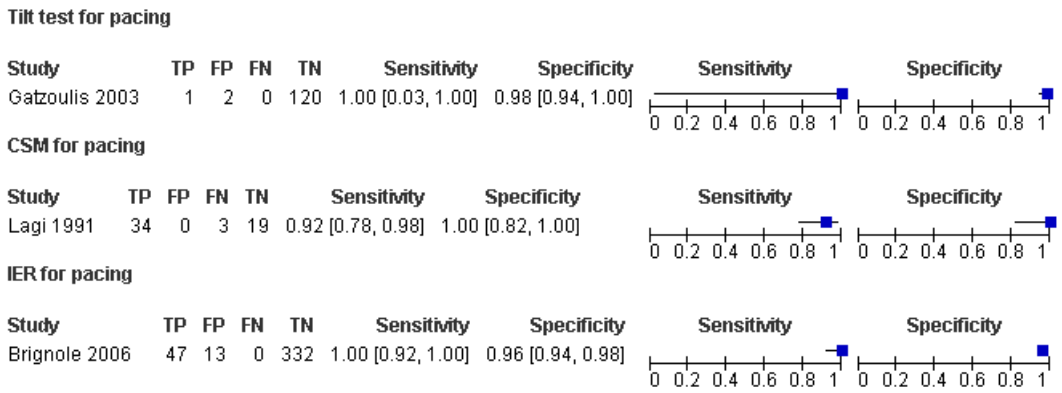
1

Table 34: 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 (Table 35), together with the non-significant results for time to first recurrence (i.e. after IER implantation, but before therapy).

Each of the studies showed high sensitivity and specificity, although there was much uncertainty for the Gatzoulis (2003) study for sensitivity (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 6.5), 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 6.3), but was inconclusive because there is much uncertainty in the evidence, so this remains an assumption. The former assumption is considered below (section 6.6.3).

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 6.5.

6.6.3 Evidence: diagnostic test accuracy for follow up (TLoC incidence)

The Brignole (2006) study reported the test accuracy statistics for (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% (95%CI 37 to 55) and the specificity is 51% (95%CI 44 to 58); 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% (95%CI 66 to 81) and a specificity of 94% (95%CI 90 to 97), with a positive predictive value of 88%, however it is notable that the IER did not record on every occasion that there was 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.

Diagnostic test accuracy statistics were reported for a sample of the patients in each study: patients were compared if they had 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 reported 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).

In the Farwell (2005) study, 3 of 26 (12%) patients with a negative tilt test result were found to have tachycardia.

Figure 6-6: Sensitivity and specificity of Tilt test versus IER

The diagnostic test accuracy statistics were as follows (an asterisk indicates imprecision):

Study	Asystole		Asystole or bradycardia	
	Sensitivity (95%CI)	**Specificity (95%CI)**	**Sensitivity (95%CI)**	**Specificity (95%CI)**
Brignole 2006 (NM syncope)	13% (5 – 26)	96% (85 – 99)	12% (4 – 24)	95% (84 – 99)
Farwell 2005 (unexplained)	0% (0 – 31)*	96% (81 – 100)	6% (0 – 29)	100% (83 – 100)

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.

A similar analysis was carried out for a further study (Garcia-Civera 2005) in 81 people with suspected cardiac arrhythmia syncope. The study did not report within-patient correlations for types of syncope but minimum and maximum sensitivities and specificities could be estimated from the false negative results (Figure 6-7).

Tilt result	IER for tilt results
Positive • 6 cardioinhibitory with asystole • 3 cardioinhibitory with bradycardia • 11 Vasodepressor • 18 mixed (no asystole or bradycardia)	Positive tilt results • 2 asystole • 2 sinus bradycardia • 2 normal sinus rhythm • 2 with AV block • 30 with no spontaneous TLoC events
Negative 43 people	Negative tilt results • 2 people with asystole • 2 with bradycardia • 1 with normal sinus rhythm • 6 with AV block (14% of tilt negative) • 6 with VT (14%) • 26 with no TLoC

The sensitivity and specificity for the maximum scenario for asystole were 50% (7 - 93), i.e. very imprecise, and 95% (87 – 99) 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% (16 - 94), i.e. very imprecise, and 93% (85 – 98) 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 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 35 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 35

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 Method used to explore uncertainty in the model

We used both probabilistic sensitivity analysis (PSA) and scenario analyses to explore uncertainty in the model. The approach used is similar to that used in the ambulatory ECG model as described in section 5.8.9 and the distributions applied to the parameters which are common between the models have been described previously. In addition to these, beta distributions were used to describe the uncertainty in the sensitivity and specificity estimates, the probability of achieving symptom ECG correlation during IER monitoring and the split between SSS and AV block. Dirichlet distributions were used to describe the uncertainty in the distribution of arrhythmias diagnosed by IER. Further details on the distributions used in the PSA can be found in Appendix I. Scenario sensitivity analyses were as for the ambulatory ECG model, but an additional sensitivity analysis was conducted looking at whether the cost-effectiveness was significantly different if the target condition for pacing included both bradyarrhythmias and asystole.

6.7.4 Cost-effectiveness results for testing strategies to direct pacing therapy

The basecase results are summarised in Table 36. The results show that while 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 £38,570 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 £25,470 compared to tilt testing alone.

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 £25,000. The strategy of using IER as the first-line test is not optimal for any willingness to pay threshold.

1

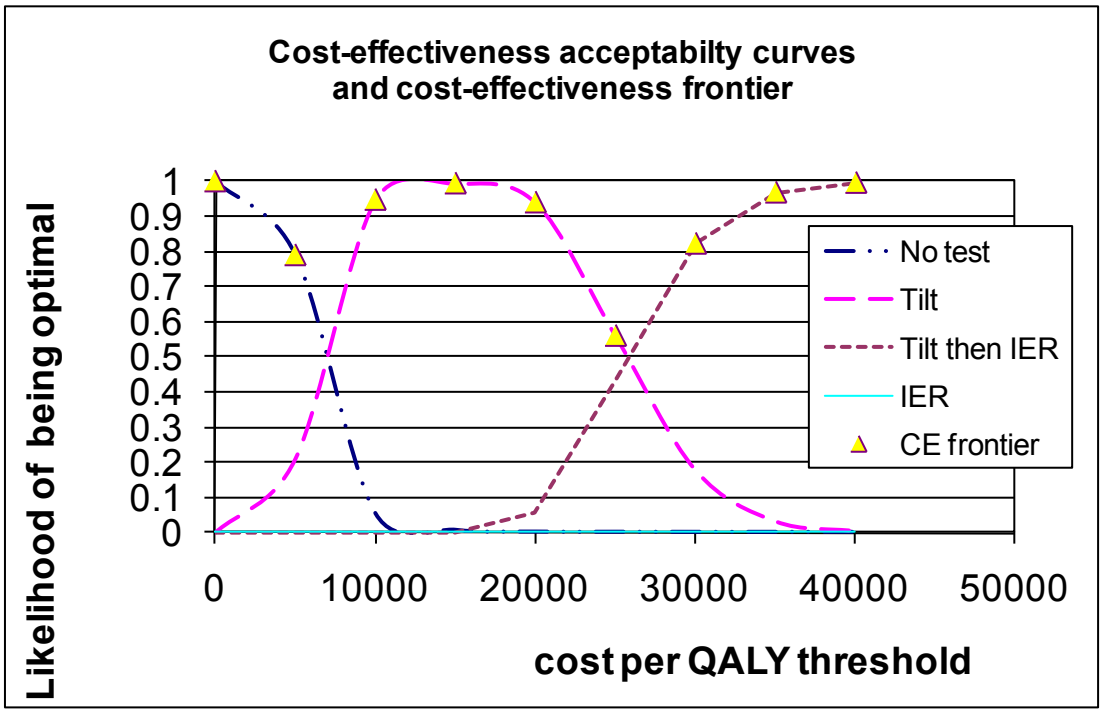
Table 36

		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	20	20	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	292	292	311
Deterministic estimates of costs and QALYs per patient tested					
Cost of testing		0	£117	£3,780	£4,020
Cost of post testing outcomes		£2,240	£2,660	£3,750	£3,410
Total costs		£2,240	£2,780	£7,530	£7,440
QALY gained		4.241	4.332	4.519	4.453
Probabilistic estimates per patient tested					
Total cost		£2,240	£2,780	£7,530	£7,440
Total QALY		4.241	4.332	4.519	4.453
Incremental cost per QALY vs no testing		NA	£5,960	£19,110	£24,620
Incremental cost per QALY vs tilt testing		NA	NA	£25,470	£38,570
Incremental net benefit compared to no testing at;	20k per QALY	NA	£1,270	£250	£-980
	£30K per QALY	NA	£2,170	£3,020	£1140
Likelihood of being optimal strategy at	20k per QALY	<1%	94.0%	<5.9%	<1%
	£30K per QALY	<1%	17.8%	82.3%	<1%

2

3

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 not fall below £20,000 in any of the scenarios but the ICER increased significantly to above £30,000 per QALY when applying the lower range of the estimate for HRQoL improvement following pacing. The ICER also increased significantly when we assumed no survival gain from pacing patients who have AV block recorded during their TLoC. This shows that there is substantial uncertainty in the cost-effectiveness of using tilt testing followed by IER to direct pacing therapy as the cost-effectiveness estimates for this strategy are sensitive to the assumptions used to model the HRQoL and survival benefits of pacing. The cost-effectiveness of tilt testing compared to no testing is less sensitive to these assumptions.

Table 37: Scenario sensitivity analysis			
	Incremental cost per QALY		
Scenario	Tilt testing vs no testing	Tilt then IER if negative vs tilt	IER vs tilt
Basecase	£5,960	£25,470	£38,570
No survival gain from pacing after AV block observed during syncope	£8,210	£33,580	£49,710
Bradycardia treated with pacemaker as well as asystole	£6,130	£24,410	£35,330
Recurrences continue beyond 2 years in unpaced patients with AV block or SSS	£5,800	£25,320	£38,450
Recurrences results in short stay admission	£5,920	£25,390	£38,390
Continued recurrences beyond 2 years that results in short stay admission	£5,590	£25,130	£38,370
Unpaced patients with AV block or SSS experience an average of one admission per annum	£3,160	£22,940	£36,220
Lower limit for utility gain after pacing and no utility gain after ICD therapy	£7,560	£31,310	£46,610
No uplift in IER device cost since 2004 (£1,400 instead of £1,600)	£5,960	£24,460	£36,850
Costs and benefits of pacing estimated over 6 year horizon	£8,590	£35,690	£52,640

6.7.5 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.

6.7.6 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 as the first-line test. There was considerable uncertainty in the incremental cost-effectiveness of using IER after a negative tilt test compared to using tilt testing alone. 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 2 randomised trials in 154 patients 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 3 randomised trials in 155 patients 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 each of three 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, with little uncertainty, for IER in directing pacing therapy in a suspected NM syncope population with a severe presentation

There was 92% sensitivity and 100% specificity, with some uncertatinty, 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 in 392 patients to show that the sensitivity and specificity for the occurrence of spontaneous TLoC during follow up are 74% and 94% respectively, with little uncertainty,

for the IER and 46% and 51%, with little uncertainty, 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- or very-low quality evidence from each of 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:

There is low quality evidence from a sample population of 94 patients from one study (Brignole 2006), which showed a low sensitivity (13%) and a high specificity (96%), both with little uncertainty 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%, also with little uncertainty.

There is very low-quality evidence from one study in 37 patients (Farwell 2005) to show a very low sensitivity (0%), with some uncertainty and high specificity (96%), with little uncertainty, 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% and the specificity 100%, both with a little uncertainty.

There is very low-quality evidence from a one study in 81 patients (Garcia-Civera 2005) to show a moderate sensitivity (50% maximum) with much imprecision,, a high specificity (95%0, with little uncertainty and a low positive

predictive value (33%) for an asystolic cardioinhibitory response on the tilt test relative to IER; the population was a suspected arrhythmic cause of syncope. For an asystolic or bradycardic response on tilt testing the sensitivity was 50% maximum, with much imprecision, the specificity 93%, with little imprecision and the positive predictive value 44%. Fourteen percent of the people with false negative tilt results had VT.

6.8.1.6 Cost effectiveness evidence

The cost-effectiveness of testing strategies (tilt testing, IER, tilt testing followed by IER when tilt is negative) to direct pacing therapy in people with suspected vasovagal syncope and a severe presentation was assessed using an economic model which considered both the diagnostic outcomes and the main costs and benefits of treatment following diagnosis.

Tilt testing compared to no testing had an ICER which was under £20,000 per QALY. The sensitivity analyses conducted suggest that the ICER is unlikely to be greater than £30,000 per QALY even when less favourable model assumptions are applied.

IER compared to tilt testing had an ICER above £30,000 per QALY and the sensitivity analyses conducted suggest that the ICER is unlikely to be less than £20,000 per QALY even when more favourable model assumptions are applied.

A strategy of tilt testing followed by IER if tilt-is negative, had an ICER above £20,000 per QALY when compared to tilt testing alone. The ICER ranged from above £20,000 per above £30,000 per QALY in sensitivity analysis.

6.9 Evidence to Recommendations

6.9.1 General Points

The specialist cardiovascular referral 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 cardiovascular 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.

The GDG noted that the specialist cardiovascular assessment could be carried out in a number of places, including a specialist blackout clinic, a specialist syncope service or in a cardiology department. However, they had not reviewed the evidence surrounding service delivery models and so recommended that referral should be to the most appropriate local service (recommendation 1.2.3.1).

6.9.2 Re-assessment at the start of the specialist cardiovascular referral stage (recommendation 1.3.1.1)

The GDG agreed that there was a need, at the start of the specialist cardiovascular referral 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.

Following further assessment specified in recommendation 1.3.1.1, the GDG decided that people without a diagnosis in the initial stage should be divided into four groups, those with:

- Suspected structural heart disease cause of syncope
- Suspected cardiac arrhythmic cause of syncope
- Suspected neurally mediated cause of 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'.

People with red flags should have tests appropriate to their suspected condition (recommendation 1.3.1.1) – this could include, for example, flecainide or ajmalin for people who have a family history of sudden cardiac death at an age younger than 40 years and who have a normal or near normal 12-lead ECG.

People who have a suspected structural heart disease cause of TLoC following the initial assessment should have further diagnostic testing directed according to these findings (recommendation 1.3.1.2). Further tests for structural heart disease or other conditions were not reviewed in this guideline (e.g. echocardiography), but the GDG wished to indicate that appropriate tests should be conducted. The GDG considered it important that, in people with structural heart disease, healthcare professionals do not assume that the cause is mechanical or due to a cardiac arrhythmia and that they consider the possibilities of orthostatic hypotension (often caused or exacerbated by drug therapy) and neurally mediated syncope as well. 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 (recommendation 1.3.1.2).

The GDG's reasons for treating the other 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 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 among

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.

6.9.3 Recommendations for people with exercise-induced syncope (recommendations1.3.2.1 – 1.3.2.3)

The GDG identified people with exercise-induced syncope during exercise as a group requiring prompt assessment and made separate recommendations for this group of people.

The GDG considered the very 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 estimates had some uncertainty surrounding them.

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 wished to distinguish between syncope occurring *during* exercise and syncope occurring *after* exercise, drawing on some low quality evidence from the review on predictors for cardiac syncope (section 3.3.5.5), which showed syncope during effort to be a strong univariate predictor of cardiac syncope. Syncope after exercise was more likely to be vasovagal syncope. They therefore made recommendation 1.3.2.1 to advise health care professionals of this distinction.

The GDG noted that exercise testing should not be a first-line investigation in people who had TLoC during exercise and who have clinical or other evidence of severe aortic stenosis or hypertrophic cardiomyopathy. In such people, imaging techniques such as echocardiography should be carried out as a first-line investigation (recommendation 1.3.1.2).

The GDG noted that exercise testing does not always identify the cause of TLoC in people who have experienced TLoC during exercise, 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. The GDG's consensus was that exercise testing should be carried out within about a week and added this time frame to the recommendation.

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.

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 and a positive tilt test is defined by the presence of TLoC with asystole, bradycardia and/or vasodepression, the GDG were concerned as to whether a tilt test provided accurate information in this population. The GDG noted that the role of any diagnostic test is to establish the cause of a person's spontaneous episodes, and the choice of the test should ideally reflect this: for example, if an episode is provoked by a tilt test, this does not neccessarily indicate that the individual's habitual TLoC has the same cause. The GDG thought that the best type of investigation was likely to be one which establishes the cardiac rhythm at the time of a spontaneous attack ("electro-clinical correlation”). 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, but there was much imprecision in the sensitivity estimate. The GDG was concerned that the tilt test was unable to indentify primary cardiac arrhythmias and 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 recommendation 1.3.2.4 with this practical application in mind.

6.9.5 People with suspected carotid sinus syncope

The GDG considered the low-quality evidence from case control studies for the diagnostic test accuracy of carotid sinus massage (CSM) for diagnosing carotid sinus syncope with a cardioinhibitory component. The evidence showed a low sensitivity of 12 to 42% for CSM, with heterogeneity, but very high specificity (100%), albeit in a case control population with controls not having TLoC.

The GDG also considered low-quality evidence from RCTs on the effectiveness of pacemakers in people with suspected carotid sinus syncope (CSS) or unexplained syncope, who had a cardioinhibitory response to carotid sinus massage (CSM). The review concluded that pacemakers were highly effective in this patient group.

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).

Support for the age cut-off of 60 years came from a UK-based retrospective analysis of a cohort study of 373 people who received CSM (Humm 2006). This study reported that 14% of patients had CSH overall; the diagnostic yield was 0% in the range 40–49 years; 2.4% in the 50–59 years group; 9% in the 60-69 years group; reaching 40% in people over 80 years.

On the basis of these pieces of evidence, the GDG decided that CSM could be used as an initial screening test for carotid sinus syncope. People who were positive on CSM could be diagnosed with carotid sinus syncope because there were almost no false positive cases, and the GDG was confident in the CSM test from their experience.

The GDG recommended that CSM should be carried out in a controlled environment, with ECG recording and with resuscitation equipment and a skilled team immediately available (recommendations 1.3.2.7 and 1.3.2.8).

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 vasovagal syncope for the purpose of diagnosing the cause of TLoC.

6.9.6.1 Tilt test not to be used to confirm vasovagal 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 vasovagal 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 vasovagal syncope following history-taking.

The GDG also took into account the good prognosis for most people with vasovagal 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 vasovagal 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 vasovagal 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. They also took into consideration the likely costs of tilt testing (see 6.7.2.2).

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 costs, benefits and harms and concluded that the tilt test should not be used for people who already had a diagnosis of vasovagal syncope (recommendation 1.3.2.5).

6.9.6.2 Tilt test not to be used generally in people with cardioinhibitory vasovagal syncope

The GDG then considered whether tilt testing had particular benefits in any subgroup of people with vasovagal syncope. The GDG considered that tilt testing was unlikely to be beneficial or cost-effective unless it was used to inform a change in management. They were therefore interested in whether people with a cardioinhibitory form of vasovagal syncope might benefit from diagnosis and subsequent treatment, including pacing.

The evidence was very uncertain on the clinical effectiveness of pacemakers in people with cardioinhibitory vasovagal syncope identified by tilt testing, and it is difficult to draw conclusions both on the efficacy of pacemakers and the ability of tilt testing to identify these people. This was partly because two of the three studies included less than 30% of patients with cardioinhibitory NM sycope (CI NM syncope) and in each study there were more of these patients in the control group. 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 would 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, and this was observed. The GDG noted that many of these uncertainties would be expected to resolve following publication of the ISSUE 3 study.

The evidence reviewed on the diagnostic test accuracy of tilt testing to select patients for pacing was considered to be biased, so the GDG did not take this into account.

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 reported 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. Having taken this into account, the GDG did not consider it likely that tilt testing would be sufficiently beneficial or cost-effective when used in the population with vasovagal syncope to identify those with cardioinhibitory vasovagal syncope.

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 vasovagal syncope 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.

The GDG considered the low quality evidence from one study (Fitchet 2003) in an indirect population (people with suspected vasovagal syncope who were not selected on the basis of a high symptom burden) which compared 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 GDG also considered the low quality evidence from one study that determined the diagnosic test accuracy of a tilt test compared with IER, and reported a sensitivity of 13% and specificity of 96%, with little uncertainty, for the target condition, asystole, in the severe vasovagal syncope population, and values of 12% and 95% for the target condition, asystole or bradycardia.

We note that the IER did not make a diagnosis for all TLoCs (26% missed of those with 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 cardioinhibitory 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 compared to IER (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, while 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. These conclusions did not change materially when various assumptions used in the model were tested through sensitivity analysis which gave the GDG additional confidence in the cost-effectiveness of tilt testing. For the strategy of using tilt testing followed by IER when tilt testing is negative, the basecase ICER was above £20,000 per QALY and sensitivity analyses on the HRQoL and survival benefits of pacing increased the ICER to above £30,000 per QALY.The GDG considered that the benefits of offering IER after a negative tilt test were too uncertain to recommend IER after tilt testing. Therefore tilt testing was considered to be the most cost-effective testing strategy in this population. Consequently the GDG framed recomemendation 1.3.2.6.

6.9.7 People with unexplained syncope

6.9.7.1 CSM in people aged 60 years and over

The clinical benefits and cost-effectiveness of CSM are discussed above under section 6.9.5. 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 (recommendation 1.3.2.7). 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) (recommendation 1.3.2.8).

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 Ambulatory ECG should be used and tilt testing should not be used prior to ambulatory ECG in this population (recommendation 1.3.2.9)

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. They took into account the low- and very low-quality evidence from one study (Farwell 2005) comparing a tilt test versus a reference standard of IER in a population with unexplained syncope. This UK-based study showed similar diagnostic test accuracy of the tilt test as was found in the Brignole (2006) study in a severe vasovagal population, i.e. low sensitivity (0 and 6%), with some uncertainty, and high specificity (96 and 100% respectively) for asystole and asystole plus bradycardia. One 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 as an initial investigation 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 (recommendation 1.3.2.8). 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.

The GDG recognised that many of the studies used earlier models of the IER device and that improvements have been made to overcome problems since the studies were conducted. The GDG felt that early presentation had the additional benefit of allowing the clinician to re-assess and talk with the patient.

6.10 Recommendations

1.3.2 Diagnostic tests for different types of syncope

1.3.2.1 Use the person's history to distinguish people whose exercise-induced syncope occurred **during exercise** (when a cardiac arrhythmic cause is probable) from those whose syncope occurred **shortly after stopping exercise** (when a vasovagal cause is more likely).

1.3.2.2 For people who have experienced syncope during exercise, offer urgent (within 7 days) exercise testing, unless there is a possible contraindication (such as suspected aortic stenosis or hypertrophic cardiomyopathy requiring initial assessment by imaging). Advise the person to refrain from exercise until informed otherwise following further assessment.

1.3.2.3 If the mechanism for exercise-induced syncope is identified by exercise testing, carry out further investigation or treatment as appropriate in

each individual clinical context. Otherwise, carry out further investigations assuming a suspected cardiac arrhythmic cause.

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

- TLoC at least several times a week, 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.
- 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.
- TLoC infrequently (less than once 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.

1.3.2.5 Do not offer a tilt test to people who have a diagnosis of vasovagal syncope on initial assessment.

1.3.2.6 For people with suspected vasovagal syncope with recurrent episodes of TLoC adversely affecting their quality of life, or representing a high risk of injury, consider a tilt test to assess whether the syncope is accompanied by a severe cardioinhibitory response (usually asystole).

1.3.2.7 For people with suspected carotid sinus syncope and for people with unexplained syncope who are aged 60 years or older, offer carotid sinus massage as a first-line investigation. This should be conducted in a controlled environment, with ECG recording, and with resuscitation equipment and a skilled team immediately available.

1.3.2.8 Diagnose carotid sinus syncope if carotid sinus massage reproduces syncope due to marked bradycardia/asystole and/or marked

hypotension. Do not diagnose carotid sinus syncope if carotid sinus massage causes asymptomatic transient bradycardia or hypotension (see recommendation 1.3.2.9).

1.3.2.9 For all people with unexplained syncope (including after negative carotid sinus massage test in those for whom this is appropriate), offer ambulatory ECG (see recommendation 1.3.2.4). Do not offer a tilt test before the ambulatory ECG.

1.3.2.10 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[7] follow-up (data interrogation of the device) after they have any further TLoC.

[7] The timing of the follow-up is dependent on the storage o the device and the condition of the person.

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