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Solbiati M, Costantino G, Casazza G, Dipaola F, Galli A, Furlan R, Montano N, Sheldon R

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[Intervention Review]

Implantable loop recorder versus conventional diagnostic workup for unexplained recurrent syncope

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ABSTRACT

Background

The most recent syncope guideline recommends that implantable loop recorders (ILRs) are implanted in the early phase of evaluation of people with recurrent syncope of uncertain origin in the absence of high-risk criteria, and in high-risk patients after a negative evaluation. Observational and case-control studies have shown that loop recorders lead to earlier diagnosis and reduce the rate of unexplained syncopes, justifying their use in clinical practice. However, only randomised clinical trials with an emphasis on a primary outcome of specific ILR-guided diagnosis and therapy, rather than simply electrocardiogram (ECG) diagnosis, might change clinical practice.

Objectives

To assess the incidence of mortality, quality of life, adverse events and costs of ILRs versus conventional diagnostic workup in people with unexplained syncope.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 3, 2015), MEDLINE, EMBASE, ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal in April 2015. No language restriction was applied.

Selection criteria

We included all randomised controlled trials of adult participants (i.e. ≥ 18 years old) with a diagnosis of unexplained syncope comparing ILR with standard diagnostic workup.

Data collection and analysis

Two independent review authors screened titles and abstracts of all potential studies we identified as a result of the literature search, extracted study characteristics and outcome data from included studies and assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*. We contacted authors of trials for missing data. We analysed dichotomous data (all-cause mortality and aetiologic diagnosis) as risk ratios (RR) with 95% confidence intervals (CI). We used the Chi^2 test to assess statistical heterogeneity (with $P < 0.1$) and the I^2 statistic to measure heterogeneity among the trials. We created a 'Summary of findings' table using the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes.

Main results

We included four trials involving a total of 579 participants. With the limitation that only two studies reported data on mortality and none of them had considered death as a primary endpoint, the meta-analysis showed no evidence of a difference in the risk of long-term mortality between participants who received ILR and those who were managed conventionally at follow-up (RR 0.97, 95% CI 0.41 to 2.30; participants = 255; studies = 2; very low quality evidence) with no evidence of heterogeneity. No data on short term mortality were available. Two studies reported data on adverse events after ILR implant. Due to the lack of data on adverse events in one of the studies' arms, a formal meta-analysis was not performed for this outcome.

Data from two trials seemed to show no difference in quality of life, although this finding was not supported by a formal analysis due to the differences in both the scores used and the way the data were reported. Data from two studies seemed to show a trend towards a reduction in syncope relapses after diagnosis in participants implanted with ILR. Cost analyses from two studies showed higher overall mean costs in the ILR group, if the costs incurred by the ILR implant were counted. The mean cost per diagnosis and the mean cost per arrhythmic diagnosis were lower for participants randomised to ILR implant.

Participants who underwent ILR implantation experienced higher rates of diagnosis (RR (in favour of ILR) 0.61, 95% CI 0.54 to 0.68; participants = 579; studies = 4; moderate quality evidence), as compared to participants in the standard assessment group, with no evidence of heterogeneity.

Authors' conclusions

Our systematic review shows that there is no evidence that an ILR-based diagnostic strategy reduces long-term mortality as compared to a standard diagnostic assessment (very low quality evidence). No data were available for short-term all-cause mortality. Moderate quality evidence shows that an ILR-based diagnostic strategy increases the rate of aetiologic diagnosis as compared to a standard diagnostic pathway. No conclusive data were available on the other end-points analysed.

Further trials evaluating the effect of ILRs in the diagnostic strategy of people with recurrent unexplained syncope are warranted. Future research should focus on the assessment of the ability of ILRs to change clinically relevant outcomes, such as quality of life, syncope relapse and costs.

PLAIN LANGUAGE SUMMARY

Implantable loop recorder versus conventional diagnostic assessment for people with unexplained recurrent fainting

Review question

The aim of this study was to assess the evidence about potential benefits and harms of implantable loop recorders (ILRs) compared to standard diagnostic assessment for people with unexplained recurrent faints or blackouts.

Background

Syncope (commonly referred to as fainting or blackout) is a temporary loss of consciousness due to momentary lack of blood flow to the brain. It is characterised by rapid onset, short duration and spontaneous complete recovery. Syncope may be the common presentation of different conditions, spanning from harmless to life-threatening, such as cardiac arrhythmias (i.e. sudden increased or decreased heartbeat). The electrocardiogram registration during syncope allows physicians either to confirm or exclude an arrhythmia as the mechanism of syncope.

ILRs are pen drive-sized devices implanted under the skin. They have a retrospective (loop) memory that continuously records and deletes the patient's electrocardiogram. ILR implant is suggested in the early phase of the evaluation of syncope patients.

The aim of this systematic review was to compare the potential benefits and harms of ILRs with conventional diagnostic assessment in people with unexplained syncope.

Study characteristics

We searched scientific databases and found four randomised controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) including 579 adults, which met our inclusion criteria. This review includes evidence identified up to April 2015.

Key results

All-cause mortality (death from any cause) was no different in people who received the ILR. Loop recorders do not seem to change quality of life, although people with ILR had a significantly higher rate of diagnosis compared to participants in the standard assessment group. Moreover, data seem to show a trend towards a reduction in syncope recurrences after diagnosis in people implanted with ILR. Finally, costs were higher in the group of participants in which the ILR was implanted but the cost per diagnosis and the cost to diagnose an arrhythmia were much lower for participants randomised to ILR implant.

Quality of the evidence

There was low quality evidence that ILR does not change mortality if compared to a standard diagnostic assessment of people with syncope. There was moderate quality evidence that ILR increases the rate of diagnosis if compared to a standard diagnostic assessment. Future research is needed in order to clarify if ILRs can improve quality of life and reduce syncope recurrences and costs.

All the included studies were funded: two of them by scientific societies, the remaining were partially supported by the ILR's manufacturers.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

| Implantable loop recorders compared with conventional diagnostic workup for unexplained syncope | | | | | | |
|---|--|----------------------------|--------------------------|------------------------------|---------------------------------|--|
| Patient or population: people with unexplained recurrent syncope Settings: any Intervention: implantable loop recorders Comparison: conventional diagnostic workup | | | | | | |
| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
| | Assumed risk | Corresponding risk | | | | |
| | Conventional diagnostic workup | Implantable loop recorders | | | | |
| All-cause mortality | short-term | See comment | See comment | Not estimable | 0 | See comment No data on short-term mortality were available |
| All-cause mortality | long-term | Study population | | RR 0.97 (0.41 to 2.30) | 255 (2 RCTs) | ⊕○○○ very low ^{1,2,3} |
| | | 71 per 1000 | 67 per 1000 (28 to 161) | | | |
| Other adverse events | | See comment | See comment | Not estimable | 447 (2 RCTs) | See comment No complications were observed following the procedure in either of the studies. Due to the lack of data on adverse events in the control group in one of the studies, we did not perform a formal meta-analysis for this outcome |

| | | | | | | |
|-----------------------------|-------------------------|----------------------------------|-------------------------------|-----------------|--------------------------------------|---|
| Quality of life | See comment | See comment | Not estimable | 279 (2 RCTs) | See comment | Due to the differences in the scores used and the way data were reported, we could not perform a formal meta-analysis. Please, see footnote ⁴ |
| Syncope relapse | See comment | See comment | Not estimable | 507 (3 RCTs) | See comment | Two studies showed a significant reduction in syncope recurrence after ECG-directed treatment. Please, see footnote ⁵ . |
| Economic costs | See comment | See comment | Not estimable | 261 (2 RCTs) | See comment | Given the high heterogeneity in both the results and the cost-assessments across the studies, we were unable to perform a quantitative analysis. Please see footnote ⁶ |
| Aetiologic diagnosis | Study population | | RR 0.61 (0.54 to 0.68) | 579 (4 RCTs) | ⊕⊕⊕○ moderate ¹ | |
| | 125 per 1000 | 77 per 1000 (68 to 85) | | | | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk Ratio, **RCT:** Randomised controlled trial.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: 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 quality: We are very uncertain about the estimate.

¹ Downgraded by one level for high risk of bias in the included studies.

^{2,3} Downgraded by two levels for very serious risk of imprecision, as the CI fails to exclude important benefits or important harms and a small number of events have been observed.

⁴ In one trial quality of life was measured by the 12-item short form of the Medical Outcomes Questionnaire (SF-12) and a visual analogue scale (VAS). A first report showed that quality of life was similar in both groups. At the 18-month follow-up there was a trend towards improved quality of life in the ILR group compared with that of controls with significant increases observed in VAS of general well being ($P = 0.03$), no change was noted in SF-12 scores. In the second trial an analysis of quality of life using the 36-Item Short Form Health Survey (SF-36) questionnaire was performed at baseline, six months and after 14 months' follow-up. There were no differences between the main composite scores suggestive of general physical and psychological well being. While there were no differences in physical functioning (i.e. intensity of exercise or walking distance), social functioning or mental health between the two groups, there was a significantly better score in "role limitations due to physical problems" in the ILR group. The scores for "role limitations due to emotional problems" were not statistically different between the two groups.

⁵ One of the studies was a cross-over trial, and data from this study could not be analysed, as the participants were offered cross-over to the alternative strategy after the first syncope recurrence if no diagnosis was made. Two studies showed significant reductions in syncope recurrence after treatment. Due to the differences in the way the data were reported, a formal meta-analysis could not be performed for this outcome.

⁶ In the first study the ILR's cost was not included in the analysis. Overall mean costs were lower in the ILR group than in the conventional management group, without statistical significance. In the second study the mean cost of the investigation with the conventional strategy was significantly less than investigation with the primary strategy of monitoring but the cost per diagnosis was significantly greater.

BACKGROUND

Description of the condition

Syncope is defined as “a transient loss of consciousness due to transient global cerebral hypoperfusion characterised by rapid onset, short duration and spontaneous complete recovery” (Moya 2009). It is a common symptom that can be remarkably debilitating and is associated with high healthcare costs (Sun 2013). Its true incidence is difficult to estimate due to variation in definition, differences in population prevalence and under-reporting in the general population. In the Framingham offspring study, 44% of participants with an episode of syncope reported that they did not seek medical advice (Soteriades 2002) and the proportion of participants not seeking medical evaluation in the younger population was much higher (Ganzeboom 2003; Serletis 2006). An estimated 40% of people faint at least once in their lifetime (Ganzeboom 2006). The median peak of first syncope is around 15 years, with a sharp increase after 70 years (Soteriades 2002). Data from the USA and Europe show that syncope accounts for between 1% to 3% of hospital emergency department (ED) visits (Soteriades 2002) and up to 6% of hospitalisations (Gendelman 1983).

From a pathophysiological standpoint, the causes of syncope are typically divided between cardiovascular (due to brady- or tachyarrhythmias or structural heart disease) and non-cardiac, which include orthostatic hypotension and reflex syncope (vasovagal, situational and carotid sinus syndrome) (Moya 2009; Reed 2015). Vasovagal syncope is the most common cause of syncope for all age groups, but cardiac causes become more common with advancing age. The prognosis of syncope patients is heterogeneous (Solbiati 2015a) and depends on whether the aetiology is cardiac or non-cardiac. While the latter is associated with a benign mortality prognosis, similar to that of syncope-free control individuals, people with cardiac syncope have a one-year overall mortality rate of up to 30% (Eagle 1985; Kapoor 1983; Soteriades 2002), which is mainly due to coronary artery disease, myocardial infarction and cerebrovascular disease (Soteriades 2002). For people aged over 65 years, cardiovascular disease in clinical history, syncope without prodromes and abnormal electrocardiogram (ECG) are independent predictors of one-year cardiovascular and non-cardiovascular mortality (Colivicchi 2003). However, their true relation to syncope outcomes and their role in short-term risk stratification is debated (Costantino 2014A; Costantino 2014B),

In the absence of more recent epidemiological data, the high historic mortality associated with cardiac syncope justifies the large amount of energy, time and money spent on the evaluation of syncope. Nevertheless, approximately 5% to 30% of syncopes remain unexplained after intensive diagnostic evaluation (EGSYS-2 2006; Sarasin 2001; Shen 2004). On the other hand, despite its benign prognosis, even recurrent vasovagal syncope may lead to a significant decrease in quality of life because of trauma, and psychological, driving, employment and financial implications. There-

fore, many low-risk syncope patients require extensive investigation or more aggressive treatments in selected cases (Costantino 2015). In case treatment is deemed necessary because of the high burden of symptoms, both pharmacological (beta-blockers, fludrocortisone, alpha-adrenergic agonists, selective serotonin reuptake inhibitors, angiotensin-converting enzyme inhibitors, disopyramide, anticholinergic agents or salt tablets) and dual-chamber pacemaker treatment have been proposed (Kuriachan 2008; Raj 2013; Solbiati 2014). However, a systematic review of randomised controlled trials (RCTs) of pharmacological or dual-chamber pacemaker treatment in reflex syncope showed that existing studies are small and heterogeneous in control treatments, outcomes considered and results, thus suggesting that evidence to support the use of any of these for vasovagal and carotid sinus syncope is weak (Romme 2011).

Description of the intervention

The ECG registration during syncope allows physicians either to confirm or exclude an arrhythmia as the mechanism of syncope (Krahn 2004). ECG monitoring is the most common procedure for diagnosing intermittent arrhythmias. Several systems of ECG ambulatory monitoring are currently available: in-hospital monitoring, conventional ambulatory Holter monitoring, event recorders, external or implantable loop recorders, and remote (at home) telemetry. In people with frequent symptoms, relatively short-term (one month) non-invasive ECG monitoring (e.g. with either event recorders or external loop recorders) may suffice. However, syncopal episodes usually occur less frequently, and for this reason long-term implantable loop recorders (ILRs) have been developed.

ILRs are pen drive-sized devices implanted subcutaneously under local anaesthesia in the left side of the chest and have a battery life of up to 36 months. They have no intravascular leads, recording a bipolar ECG signal from small electrodes on either end of the devices. ILRs have a retrospective (loop) memory that continuously records and deletes the patient's ECG. They include a patient-activation function that allows the patient or a bystander to activate ECG storage in case of syncope and an auto-activation feature capturing pre-defined arrhythmias (Krahn 2004). Like all implanted devices, ILRs also carry the risk of pocket infections that resolve with device explantation. This complication, which can occur either in the peri-procedural phase or late during the follow-up, was reported in 1% to 5% of patients (Brignole 2006; Krahn 1999).

How the intervention might work

The ILR may be most useful in people with infrequent symptoms and a suspected arrhythmia in whom noninvasive testing is negative or inconclusive. In such people, transient bradycar-

dia is frequently found to be responsible, although infrequent tachyarrhythmias are also documented. Symptoms associated with normal sinus rhythm (thus excluding arrhythmias) are also a common finding (Krahn 1999).

Many studies have analysed the utility of ILRs in recurrent unexplained or high risk syncope. These studies suggest that early use of the ILR provides more and earlier diagnoses and could help in selecting people who might benefit from pacemaker therapy (Brignole 2006; EGSYS-2 2006; Krahn 1999; Krahn 2004).

Why it is important to do this review

Since its introduction, the ILR has become the investigative tool of choice in recurrent unexplained syncope following negative initial investigations. The European Society of Cardiology's (ESC) guidelines now recommend that ILRs are implanted in the early phase of evaluation of people with recurrent syncope of uncertain origin in the absence of high-risk criteria, and in high-risk patients after a negative evaluation (Moya 2009). According to ESC guidelines, ILR implant may also be indicated to assess the contribution of bradycardia in people with suspected or certain neurally-mediated syncope, presenting with frequent or traumatic syncopal episodes, before considering permanent pacing, and in people with transient loss of consciousness of uncertain syncopal origin in order to exclude an arrhythmic aetiology.

In a previous narrative review, Parry 2010 searched for studies involving the ILR as a part of the diagnostic workup of recurrent unexplained or neurally-mediated syncope. Most were small observational studies and, even if a systematic literature search was performed, no attempt to combine the available data was made. Observational and case-control studies have shown that loop recorders lead to earlier diagnosis and reduce the rate of unexplained syncopes, justifying their use in clinical practice. However, only RCTs with emphasis on a primary outcome of specific ILR-guided diagnosis and therapy, rather than simply ECG diagnosis, might change clinical practice.

OBJECTIVES

To assess the incidence of mortality, quality of life, adverse events and costs of ILRs versus conventional diagnostic workup in people with unexplained syncope.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs comparing ILR to conventional diagnostic workup in people with unexplained syncope. We included studies reported as full-text articles, those published as abstract only, and unpublished data. We excluded cluster-RCTs to avoid the risk of introducing biases (Higgins 2011a).

Types of participants

We included studies enrolling adult participants (i.e. ≥ 18 years old) with a diagnosis of unexplained syncope (i.e. syncope, as defined in the single studies, without a definite cause after an initial evaluation). We excluded studies that enrolled only paediatric patients (i.e. < 18 years old); we included studies enrolling a mixed population (i.e. studies in which most (i.e. $> 80\%$) of the participants were adults, even if the age range of the included participants was below 18 years). We also excluded studies including only participants with a history of heart disease or ECG abnormalities.

Types of interventions

We included trials comparing ILR with standard diagnostic workup (i.e. any other tests or clinical follow-up aimed at identifying the cause of syncope).

Types of outcome measures

Primary outcomes

1. Short (i.e. within 30 days) and long-term all-cause mortality.
2. Other adverse events (cardiopulmonary resuscitation, intensive care unit admittance, major trauma, acute myocardial infarction, pulmonary embolism, major bleeding, aortic dissection, ILR-related adverse events requiring either explant or treatment).
3. Quality of life during follow-up (as defined in the single studies).

Secondary outcomes

1. Syncope relapse (i.e. a second syncope recurrence after randomisation).
2. Economic costs.
3. Aetiological diagnosis.

Search methods for identification of studies

Electronic searches

We identified trials through systematic searches of the following bibliographic databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3 of 12, 2015);
2. MEDLINE, 1946 to April week 3 2015 (Ovid);
3. EMBASE, 1974 to 2015 April 24 (Ovid).

We adapted the preliminary search strategy for MEDLINE (Ovid) to searches of other databases ([Appendix 1](#)). We applied the Cochrane sensitivity-maximising RCT filter ([Lefebvre 2011](#)) to MEDLINE and an adaptation of it to EMBASE.

Also, we conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (<http://apps.who.int/trialsearch/>) ([Appendix 1](#)).

We searched all databases from the earliest date available in each database to the present, and we imposed no restriction on language of publication. Searches were performed for all databases on 27 April 2015.

Searching other resources

We checked reference lists of all included studies, international guidelines ([Huff 2007](#); [Moya 2009](#); [Sheldon 2011](#)) and review articles ([Parry 2010](#)) for additional references. We searched relevant manufacturers' websites for trial information ([Medtronic](#); [St. Jude](#)) on 27 April 2015 as well.

Data collection and analysis

Selection of studies

Two review authors (FD, AG) independently screened titles and abstracts of all potential studies we identified as a result of the literature search, and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there were any disagreements, a third review author (MS) arbitrated. We retrieved the full-text study reports/publications coded 'retrieve'. Two review authors (FD, AG) independently screened the full-text articles and identified studies for inclusion, and identified and recorded reasons for exclusion of the ineligible studies. We resolved any disagreements through discussion or, if required, we consulted a third review author (MS). We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram ([Liberati 2009](#)) and 'Characteristics of excluded studies' table.

Data extraction and management

We used a data collection form for study characteristics and outcome data which was piloted on at least one study in the review. Two review authors (MS, GCo) independently extracted study

characteristics from the included studies. We resolved any disagreements through discussion or, if required, we consulted a third review author (GCa). We extracted the following study characteristics.

1. Methods: study design, total duration of study, number of study centres and location, study setting, withdrawals and date of study.
2. Participants: number (N), mean age, age range, gender, severity of condition, known cardiovascular disease, ECG abnormalities, inclusion and exclusion criteria.
3. Interventions: type of ILR (intervention), type of comparison.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (MS, GCo) independently extracted outcome data from the included studies. We resolved disagreements by consensus or by involving a third review author (GCa). One review author (MS) transferred data into the Review Manager (RevMan) ([RevMan 2014](#)) file. We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (GCa) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (MS, GCo) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)). We resolved any disagreements by discussion or by involving another review author (GCa). We assessed the risk of bias according to six domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting.

We graded each potential source of bias as either 'high', 'low' or 'unclear' and provided a justification for our judgment in the 'Risk of bias' table. We summarised the risk of bias judgements across different studies for each of the domains listed.

Within a trial, we gave a summary assessment of low risk of bias when there was a low risk of bias for all domains, unclear risk of bias when there was an unclear risk of bias for one or more domains, or high risk of bias when there was a high risk of bias for one or more domains.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

We used the following criteria for the risk of bias judgements:

1. Random sequence generation
 - i) Low risk of bias - adequate generation of the allocation sequence (e.g. computer-generated random numbers, table of random numbers or similar);

ii) Unclear risk of bias - unclear about whether the allocation was adequately generated (e.g. where the method of sequence generation is not described or not described in sufficient detail to allow a definite judgement);

iii) High risk of bias - inadequate generation of the allocation sequence (e.g. sequence generation by the date of admission, clinical record number and odd/even status).

2. Allocation concealment

i) Low risk of bias - adequate concealment of the allocation (e.g. sequentially numbered, sealed, opaque envelopes or centralised or pharmacy-controlled randomisation);

ii) Unclear risk of bias - unclear about whether the allocation was adequately concealed (e.g. where the method of concealment is not described or not described in sufficient detail to allow a definite judgement);

iii) High risk of bias - inadequate allocation concealment (e.g. predictable methods such as using an open allocation schedule as well as non-opaque, non-sealed or non-sequential numbered envelopes).

3. Blinding of participants and personnel

i) Low risk of bias - adequate blinding of participants and personnel (e.g. using sham ILR in the control group or performing sham diagnostic tests to patients in the intervention group);

ii) Unclear risk of bias - unclear about whether participants and personnel were blind to diagnostic strategy (e.g. whether blinding was not described or not described in sufficient detail to allow a definite judgement);

iii) High risk of bias - inadequate blinding of participants and personnel (e.g. participants or personnel, or both, were not blinded to the intervention group allocation).

4. Blinding of outcome assessment

i) Low risk of bias - adequate blinding of outcome assessors (e.g. outcome assessors unaware of the intervention group allocation);

ii) Unclear risk of bias - unclear about whether outcome assessors were blind to diagnostic strategy (e.g. whether blinding was not described or not described in sufficient detail to allow a definite judgement);

iii) High risk of bias - inadequate blinding of outcome assessors (e.g. outcome assessors were not blinded to the intervention group allocation).

5. Incomplete outcome data

i) Low risk of bias - adequate reporting of withdrawals, dropouts and protocol deviations (e.g. no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome; missing outcome data balanced in numbers across intervention groups; missing data have been imputed using appropriate methods);

ii) Unclear risk of bias - insufficient reporting of attrition/exclusions to permit judgement (e.g. number randomised not stated, no reasons for missing data provided);

iii) High risk of bias - reason for missing outcome data likely to be related to true outcome (e.g. either imbalance in numbers or reasons for missing data across intervention groups; “as-treated” rather than “intention-to-treat” analysis done, with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation).

6. Selective outcome reporting

i) Low risk of bias - adequate reporting of the study outcomes (e.g. the study protocol was available and all of the study's pre-specified outcomes that were of interest in the review were reported in the pre-specified way);

ii) Unclear risk of bias - insufficient information to permit judgement;

iii) High risk of bias - inadequate reporting of the study outcomes (e.g. not all of the study's pre-specified primary outcomes have been reported; one or more primary outcome was reported using measurements, analysis methods or subsets of the data that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the review were reported incompletely so that they could not be entered in a meta-analysis; the study report failed to include results for a key outcome that would have been expected to have been reported for such a study).

Assessment of bias in conducting the systematic review

We conducted the Cochrane review according to the published Cochrane protocol and reported any deviations in the 'Differences between protocol and review' section of the review ([Solbiati 2015b](#)).

Measures of treatment effect

We analysed dichotomous data (all-cause mortality and aetiologic diagnosis) as risk ratios (RR) with 95% confidence intervals (CI). We had planned to analyse continuous data (quality of life and economic costs) as mean difference (MD) or, when studies used different scales of measurements, standardised mean difference (SMD) with 95% CI.

Unit of analysis issues

We included RCTs in which the individual is randomised. We excluded cluster-RCTs to avoid the risk of introducing biases ([Deeks 2011](#)).

Dealing with missing data

We contacted investigators in order to obtain missing numerical outcome data where possible.

We contacted the authors of one trial published in abstract form requesting additional information on the trial design and methodology, clarification regarding data discrepancies, further detail about patient demographics or additional data, or both. The trial authors responded that the trial was being published in full in a few weeks, and we have been able to obtain data from that report (Sulke 2015).

We contacted a further trial author in order to clarify the data on mortality provided in the published report but we got no answer and we have not been able to include the study in that outcome analysis (Podoleanu 2014).

We had planned to explore the impact of including studies with missing data by a sensitivity analysis. Due to the small number of included studies we were unable to do so.

Assessment of heterogeneity

We used the Chi^2 test to assess statistical heterogeneity (with $P < 0.1$) and the I^2 statistic to measure heterogeneity among the trials (Higgins 2003). We would have reported and explored possible causes of heterogeneity by prespecified subgroup analysis if we had identified substantial heterogeneity (I^2 statistic $> 50\%$). Since we found no heterogeneity, we did not perform subgroup analyses.

Assessment of reporting biases

We had planned to create and examine a funnel plot to explore possible small study biases for the primary outcomes. Due to the small number of included studies, we have not been able to do so (Sterne 2011).

Data synthesis

We undertook meta-analyses with the RevMan 2014 software, using a fixed-effects model, as no heterogeneity was found. We included all studies in the main analyses irrespective of risk of bias. Within each included trial, we analysed all participants in the treatment groups to which they had been randomised. One study reported data from a cross-over trial (Krahn 2001). As suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c), in order to avoid carry-over, we included only data from the first period.

Subgroup analysis and investigation of heterogeneity

If sufficient data existed, we aimed to conduct the following subgroup analyses.

1. Type of ILR implanted.
2. Percentage of participants identified as having a cardiac cause of syncope at follow-up.
3. Percentage of participants with known cardiovascular disease or ECG abnormalities.

We planned to use the following outcomes in subgroup analyses.

1. All-cause mortality.

2. Other adverse events (cardiopulmonary resuscitation, intensive care unit admittance, major trauma, acute myocardial infarction, pulmonary embolism, major bleeding, aortic dissection).

3. Quality of life.

We planned to use the formal test for subgroup interactions in RevMan 2014, but data were insufficient to do so.

Sensitivity analysis

We planned to perform sensitivity analyses by excluding studies with high and unclear risk of bias and studies published only as abstracts, but the data were limited due to the small number of included studies.

Summary of findings

We created a 'Summary of findings' table (Schünemann 2011a) using the following outcomes:

1. short- (i.e. within 30 days) and long-term all-cause mortality;
2. other adverse events (cardiopulmonary resuscitation, intensive care unit admittance, major trauma, acute myocardial infarction, pulmonary embolism, major bleeding, aortic dissection, ILR-related adverse events requiring either explant or treatment);
3. quality of life (as defined in the single studies);
4. syncope relapse;
5. economic costs;
6. aetiological diagnosis.

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Section 8.5 (Higgins 2011b) and Chapter 12 (Schünemann 2011b) of the *Cochrane Handbook for Systematic Reviews of Interventions*. We justified all decisions to down- or up-grade the quality of studies using footnotes and we made comments to aid the reader's understanding of the review where necessary.

RESULTS

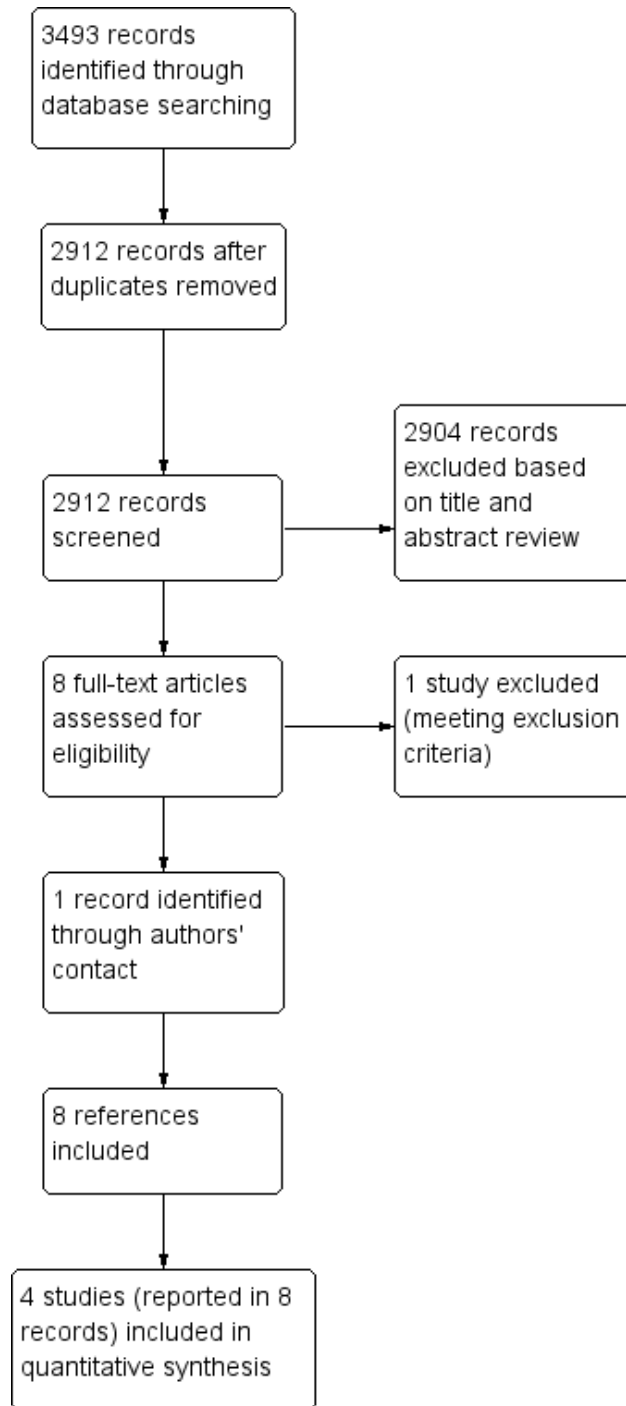
Description of studies

Results of the search

We identified 2912 de-duplicated references. By reviewing titles and abstracts, we excluded 2904 references, leaving eight records

as potentially eligible, two published in abstract form and six as full texts. One of these was excluded after full-text review, in accordance with our exclusion criteria. We found one additional reference after contact with the authors of one trial published in abstract form. These eight reports included four trials and we included them in our analysis ([Figure 1](#)).

Figure 1. Study flow diagram.



Searches of clinical trial registers provided references to two additional published protocols. No published results were found for either of them. The contact information for one was unavailable and we were not able to find any recent publication for the author on either PubMed or Scopus. We emailed the second contact for information about the trial. He answered that the trial had never started.

Included studies

We analysed four studies, with a total of 579 participants (Farwell 2006; Krahn 2001; Podoleanu 2014; Sulke 2015). Two studies included participants with either recurrent syncope or a single traumatic syncopal episode (Krahn 2001; Podoleanu 2014). Two studies included only participants with recurrent syncope (Farwell 2006; Sulke 2015). All the studies excluded participants with known or suspected cardiac disease as the cause of syncope.

The studies were published from 2001 to 2015. One of them was conducted in Canada (Krahn 2001) and three in Europe: two in the UK (Farwell 2006; Sulke 2015) and one in France (Podoleanu 2014); all of them were single centre studies. Mean follow-up ranged from one year (Krahn 2001) to 20 months (Sulke 2015). The number of participants enrolled in each study varied between 60 (Krahn 2001) and 246 (Sulke 2015). The percentage of men in each study varied between 40 (Sulke 2015) and 55 (Krahn 2001) and the mean age of the population recruited varied between 66 (Krahn 2001; Podoleanu 2014) and 74 years (Farwell 2006).

Medtronic Reveal and Reveal Plus were the ILRs implanted in three of the studies (Farwell 2006; Krahn 2001; Podoleanu 2014); participants in the last study (Sulke 2015) were implanted with the Transoma Sleuth ILR. Participants in the control group underwent conventional management by the attending physician in two studies (Farwell 2006; Podoleanu 2014) and a two- to four-week period of monitoring with an external loop recorder, followed by tilt table, and electrophysiological testing in one study (Krahn 2001). The latter was designed as a cross-over study and

patients were offered cross-over to the alternate strategy if the assigned strategy did not provide a diagnosis. Finally, participants from one study were randomised into four groups: 1) immediate implant of the ILR without hospital admission; 2) ILR and attendance at a dedicated syncope clinic for follow-up within two weeks; 3) syncope clinic group; 4) conventional management by the referring physician (Sulke 2015). The management of the participants in the conventional management arm of three studies (Farwell 2006; Podoleanu 2014; Sulke 2015) had not been standardised and was left to the referring physician's discretion.

Two studies were partially funded by the ILR manufacturers (Farwell 2006; Sulke 2015); the others received grants from both the Société Française de Cardiologie (Podoleanu 2014) and the Heart and Stroke Foundation of Ontario (Krahn 2001).

Tables of [Characteristics of included studies](#) show detailed descriptions of the studies.

Excluded studies

We excluded one trial from the review following full-text eligibility assessment (Da Costa 2013). The study met one of the exclusion criteria, as only people with ECG abnormalities (i.e. any bundle branch block or QRS greater or equal to 120 ms) were enrolled (see [Characteristics of excluded studies](#)).

Risk of bias in included studies

We give a description of the risk of bias for individual studies in the [Characteristics of included studies](#) tables. We deemed all the studies to be at a high risk of bias, as none of them blinded participants, personnel or outcome assessors to the intervention group allocation.

We give a summary of the risk of selection bias, performance and detection bias, attrition bias and reporting bias below. See [Figure 2](#) and [Figure 3](#) for details.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

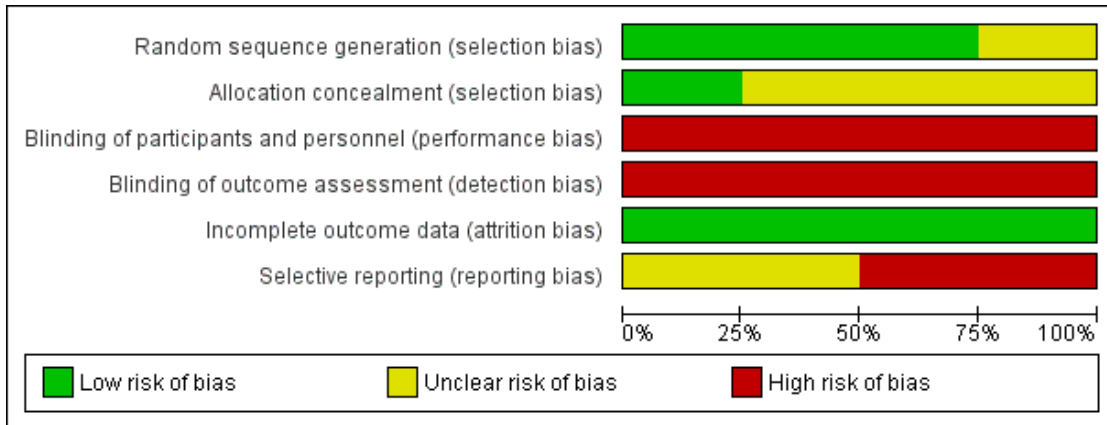


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

| | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) |
|----------------|---|---|---|---|--|--------------------------------------|
| Farwell 2006 | + | + | - | - | + | ? |
| Krahn 2001 | ? | ? | - | - | + | ? |
| Podoleanu 2014 | + | ? | - | - | + | - |
| Sulke 2015 | + | ? | - | - | + | - |

Allocation

Risk of bias arising from the method of generation of the random sequence was considered low in three trials (Farwell 2006; Podoleanu 2014; Sulke 2015). Risk of bias from the method of concealment of the allocation was considered low in one study (Farwell 2006) and unclear in two studies (Podoleanu 2014; Sulke 2015), as the method of concealment was not described.

In one included study, the study authors did not describe the method of sequence generation or allocation concealment, making the risk of selection bias unclear. However, the characteristics of each group were similar at baseline (Krahn 2001).

Blinding

None of the studies blinded participants or personnel to the intervention group allocation. There was inherent difficulty blinding the interventions, because the intervention required a procedure and long-term device management. Due to the lack of blinding, the included studies had a high risk of performance bias.

Because outcome assessors were also not blinded to the intervention group allocation, the risk of detection bias was also high in all the studies.

Incomplete outcome data

Risk of attrition bias was rated as low in all the trials. In two of them (Krahn 2001; Podoleanu 2014) no participant was lost to follow-up; one study (Farwell 2006) balanced missing outcome data in numbers across intervention groups.

In one study (Sulke 2015) five participants declined ILR implantation after enrolment and one participant requested to have his ILR explanted at eight months due to intolerance; analysis was by intention-to-treat, and the absence of outcome data was considered to be unrelated to the true outcome.

Selective reporting

Only one of the studies published the protocol in advance (Sulke 2015). This study was considered at high risk of bias as the cost analysis, which was one of the pre-defined outcomes, was not reported in the published reports. Another trial was considered at high risk of bias (Podoleanu 2014) because the results of the cost analysis, which was one of the study's aims, were not reported in the study.

We considered two trials (Farwell 2006; Krahn 2001) to have an unclear risk of reporting bias as the study protocol was not available.

Effects of interventions

See: [Summary of findings for the main comparison Summary of findings for the main comparison. Implantable loop recorder versus conventional diagnostic workup for unexplained recurrent syncope](#)

See [Summary of findings for the main comparison for the main comparison.](#)

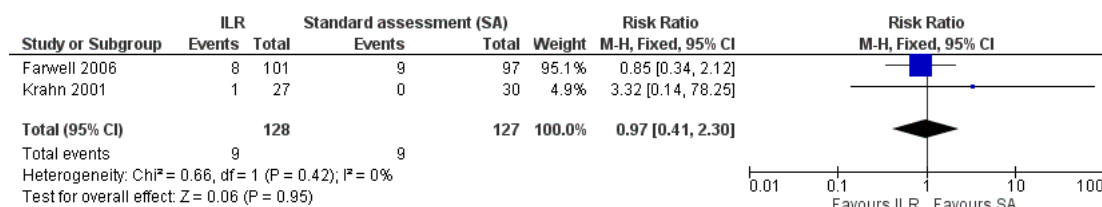
Primary outcomes

All-cause mortality

Two studies (255 participants) reported data on mortality at one year (Krahn 2001) and 18 months (Farwell 2006).

Overall, there was no evidence of a difference in the risk of mortality between participants who received ILR and those who were managed conventionally at long-term follow-up (9/128 versus 9/127; RR 0.97, 95% CI 0.41 to 2.30; participants = 255; studies = 2; very low quality evidence) with no evidence of heterogeneity (Analysis 1.1; Figure 4).

Figure 4. Forest plot of comparison: 1 ILR vs SA, outcome: 1.1 All-cause mortality.



No data on short-term mortality were available.

Other adverse events

Two studies (Farwell 2006; Sulke 2015) reported data on adverse events after ILR implant. No complications were observed following the procedure in either of the studies. We did not perform a formal meta-analysis for this outcome due to the lack of data on adverse events in the control group (i.e. both the syncope clinic and conventional management arms) in Sulke 2015.

Quality of life

Two trials analysed quality of life (Farwell 2006; Podoleanu 2014). Farwell 2006 measured quality of life by the 12-item short form of the Medical Outcomes Questionnaire (SF-12) and a visual analogue scale (VAS) at induction and at 6, 12 and 18 months. A first report showed that quality of life was similar in both groups. At the 18-month follow-up there was a trend towards improved quality of life in the ILR group compared with that of the control group, with significant increases observed in VAS of general well being ($P = 0.03$). No change was noted in SF-12 scores.

Podoleanu 2014 performed an analysis of quality of life using the 36-Item Short Form Health Survey (SF-36) questionnaire at baseline, six months and after 14 months of follow-up. There were no differences between the main composite scores, suggestive of general physical and psychological well being. While there were no differences in physical functioning (i.e. intensity of exercise or walking distance), social functioning or mental health between the two groups, there was a significantly better score in "role limitations due to physical problems" in the ILR group. The scores for "role limitations due to emotional problems" were not statistically different between the two groups.

Due to the differences in both the scores used and the way data were reported, we could not perform a formal meta-analysis for this outcome.

Secondary outcomes

Syncope relapse

Three studies reported a second recurrence of syncope after randomisation (Farwell 2006; Krahn 2001; Sulke 2015). One of them, Krahn 2001, was a cross-over trial and it evaluated syncope recurrences after both the primary and the secondary strategy, leading to a possible carry-over. We could not analyse the data from this study, as the participants were offered cross-over to the alternative strategy after the first syncope recurrence if no diagnosis was made.

Both the EaSyAS (Farwell 2006) and EaSyAS II (Sulke 2015) studies showed significant reductions in syncope recurrence after treatment. Farwell 2006 demonstrated similar rates of second syncope

(between groups) up to about 300 days from randomisation; at this point, the curves diverge with a reduction in the rate of further events in the ILR group ($P = 0.04$). Sulke 2015 confirmed that ILR participants were less likely to have a second post-randomisation syncope compared with conventionally managed patients (i.e. both the syncope clinic and conventional management arms) (HR 0.38, 95% CI 0.17 to 0.86, $P = 0.02$).

Due to the differences in the way data were reported, we could not perform a formal meta-analysis for this outcome.

Economic costs

Two trials analysed the cost implication of a diagnostic strategy based on either ILR or conventional management (Farwell 2006; Krahn 2001).

Farwell 2006, which was carried out in the UK, based costs incurred by further hospital admission and investigations for syncope, calculated from time of device implantation to the study's conclusion, on local National Health Service (NHS) costs. They did not include the cost of the ILR in the analysis, but the study authors stated that ILR UK list price at the time of the study was GBP 1350. Overall mean costs (including hospital stay) were lower in the ILR group (GBP 820, median GBP 0, interquartile range (IQR) GBP 0-200) than in the conventional management group (GBP 1380, median GBP 100, IQR GBP 0-800), without statistical significance (mean difference GBP 555, 95% CI GBP 252 to GBP 1990, $P = 0.28$).

Krahn 2001 calculated the costs of investigations based on the Ontario Health Insurance Program fee schedule for technical and professional fees and also included an estimate of materials, labour, maintenance, and overheads for hospital-based investigations. They considered all costs to be direct medical costs that were assessed from a societal perspective and expressed in 2002 Canadian Dollars (CAD). The mean cost of a primary strategy of monitoring was CAD 2731 ± CAD 285, and the cost per diagnosis was CAD 5852 ± CAD 610. The cost of the investigation with the conventional strategy was significantly less than investigation with the primary strategy of monitoring (CAD 1683 ± CAD 505, $P < 0.0001$) but the cost per diagnosis was significantly greater (CAD 8414 ± CAD 2527, $P < 0.0001$).

Given the difficulty in comparing data from different health care settings and the high heterogeneity in both the results and the cost-assessments across the studies, we were unable to perform a quantitative analysis. In order to give a comparable estimate across the studies, we added the ILR cost (GPB 1350) to the first study's ILR group, we converted the mean cost per participant to Euros (at the exchange rate on 16 October 2015) and we calculated:

1. mean costs per diagnosis;
2. mean costs per arrhythmic diagnosis; and
3. mean costs per diagnosis requiring invasive procedures (i.e. permanent pacemaker or implantable cardioverter defibrillator placement or catheter ablation).

We have reported the results in [Table 1](#). Please note: these results are approximate and readers should interpret the data only by comparing the two randomised groups within a single study.

Aetiological diagnosis

All the trials (579 participants) reported data on aetiological diagnosis. The mean duration of follow-up ranged from one year ([Krahn 2001](#)) to 20 months ([Sulke 2015](#)).

Overall, there was a significant difference in the number of diagnoses between participants who received ILR and those who were managed conventionally at long-term follow-up (137/292 versus 36/287; RR (in favour of ILR) 0.61, 95% CI 0.54 to 0.68; participants = 579; studies = 4; moderate quality evidence), as compared to participants in the standard assessment group, with no evidence of heterogeneity. ([Analysis 1.2](#); [Figure 5](#)).

Figure 5. Forest plot of comparison: 1 ILR vs SA, outcome: 1.2 Diagnosis.



DISCUSSION

Summary of main results

Observational and case-control studies have shown that loop recorders lead to earlier diagnosis and reduce the rate of unexplained syncope ([Brignole 2006](#); [EGSYS-2 2006](#); [Krahn 1999](#); [Krahn 2004](#)). However, only RCTs showing benefit on a primary outcome of specific ILR-guided diagnosis and therapy, rather than simply ECG diagnosis, should significantly change clinical practice. Therefore our review focused mainly on mortality and quality of life, as well as on diagnosis and syncope recurrence, which are their surrogate end-points.

We only identified four studies, incorporating 579 participants. The primary outcomes for all the included studies were the assessment of the diagnostic yield of ILR compared to the standard

assessment commonly used by the referring physician, as well as intensive diagnostic strategy performed in the context of a syncope unit. None of the included studies had considered either mortality or major adverse events as primary outcomes.

Due to the small number of included studies and the difference in the endpoint assessment between the studies, we were able to meta-analyse only two outcomes: mortality and aetiological diagnosis. Regarding the other four considered endpoints (adverse events, quality of life, syncope recurrence and costs), only a qualitative analysis was possible ([Summary of findings for the main comparison](#)).

We found no significant differences in reducing overall long-term mortality. The strength of this statement has some limitations: data on mortality were available only from two studies and were mainly driven by the largest. Moreover, none of the studies had been designed to assess mortality, as this is relatively uncommon in unexplained syncope patients.

There were no complications following the ILR implant in the studies analysing this outcome.

The included trials seemed to show no difference in quality of life. Since only two studies reported data on this outcome and used different quality of life assessments (scores, length of follow-up, data reporting) this finding is not conclusive.

Data from two studies seemed to show a trend towards a reduction in syncope relapses after diagnosis in participants implanted with ILR. Again, the paucity of data does not allow us to derive definitive conclusions.

Cost analyses showed higher mean costs in the ILR group when the ILR cost is counted. However the cost per diagnosis and the cost to diagnose an arrhythmia were lower for participants randomised to ILR implant. To interpret these data we have to remember that the ILR cost-effectiveness depends on both the population selected and the kind of diagnoses we are interested in. Indeed, if ILRs are used in a population at a high risk of recurrence (such as people with vasovagal syncope), we could paradoxically observe a very high diagnostic rate and hence a low cost per diagnosis. However, when implanting an ILR, we are usually interested in diagnosing potentially dangerous and treatable diseases, rather than benign conditions. Moreover, length of follow-up might influence costs, as a higher early expense due to the cost of ILR itself might be balanced by a lower need for tests and hospital admissions in the long term. Finally, we did not analyse the influence of an ILR-directed treatment on further costs.

Participants who underwent ILR implantation experienced higher rates of ECG diagnosis, as compared to participants in the standard assessment group.

Overall completeness and applicability of evidence

Our review identified only four studies addressing the benefits and harms of loop recorder implants in people with unexplained syncope randomised to either ILR or conventional diagnostic workup. The primary outcomes we were interested in were mortality, adverse events and quality of life. Syncope relapse, costs and aetiological diagnosis were secondary outcomes.

The studies were published from 2001 to 2015. One of them was conducted in Canada and three in Europe; all of them were single centre studies. Mean follow-up ranged from one year to 20 months.

The number of participants enrolled in each study varied between 60 and 246. The percentage of men in each study varied between 40 and 55, and the mean age of the population recruited varied between 66 and 74 years.

The generalisability of the results of this review might be limited, as the included studies were conducted in tertiary care centres. Since the diagnostic strategy of participants in the conventional management arm was almost always left to the referring physician, participants referred to centres with a different expertise on syncope might have different outcomes. Moreover all the available literature comes from Western countries, thus limiting the external

validity.

The data were sufficient to comment on aetiological diagnosis and mortality, although we must acknowledge two limitations in the interpretation of the latter. First, death was a relatively uncommon event and none of the included trials was designed and powered to assess it; second, long-term mortality might be influenced by conditions unrelated to syncope. Therefore ILR implant seems to result in a higher number of diagnoses without affecting long-term mortality.

There were insufficient data to comment on the quality of life, cost analysis and ability to prevent recurrences of ILR versus conventional management in people with unexplained syncope. The outcomes of quality of life, costs and adverse events are important clinical endpoints to consider when deciding the best diagnostic strategy for people with unexplained syncope.

Quality of the evidence

The trials had a high risk of performance bias and detection bias due to the lack of blinding. These limitations may lead to an overestimation of the effect of ILR over conventional management, but are difficult to quantify and to overcome, as the intervention requires an invasive procedure and post-implant management and follow-up.

We used the GRADE methodology in order to assess the quality of the body of evidence for the prespecified outcomes. There was a very low quality of evidence in our primary outcome, all-cause mortality, and a moderate quality of evidence in the secondary outcome of diagnostic rate.

Potential biases in the review process

We used a prespecified protocol for our review and complemented our search of published literature with handsearching and contacting study authors. We consider that there was a high likelihood that we included all published studies. However, since there were few published studies, we could not perform a formal assessment of publication bias. We followed guidelines from the *Cochrane Handbook for Systematic Reviews of Interventions* to perform our title screening and data extraction to minimise bias and believe the review process has a low risk of introducing bias (Higgins 2011a).

Agreements and disagreements with other studies or reviews

To our knowledge, there are no other systematic reviews comparing RCTs of ILR versus conventional diagnostic strategies in people with unexplained syncope. A previous narrative review (Parry 2010) reported data from observational and case-control studies showing that loop recorders lead to earlier diagnosis and reduce the rate of unexplained syncope. However, both the studies included and the review focused mainly on the ability of ILR to reach a diagnosis rather than to change patients' outcomes or quality of

life. Moreover, even if a systematic literature search was performed, no attempt to combine the available data was made. Interestingly, despite this lack of conclusive evidence on the utility of ILR in the diagnostic strategy of syncope, the ESC (Moya 2009) and European Heart Rhythm Association 2009 guidelines (Brignole 2009) recommend that ILRs are implanted in the early phase of evaluation of patients with recurrent syncope of uncertain origin in the absence of high-risk criteria, and in high-risk patients after a negative evaluation (Class IB and IA, respectively). This could be the consequence of the fact that clinicians are much more confident when the ECG registration during symptoms is available. However, a higher diagnostic rate does not necessarily lead to a better outcome or a higher quality of life and more evidence is needed before ILR implant will be routinely recommended in people with unexplained syncope.

AUTHORS' CONCLUSIONS

Implications for practice

Our systematic review shows that there is no evidence that an ILR-based diagnostic strategy reduces long-term mortality as compared to a standard diagnostic assessment (very low quality evidence).

No data were available for short-term all-cause mortality. Moderate quality evidence shows that an ILR-based diagnostic strategy increases the rate of aetiologic diagnosis compared to a standard diagnostic pathway. No conclusive data were available on the other end-points analysed.

Currently there is no strong evidence that an ILR-based diagnostic strategy might change patient-centred outcomes like mortality, adverse events, quality of life and syncope relapses.

Implications for research

Further trials evaluating the effect of ILRs in the diagnostic strategy of people with recurrent unexplained syncope are warranted. Future research should focus on the assessment of the ability of ILRs to change clinically relevant outcomes besides increasing the diagnostic rate. Cost analysis should include both costs for achieving the diagnosis and those incurred by further hospital admission and events following aetiologic treatment.

ACKNOWLEDGEMENTS

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REFERENCES

References to studies included in this review

Farwell 2006 *{published data only}*

Farwell DJ, Freemantle N, Sulke AN. Use of implantable loop recorders in the diagnosis and management of syncope. *European Heart Journal* 2004;**25**:1225–63.

* Farwell DJ, Freemantle N, Sulke N. The clinical impact of implantable loop recorders in patients with syncope. *European Heart Journal* 2006;**27**:351–6.

Krahn 2001 *{published data only}*

Krahn AD, Klein GJ, Yee R, Hoch JS, Skanes AC. Cost implications of testing strategy in patients with syncope. *Journal of the American College of Cardiology* 2003;**42**:495–501.

* Krahn AD, Klein GJ, Yee R, Skanes AC. Randomized assessment of syncope trial: conventional diagnostic testing versus a prolonged monitoring strategy. *Circulation* 2001; **104**:46–51.

Podoleanu 2014 *{published data only}*

Podoleanu C, Da Costa A, Defaye P, Taieb J, Galley D, Bru P, et al. Early use of an implantable loop recorder in syncope evaluation: a randomized study in the context of the French healthcare system (FRESH study). *Archives of Cardiovascular Diseases* 2014;**107**:546–52.

Sulke 2015 *{published data only}*

Hong PS, Hunt J, Freemantle N, Sulke N. The utilisation of a remotely monitored implantable loop recorder as first line investigation in the diagnosis of syncope: The EaSyAS II. *Canadian Journal of Cardiology* 2011;**1**:S295.

Sulke N, Hong PSG, Hunt J, Freemantle N, Podd SJ, Fonseka M, et al. Immediate use of a remotely monitored implantable loop recorder in diagnosing unexplained syncope: The Second Eastbourne Syncope Assessment Study (EaSyAS II). *Europace* 2010;**12**:ii7.

* Sulke N, Sugihara C, Hong P, Patel N, Freemantle N. The benefit of a remotely monitored implantable loop recorder as a first line investigation in unexplained syncope: the EaSyAS II trial. *Europace* 2015;**Oct 12**:Epub ahead of print. [DOI: 10.1093/europace/euv228]

References to studies excluded from this review

Da Costa 2013 *{published data only}*

Da Costa A, Defaye P, Romeyer-Bouchard C, Roche F, Dauphinot V, Deharo JC, et al. Clinical impact of the implantable loop recorder in patients with isolated syncope, bundle branch block and negative workup: a randomized multicentre prospective study. *Archives of Cardiovascular Disease* 2013;**106**:146–54.

Additional references

Brignole 2006

Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Moya A, Wieling W, et al. Early application of an implantable loop recorder allows effective specific therapy in patients with recurrent suspected neurally mediated syncope. *European Heart Journal* 2006;**27**(9):1085–92.

Brignole 2009

Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, Ricci R, et al. Indications for the use of diagnostic implantable and external ECG loop recorders. *Europace* 2009;**11**:671–87.

Colivicchi 2003

Colivicchi F, Ammirati F, Melina D, Guido V, Imperoli G, Santini M. Development and prospective validation of a risk stratification system for patients with syncope in the emergency department: the OESIL risk score. *European Heart Journal* 2003;**24**(9):811–9. [DOI: 10.1016/S0195-668X(02)00827-8]

Costantino 2014A

Costantino G, Dipaola F, Solbiati M, Bulgheroni M, Barbic F, Furlan R. Is hospital admission valuable in managing syncope? Results from the STePS study. *Cardiology Journal* 2014;**21**:606–10.

Costantino 2014B

Costantino G, Casazza G, Reed M, Bossi I, Sun B, Del Rosso A, et al. Syncope risk stratification tools vs clinical judgment: an individual patient data meta-analysis. *American Journal of Medicine* 2014;**127**:1126.e13–25.

Costantino 2015

Costantino G, Sun BC, Barbic F, Bossi I, Casazza G, Dipaola F, et al. Syncope clinical management in the emergency department: a consensus from the first international workshop on syncope risk stratification in the emergency department. *European Heart Journal* 2015;**Aug 4**:Epub ahead of print. [DOI: 10.1093/eurheartj/ehv378]

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. Date accessed: 1 Feb 2016.

Eagle 1985

Eagle KA, Black HR, Cook EF, Goldman L. Evaluation of prognostic classifications for patients with syncope. *American Journal of Medicine* 1985;**79**(4):455–60.

EGSYS-2 2006

Brignole M, Ungar A, Bartoletti A, Ponassi I, Lagi A, Mussi C, et al. Standardized-care pathway vs. usual management of syncope patients presenting as emergencies at general hospitals. *Europace* 2006;**8**(8):644–50.

Ganzeboom 2003

Ganzeboom KS, Colman N, Reitsma JB, Shen WK, Wieling W. Prevalence and triggers of syncope in medical students. *American Journal of Cardiology* 2003;**91**(8):1006–8.

Ganzeboom 2006

Ganzeboom KS, Mairuhu G, Reitsma JB, Linzer M, Wieling W, Van Dijk N. Lifetime cumulative incidence of syncope in the general population: a study of 549 Dutch subjects aged 35–60 years. *Journal of Cardiovascular Electrophysiology* 2006;**17**(11):1172–6.

Gendelman 1983

Gendelman HE, Linzer M, Gabelman M, Smoller S, Scheuer J. Syncope in a general hospital patient population. Usefulness of the radionuclide brain scan, electroencephalogram, and 24-hour Holter monitor. *New York State Journal of Medicine* 1983;**83**(11-2):1161–5.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557–60.

Higgins 2011a

Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. Date accessed: 1 Feb 2016.

Higgins 2011b

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. Date accessed: 1 Feb 2016.

Higgins 2011c

Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. Date accessed: 1 Feb 2016.

Huff 2007

Huff JS, Decker WW, Quinn JV, Perron AD, Napoli AM, Peeters S, et al. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with syncope. *Annals of Emergency Medicine* 2007;**49**(4):431–44.

Kapoor 1983

Kapoor WN, Karpf M, Wieand S, Peterson JR, Levey GS. A prospective evaluation and follow-up of patients with syncope. *New England Journal of Medicine* 1983;**309**(4):197–204.

Krahn 1999

Krahn AD, Klein GJ, Yee R, Takle-Newhouse T, Norris C. Use of an extended monitoring strategy in patients with

- problematic syncope. Reveal Investigators. *Circulation* 1999;**99**(3):406–10.
- Krahn 2004**
Krahn AD, Klein GJ, Skanes AC, Yee R. Insertable loop recorder use for detection of intermittent arrhythmias. *Pacing and Clinical Electrophysiology* 2004;**27**(5):657–64.
- Kuriachan 2008**
Kuriachan V, Sheldon RS, Platonov M. Evidence-based treatment for vasovagal syncope. *Heart Rhythm* 2008;**5**(11):1609–14. [DOI: 10.1016/j.hrthm.2008.08.023]
- Lefebvre 2011**
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. Date accessed: 1 Feb 2016.
- Liberati 2009**
Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine* 2009;**6**:e1000100.
- Moya 2009**
Task Force for the Diagnosis and Management of Syncope, European Society of Cardiology (ESC), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA), Heart Rhythm Society (HRS), Moya A, et al. Guidelines for the diagnosis and management of syncope (version 2009). *European Heart Journal* 2009;**30**(21):2631–71.
- Parry 2010**
Parry SW, Matthews IG. Implantable loop recorders in the investigation of unexplained syncope: a state of the art review. *Heart* 2010;**96**(20):1611–6.
- Raj 2013**
Raj SR, Coffin ST. Medical therapy and physical maneuvers in the treatment of the vasovagal syncope and orthostatic hypotension. *Progress in Cardiovascular Diseases* 2013;**55**(4):425–33. [DOI: 10.1016/j.pcad.2012.11.004]
- Reed 2015**
Williamson C, Reed MJ. Syncope: the emergency department and beyond. *Internal and Emergency Medicine* 2015;**10**:843–50.
- RevMan 2014 [Computer program]**
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
- Romme 2011**
Romme JJ, Reitsma JB, Black CN, Colman N, Scholten RJ, Wieling W, et al. Drugs and pacemakers for vasovagal, carotid sinus and situational syncope. *Cochrane Database of Systematic Reviews* 2011, Issue 10. [DOI: 10.1002/14651858.CD004194.pub3]
- Sarasin 2001**
Sarasin FP, Louis-Simonet M, Carballo D, Slama S, Rajeswaran A, Metzger JT, et al. Prospective evaluation of patients with syncope: a population-based study. *American Journal of Medicine* 2001;**111**(3):177–84.
- Schünemann 2011a**
Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and ‘Summary of findings’ tables. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. Date accessed: 1 Feb 2016.
- Schünemann 2011b**
Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. Date accessed: 1 Feb 2016.
- Serletis 2006**
Serletis A, Rose S, Sheldon AG, Sheldon RS. Vasovagal syncope in medical students and their first-degree relatives. *European Heart Journal* 2006;**27**(16):1965–70.
- Sheldon 2011**
Sheldon RS, Morillo CA, Krahn AD, O’Neill B, Thiruganasambandamoorthy V, Parkash R, et al. Standardized approaches to the investigation of syncope: Canadian Cardiovascular Society Position Paper. *Canadian Journal of Cardiology* 2011;**27**:246–53.
- Shen 2004**
Shen WK, Decker WW, Smars PA, Goyal DG, Walker AE, Hodge DO, et al. Syncope Evaluation in the Emergency Department Study (SEEDS): a multidisciplinary approach to syncope management. *Circulation* 2004;**110**(24):3636–45.
- Solbiati 2014**
Solbiati M, Sheldon RS. Implantable rhythm devices in the management of vasovagal syncope. *Autonomic Neuroscience: Basic & Clinical* 2014;**184**:33–9. [DOI: 10.1016/j.autneu.2014.05.012]
- Solbiati 2015a**
Solbiati M, Casazza G, Dipaola F, Rusconi AM, Cernuschi G, Barbic F, et al. Syncope recurrence and mortality: a systematic review. *Europace* 2015;**17**:300–8.
- Soteriades 2002**
Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ, et al. Incidence and prognosis of syncope. *New England Journal of Medicine* 2002;**347**(12):878–85.
- Sterne 2011**
Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Intervention*. Version 5.1.0 (updated March 2011).

The Cochrane Collaboration, 2011. Available from
www.cochrane-handbook.org. Date accessed: 1 Feb 2016.

Sun 2013

Sun BC. Quality-of-life, health service use, and costs associated with syncope. *Progress in Cardiovascular Diseases* 2013;**55**(4):370–5.

References to other published versions of this review

Solbiati 2015b

Solbiati M, Costantino G, Casazza G, Dipaola F, Galli A, Furlan R, et al. Implantable loop recorder versus conventional diagnostic workup for unexplained recurrent syncope. *Cochrane Database of Systematic Reviews* 2015, Issue 4. [DOI: 10.1002/14651858.CD011637]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Farwell 2006

| | |
|---------------|---|
| Methods | Randomised clinical trial |
| Participants | <p>Consecutive patients with recurrent syncope (i.e. two or more episodes in the past year) and without a definite diagnosis following initial clinical workup (comprising history and a physical examination, 12-lead ECG, full blood count, urea and electrolytes, plasma glucose and Holter monitoring in the patients with suspected cardiac syncope)</p> <p>103 participants randomised to ILR; 98 participants randomised to conventional management</p> <p>46% men</p> <p>Median (IQ range) age: 74 (61-81) years</p> <p>Two participants in the ILR group and one participant in the conventional management group were reported as lost to follow-up</p> |
| Interventions | <p>Group 1: Medtronic Reveal Plus ILR</p> <p>Group 2: conventional management</p> |
| Outcomes | <p>Primary: Time to ECG diagnosis</p> <p>Secondary: (1) Time to first recurrence of syncope following study induction. (2) Time to second recurrence of syncope following study induction. (3) Time to the introduction of ECG-guided therapy</p> <p>Tertiary: (1) Quality of life. Measured by SF-12 questionnaire and visual analogue scales (VAS) at induction, 6, 12, and 18 months post-enrolment. (2) Cost effectiveness</p> <p>Even if they were not study outcomes, data on long-term mortality and adverse events were also available</p> <p>Mean follow-up 17 months</p> |
| Notes | <p>Eastbourne Syncope Assessment Study (EaSyAS)</p> <p>The study was partly supported by grants from Medtronic UK</p> |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|--|
| Random sequence generation (selection bias) | Low risk | Randomisation was by random number tables |
| Allocation concealment (selection bias) | Low risk | Participants were allocated by sealed envelopes held in the study centre |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | Neither participants nor personnel were blinded to the intervention or the control |

Farwell 2006 (Continued)

| | | |
|---|--------------|---|
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Outcome assessors were not blinded to the intervention group allocation |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Missing outcome data balanced in numbers across intervention groups |
| Selective reporting (reporting bias) | Unclear risk | The study protocol was not available |

Krahn 2001

| | | |
|---------------|---|--|
| Methods | Randomised cross-over clinical trial | |
| Participants | <p>Recurrent unexplained syncope or a single episode of syncope associated with injury that warranted cardiovascular investigation and without a definite diagnosis following initial clinical workup (comprising postural blood pressure testing, a minimum of 24 hours of baseline ambulatory monitoring or inpatient telemetry, and a transthoracic echocardiogram)</p> <p>30 participants randomised to ILR; 30 participants randomised to conventional management</p> <p>55% men</p> <p>Mean (SD) age: 66 (14) years</p> <p>Three participants in the ILR group were still in follow-up at the time of the paper publication, therefore only 27 participants were analysed in the ILR population. The cost analysis (which was published two years later) included all the randomised participants</p> | |
| Interventions | <p>Group 1: Medtronic Reveal ILR</p> <p>Group 2: a two- to four-week period of monitoring with an external loop recorder, followed by tilt table, and electrophysiological testing</p> <p>If the assigned strategy did not provide a diagnosis, participants were offered cross-over to the alternate strategy (for the purpose of our review only the primary strategy was considered)</p> | |
| Outcomes | <p>Symptom-rhythm correlation (diagnostic yield) in participants during spontaneous syncope or presyncope that resembled the symptoms before enrolment</p> <p>Even if they were not study outcomes, data on long-term mortality, syncope recurrence and costs were also available</p> <p>Mean follow-up 12 months</p> | |
| Notes | <p>Randomized Assessment of Syncope Trial (RAST)</p> <p>This study was supported by a grant from the Heart and Stroke Foundation of Ontario</p> | |

Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|--------------------|--|
| Random sequence generation (selection bias) | Unclear risk | Method of sequence generation not reported |

Krahn 2001 (Continued)

| | | |
|---|--------------|--|
| Allocation concealment (selection bias) | Unclear risk | Allocation concealment from study members not reported, but the characteristics of each group were similar at baseline |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | It does not appear that either participants or personnel were blinded to the intervention or the control |
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Outcome assessors were not blinded to the intervention group allocation |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | It does not appear that any participants were lost to follow-up, however three participants in the ILR group were still in follow-up at the time that one of the reports was published |
| Selective reporting (reporting bias) | Unclear risk | The study protocol was not available |

Podoleanu 2014

| | | |
|----------------------------|---|------------------------------|
| Methods | Randomised clinical trial | |
| Participants | <p>Patients from the hospitalisation ward or outpatient department who presented with one of the following criteria: a single syncope, if severe (i.e. not preceded by prodrome, which resulted in an injury) and recent (i.e. occurring within the previous six months); or at least two syncopes in the past 12 months. The syncope had to remain unexplained at the end of the clinical examination, and after performing a 12-lead electrocardiogram (ECG), echocardiography and head-up tilt-test, meaning that a further diagnostic workup was mandatory</p> <p>39 participants randomised to ILR; 39 participants randomised to conventional management</p> <p>41% men</p> <p>Mean (SD) age: 66.2 (14.8) years</p> <p>No participants were reported as lost to follow-up</p> | |
| Interventions | <p>Group 1: Medtronic Reveal or Reveal Plus ILR</p> <p>Group 2: conventional evaluation strategy commonly used by the attending physician</p> | |
| Outcomes | <p>Diagnostic yield, cost and impact on quality of life</p> <p>Mean follow-up 14 months</p> | |
| Notes | <p>French Study on implantable Holter Recorders in Syncope (FRESH)</p> <p>This study received a grant from the Société Française de Cardiologie</p> | |
| <i>Risk of bias</i> | | |
| Bias | Authors' judgement | Support for judgement |

Podoleanu 2014 (Continued)

| | | |
|---|--------------|--|
| Random sequence generation (selection bias) | Low risk | Computer-generated randomisation list |
| Allocation concealment (selection bias) | Unclear risk | Allocation concealment from study members not reported, but the characteristics of each group were similar at baseline |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | Neither participants nor personnel were blinded to the intervention or the control |
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Outcome assessors were not blinded to the intervention group allocation |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | No participant was lost to follow-up |
| Selective reporting (reporting bias) | High risk | Although cost analysis is one of the study's aims, its results were not reported |

Sulke 2015

| | |
|---------------|--|
| Methods | Randomised clinical trial |
| Participants | <p>Participants presented to the emergency department, to general practitioners in the community as well as to medical, surgical, and orthopaedic wards with a diagnosis of recurrent syncope (at least two syncopes in the past 24 months)</p> <p>66 participants randomised to ILR only; 59 participants randomised to ILR and syncope clinic; 60 participants randomised to syncope clinic only; 61 participants randomised to conventional management</p> <p>40.2% men</p> <p>Mean (SD) age: 70.3 (18) years.</p> <p>Five participants withdrew from the study following enrolment. Four declined to accept ILR implantation. One participant required regular MRI scans for surveillance of a benign brain tumour, so declined the ILR despite the fact that the Sleuth is MR-conditional. One participant requested to have his ILR explanted at eight months due to intolerance</p> |
| Interventions | <p>Group 1: Transoma Sleuth ILR</p> <p>Group 2: Transoma Sleuth ILR and syncope clinic</p> <p>Group 3: syncope clinic</p> <p>Group 4: conventional evaluation strategy commonly used by the referring physician</p> |
| Outcomes | <p>Primary: time to ECG diagnosis</p> <p>Secondary: time to first and second post-randomisation syncope, and time to ECG-directed therapy</p> <p>Even if they were not study outcomes, data on adverse events were also available</p> <p>Median follow-up 20.4 months</p> |

| | | |
|---|--|--|
| Notes | Eastbourne Syncope Assessment Study II (EaSyAS II) The study was part funded by an unrestricted grant from Transoma Medical Inc. The majority of funding was from the Eastbourne Cardiology Research Charity Fund | |
| Risk of bias | | |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Low risk | Computer-generated random number tables |
| Allocation concealment (selection bias) | Unclear risk | Allocation concealment from study members not reported, but the characteristics of each group were similar at baseline |
| Blinding of participants and personnel (performance bias) All outcomes | High risk | Neither participants nor personnel were blinded to the intervention or the control |
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Outcome assessors were not blinded to the intervention group allocation |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Reasons for missing outcome data unlikely to be related to true outcome: 5 participants withdrew from the study following enrolment (declined to accept ILR implantation) , 1 participant requested to have his ILR explanted at eight months due to intolerance |
| Selective reporting (reporting bias) | High risk | Although cost analysis is one of the study's aims, its results were not reported |

Characteristics of excluded studies [ordered by study ID]

| Study | Reason for exclusion |
|---------------|--|
| Da Costa 2013 | Only patients with ECG abnormalities were included |

DATA AND ANALYSES

Comparison 1. ILR vs SA

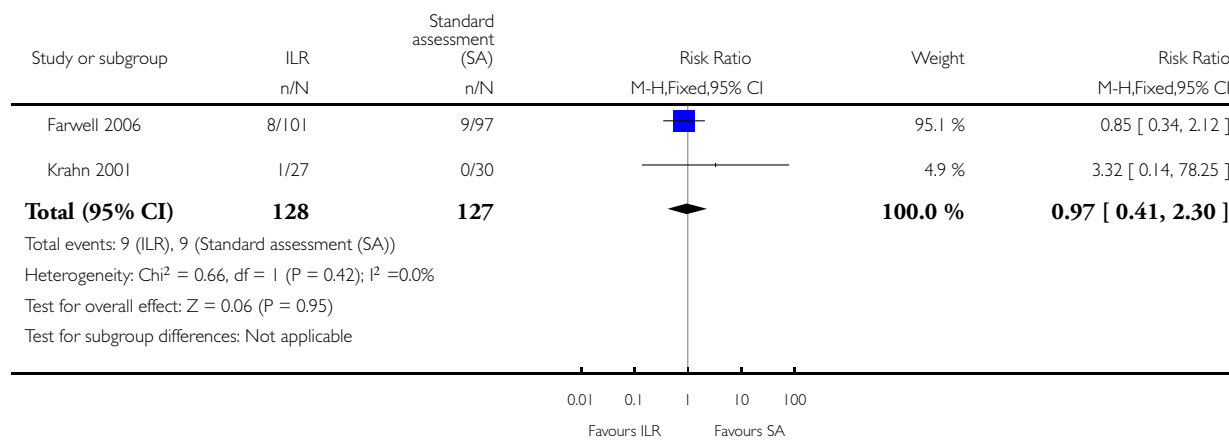
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---------------------------|----------------|---------------------|---------------------------------|-------------------|
| 1 All-cause mortality | 2 | 255 | Risk Ratio (M-H, Fixed, 95% CI) | 0.97 [0.41, 2.30] |
| 2 Diagnosis | 4 | 579 | Risk Ratio (M-H, Fixed, 95% CI) | 0.61 [0.54, 0.68] |

Analysis 1.1. Comparison 1 ILR vs SA, Outcome 1 All-cause mortality.

Review: Implantable loop recorder versus conventional diagnostic workup for unexplained recurrent syncope

Comparison: 1 ILR vs SA

Outcome: 1 All-cause mortality

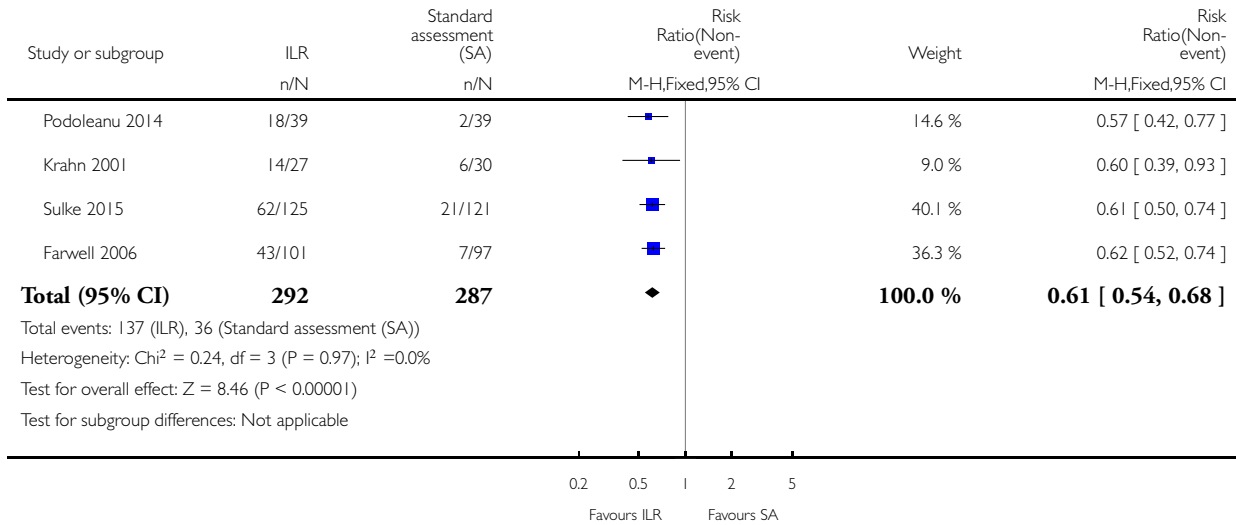


Analysis 1.2. Comparison 1 ILR vs SA, Outcome 2 Diagnosis.

Review: Implantable loop recorder versus conventional diagnostic workup for unexplained recurrent syncope

Comparison: 1 ILR vs SA

Outcome: 2 Diagnosis



ADDITIONAL TABLES

Table 1. Cost analysis

| | Farwell 2006 | | Krahn 2001 | |
|-----------------------------------|----------------------|------------------|----------------|----------------|
| | ILR | SA | ILR | SA |
| Number of participants | 101 | 97 | 30 | 30 |
| Mean follow-up (months) | 17 | | 12 | |
| Mean cost (SD) per participant | GBP 2170 | GBP 1380 | CAD 2731 (285) | CAD 1683 (505) |
| Median cost (IQR) per participant | GBP 1350 (1350-1550) | GBP 1480 (0-800) | | |
| Mean cost per participant | EUR 2952 | EUR 1877 | EUR 1863 | EUR 1148 |

Table 1. Cost analysis (Continued)

| | | | | |
|---|-----------|-----------|----------|----------|
| Number of diagnoses | 43 | 7 | 14 | 6 |
| Number of arrhythmic diagnoses | 20 | 4 | 11 | 4 |
| Number of diagnoses requiring invasive procedures | 17 | 4 | 11 | 4 |
| Mean cost per diagnosis | EUR 6934 | EUR 26010 | EUR 3992 | EUR 5740 |
| Mean cost per arrhythmic diagnosis | EUR 14908 | EUR 45517 | EUR 5081 | EUR 8610 |
| Mean cost per diagnosis requiring invasive procedures | EUR 17538 | EUR 45517 | EUR 5081 | EUR 8610 |

CAD: Canadian Dollars; EUR: Euros; GBP: GB Pounds; ILR: Implantable Loop Recorder; IQR: interquartile range; SA: standard assessment; SD: standard deviation.

APPENDICES

Appendix I. Search strategies

CENTRAL

- #1 MeSH descriptor: [Syncope] explode all trees
- #2 syncop*:ti,ab,kw (Word variations have been searched)
- #3 presyncop*:ti,ab,kw (Word variations have been searched)
- #4 faint*:ti,ab,kw (Word variations have been searched)
- #5 lipothymi*:ti,ab,kw (Word variations have been searched)
- #6 MeSH descriptor: [Dizziness] this term only
- #7 dizzy*:ti,ab,kw (Word variations have been searched)
- #8 dizzy*:ti,ab,kw (Word variations have been searched)
- #9 light headedness:ti,ab,kw (Word variations have been searched)
- #10 light-headedness:ti,ab,kw (Word variations have been searched)
- #11 lightheadedness:ti,ab,kw (Word variations have been searched)
- #12 orthostasis:ti,ab,kw (Word variations have been searched)
- #13 drop attack*:ti,ab,kw (Word variations have been searched)
- #14 MeSH descriptor: [Unconsciousness] this term only
- #15 unconscious*:ti,ab,kw (Word variations have been searched)
- #16 loss of consciou*:ti,ab,kw (Word variations have been searched)
- #17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
- #18 MeSH descriptor: [Electrocardiography, Ambulatory] this term only

#19 MeSH descriptor: [Electrocardiography] this term only
 #20 loop recorder*:ti,ab,kw (Word variations have been searched)
 #21 ilr*:ti,ab,kw (Word variations have been searched)
 #22 (implant* near/5 (ecg or electrocardiog*)):ti,ab,kw (Word variations have been searched)
 #23 ((implant* or internal or event*) near/2 record*):ti,ab,kw (Word variations have been searched)
 #24 confirm:ti,ab,kw (Word variations have been searched)
 #25 reveal:ti,ab,kw (Word variations have been searched)
 #26 sleuth:ti,ab,kw (Word variations have been searched)
 #27 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
 #28 #17 and #27

MEDLINE OVID

1. exp Syncope/
2. syncop*.tw.
3. presyncop*.tw.
4. faint*.tw.
5. lipothymi*.tw.
6. Dizziness/
7. dizzy*.tw.
8. dizzi*.tw.
9. light headedness.tw.
10. light-headedness.tw.
11. lighththeadedness.tw.
12. orthostasis.tw.
13. drop attack*.tw.
14. Unconsciousness/
15. unconscious*.tw.
16. loss of consciou*.tw.
17. or/1-16
18. Electrocardiography, Ambulatory/
19. Electrocardiography/
20. loop recorder*.tw.
21. ilr*.tw.
22. (implant* adj5 (ecg or electrocardiog*)).tw.
23. ((implant* or internal or event*) adj2 record*).tw.
24. confirm.tw.
25. reveal.tw.
26. sleuth.tw.
27. or/18-26
28. 17 and 27
29. randomized controlled trial.pt.
30. controlled clinical trial.pt.
31. randomized.ab.
32. placebo.ab.
33. drug therapy.fs.
34. randomly.ab.
35. trial.ab.
36. groups.ab.
37. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. exp animals/ not humans.sh.
39. 37 not 38
40. 28 and 39

EMBASE OVID

1. exp Faintness/
2. syncop*.tw.
3. presyncop*.tw.
4. faint*.tw.
5. lipothymi*.tw.
6. Dizziness/
7. dizzy*.tw.
8. dizzy*.tw.
9. light headedness.tw.
10. light-headedness.tw.
11. lightheadedness.tw.
12. orthostasis.tw.
13. drop attack*.tw.
14. Unconsciousness/
15. unconscious*.tw.
16. loss of consciou*.tw.
17. or/1-16
18. Electrocardiography/
19. loop recorder*.tw.
20. ilr*.tw.
21. (implant* adj5 (ecg or electrocardiog*)).tw.
22. ((implant* or internal or event*) adj2 record*).tw.
23. confirm.tw.
24. reveal.tw.
25. sleuth.tw.
26. or/18-25
27. 17 and 26
28. random\$.tw.
29. factorial\$.tw.
30. crossover\$.tw.
31. cross over\$.tw.
32. cross-over\$.tw.
33. placebo\$.tw.
34. (doubl\$ adj blind\$).tw.
35. (singl\$ adj blind\$).tw.
36. assign\$.tw.
37. allocat\$.tw.
38. volunteer\$.tw.
39. crossover procedure/
40. double blind procedure/
41. randomized controlled trial/
42. single blind procedure/
43. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44. (animal/ or nonhuman/) not human/
45. 43 not 44
46. 27 and 45

ClinicalTrials.gov

syncope AND Implantable Loop Recorders

CONTRIBUTIONS OF AUTHORS

Monica Solbiati conceptually developed, designed and co-ordinated the review; searched for articles; performed data extraction and analyses; entered data into Review Manager ([RevMan 2014](#)); drafted and approved the final review version.

Giorgio Costantino conceptually developed and designed the review; performed data extraction, drafted and approved the final review version.

Giovanni Casazza conceptually developed and designed the review; checked the data and analyses; drafted and approved the final review version.

Franca Dipaola screened articles; commented on and approved the final review version.

Andrea Galli screened articles; commented on and approved the final review version.

Raffaello Furlan interpreted the data; commented on and approved the final review version.

Nicola Montano interpreted the data; commented on and approved the final review version.

Robert Sheldon conceptually developed and designed the review; commented on and approved the final review version.

DECLARATIONS OF INTEREST

MS declares no known conflicts of interest.

GCo declares no known conflicts of interest.

GCa declares no known conflicts of interest.

FD declares no known conflicts of interest.

AG is actively involved in the Relax AHG 2 study enrolment which does not present a conflict of interest with this review.

RF declares no known conflicts of interest.

NM declares no known conflicts of interest.

RS declares no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

After the protocol was published, we realised that ILR-related complications needed to be considered as adverse events, so we added them as primary outcomes if participants needed either ILR explantation or treatment.

In the published protocol, we had anticipated that we would search all databases from 1990 as ILRs were introduced into clinical practice in the 1990s. In order to be more sensitive we conducted the searches from the earliest date available in each database instead.

In contrast with what we had planned, we included a cross-over trial. Cross-over designs may represent a problem when analysed together with parallel group trials in systematic reviews (Higgins 2011c). For example, cross-over trials may have shorter intervention periods or may include participants with less severe illness. Also, a problem associated with them is that of carry-over (a type of period-by-intervention interaction). Carry-over is the situation in which the effects of an intervention given in one period persist into a subsequent period, thus interfering with the effects of a different subsequent intervention. One of the studies we identified reported data from a cross-over trial (Krahn 2001). However, as intervention periods, participants' characteristics and type of interventions and controls were similar to those of the other studies selected, we decided to include it in the review. Since carry-over could be an issue in this case (mortality and diagnosis are irreversible), as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c), we included only data from the first period.

Differently from what we had planned in the protocol and according to the suggestions of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011), as no heterogeneity was found we used a fixed-effect rather than a random-effects model.

We have included a 'Summary of findings' table (Schünemann 2011a) and GRADE assessment (Schünemann 2011b) to comply with the latest Cochrane requirements.

We defined mixed age populations as > 80% of participants are required to be 18 years or older.