# *Implantable loop recorder for unexplained recurrent syncope*

**November 2003**

MSAC application 1061

**Assessment report**

**© Commonwealth of Australia 2005**

**ISBN 0 642 82695 1**

**ISSN (Print) 1443-7120**

**ISSN (Online) 1443-7139**

**First printed December 2005**

**Paper-based publications**

© Commonwealth of Australia 2005
This work is copyright. Apart from any use as permitted under the Copyright Act 1968, no part may be reproduced by any process without prior written permission from the Commonwealth. Requests and inquiries concerning reproduction and rights should be addressed to the Commonwealth Copyright Administration, Attorney General's Department, Robert Garran Offices, National Circuit, Canberra ACT 2600 or posted at http://www.ag.gov.au/cca

**Internet sites**
© Commonwealth of Australia 2005
This work is copyright. You may download, display, print and reproduce this material in unaltered form only (retaining this notice) for your personal, non-commercial use or use within your organisation. Apart from any use as permitted under the Copyright Act 1968, all other rights are reserved. Requests and inquiries concerning reproduction and rights should be addressed to Commonwealth Copyright Administration, Attorney General's Department, Robert Garran Offices, National Circuit, Canberra ACT 2600 or posted at http://www.ag.gov.au/cca

Electronic copies of the report can be obtained from the Medical Services Advisory Committee's Internet site at http://www.msac.gov.au/

Printed copies of the report can be obtained from:

The Secretary
Medical Services Advisory Committee
Department of Health and Ageing
Mail Drop 106
GPO Box 9848
Canberra ACT 2601

Enquiries about the content of the report should be directed to the above address.

The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

***MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.***

This report was prepared by the Medical Services Advisory Committee with the assistance of Dr Renea Johnston[a], Ms Liliana Bulfone[b], Ms Emily Petherick[a], Ms Kim Dalziel[a], Associate Professor Anthony Harris[b], Dr Elmer Villanueva[a] and Dr Silva Zavarsek[a] from the Monash Institute of Health Services Research[a] and the Centre for Health Economics[b] of Monash University. The report was edited by Dr Alana Mitchell, ScienceLink Pty Ltd. The report was endorsed by Minister for Health and Ageing on 24 June 2004.

Publication approval number: 3662 (JN9047)

# Contents

**Executive summary** ..... vii

**Introduction** ..... 1

**Background** ..... 2

The procedure ..... 4

Clinical need ..... 5

Existing procedures and comparator ..... 8

Marketing status of the device ..... 9

Current reimbursement arrangement ..... 9

**Approach to assessment** ..... 10

Review of literature ..... 10

Expert advice ..... 17

**Results of assessment** ..... 18

Is it safe? ..... 19

Is it effective? ..... 20

What are the economic considerations? ..... 28

**Conclusions** ..... 50

Safety ..... 50

Effectiveness ..... 50

Cost-effectiveness ..... 51

**Recommendation** ..... 52

**Appendix A MSAC terms of reference and membership** ..... 53

**Appendix B Advisory Panel** ..... 55

**Appendix C Internet sites searched** ..... 56

**Appendix D Search Strategies** ..... 58

**Appendix E Studies included in the review** ..... 63

**Appendix F Summary of studies of effectiveness** ..... 65

**Appendix G Studies excluded from review** ..... 83

**Appendix H Applicant information** ..... 91

**Abbreviations** ..... 92

**References** ..... 93

# Tables


Table 1 Characteristics and severity of syncope (Linzer et al 1997) ..... 3

Table 2 Incidence and prevalence of syncope from the Framingham Heart Study ..... 6

Table 3 Requested Medicare items processed from January 1999 to December 2002 ..... 7

Table 4 Electronic databases accessed during the literature search ..... 10

Table 5 Selection criteria for studies ..... 12

Table 6 Criteria and definitions for assessing validity of diagnostic studies ..... 14

Table 7 Levels of evidence for diagnostic tests ..... 14

Table 8 The generic relationship between results of the diagnostic test and disease status ..... 15

Table 9 Evidence dimensions ..... 16

Table 10 Designations of levels of evidence ..... 17

Table 11 Validity criteria according to study design ..... 17

Table 12 Adverse events associated with Reveal® implantable loop recorders in two case series ..... 19

Table 13 Technical problems associated with the first generation (Reveal®) implantable loop recorder ..... 21

Table 14 Technical problems associated with the second generation (Reveal® Plus) implantable loop recorder ..... 21

Table 15 Clinical characteristics of patients in the randomised controlled trial ..... 23

Table 16 Outcomes reported in the randomised controlled trial ..... 24

Table 17 Results of randomised controlled trial following crossover ..... 24

Table 18 Treatments following diagnosis reported in the randomised controlled trial of ILR ..... 26

Table 19 Unit costs assumed in the submitted model ..... 38

Table 20 Costs accruing for each health state included in each of the models ..... 40

Table 21 Total costs for each arm of the submitted model over three years when ILR is used in the early setting ..... 42

Table 22 Total costs for each arm of the submitted model over three years when ILR is used in the late setting ..... 43

Table 23 Total QALYs for each arm of the submitted model over three years when ILR is used in the early setting ..... 45

Table 24 Total QALYs for each arm of the submitted model over three years when ILR is used in the late setting ..... 46

Table 25 Summary of results of economic analyses presented in the application ..... 47

Table 26 Results of revised economic analysis ..... 48

Table 27 Results of one-way sensitivity analyses ..... 49
Table D1 Diagnostic search strategy terms (Medline, Premedline, CINAHL and Biological Abstracts) ..... 58
Table D2 Diagnostic search terms (EMBASE) ..... 58
Table D3 Patient outcomes following diagnosis (Medline, Premedline, CINAHL and Biological Abstracts) ..... 59
Table D4 Patient outcomes following diagnosis search strategy (EMBASE) ..... 59
Table D5 Safety search strategy (Medline, Premedline, CINAHL and Biological Abstracts) ..... 60
Table D6 Costs related to the intervention (Medline, Premedline, CINAHL and Biological Abstracts) ..... 61
Table D7 Costs related to the intervention (Medline, Premedline, CINAHL and Biological Abstracts) ..... 62
Table D8 Search terms for key authors (Medline) ..... 62
Table F1 Details of study design ..... 65
Table F2 Summary of patient characteristics ..... 66
Table F3 Device characteristics of included studies of ILR ..... 72
Table F4 Validity of included studies ..... 73
Table F5 Results of included studies ..... 74
Table H1 Estimated number of eligible patients for ILR early diagnosis: Prevalence estimates ..... 91
Table H2 Estimated number of eligible patients for ILR later diagnosis: Prevalence estimates ..... 91

# Figures


Figure 1 Flow diagram of the proposed approach to the evaluation of syncope in Australia ..... 5

Figure 2 Flowchart demonstrating selection process for articles of the implantable loop recorder ..... 18

Figure 3 Diagnostic algorithm for patients with recurrent unexplained syncope as assumed in the application in the case where ILR is available. ..... 31

Figure 4 Structure of submitted model including transition probabilities ..... 35

Figure 5 Suggested structure for a model for comparing ILR and a comparator ..... 36

Figure 6 The relationship between health-related quality of life (measured by the EQ-5D thermometer) and the frequency of symptoms (syncopal spells per month) within two risk groups (patients with less than six syncopal spells in their lifetime and patients with more than six syncopal spells in their lifetime. ..... 44

Figure 7 Structure of model used to conduct re-analysis ..... 47

# Executive summary

## The procedure

The implantable loop recorder (ILR) is a test based on an electrocardiogram (ECG). The device consists of an implantable ECG recorder and an activator. The ILR has a programmable memory feature that allows the recording of up to three episodes totalling 42 minutes of single lead electrocardiographic tracings. The recording may be programmed to activate automatically in response to an elevation or fall in heart rate at predefined programmed limits. The rhythm monitored before, during and after a symptomatic episode can be stored and recalled using an external activator. The device is implanted under local anaesthetic into a subcutaneous pocket via a small incision, most frequently in the left pectoral region, but other sites may be used, including the left submammary and right pectoral regions and intercostal spaces.

## Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. The MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the Monash Institute of Health Services Research and the Health Economics Unit of Monash University was engaged to conduct a systematic review of literature on the implantable loop recorder for recurrent unexplained syncope. An Advisory Panel with expertise in this area then evaluated the evidence and provided advice to the MSAC.

## MSAC's assessment of the implantable loop recorder

This assessment reviews the use of the ILR for patients with unexplained syncope:

- after initial medical history, physical examination, blood pressure measurement, surface ECG testing, and other tests;
- who are suspected of having arrhythmia cause or unexplained recurrent syncope; and
- who are not suspected of having a neurogenic cause or underlying structural heart disease associated with a high risk of sudden cardiac death.

### Clinical need

Syncope can be defined as a sudden, transient loss of consciousness and postural tone with spontaneous recovery. The causes of syncope fall into five main categories: neurally

mediated, orthostatic hypotensive, psychiatric, neurologic and cardiac. The prognosis of patients depends on the type of syncope diagnosed. The Framingham Study, a longitudinal population-based study that measured the prevalence and incidence of syncope in the United States (US), reported that neurally mediated syncope occurs most frequently and usually has a benign prognosis with no increase in the risk of death compared to persons who do not have syncope. However, the risk of death was increased by 31 per cent among all participants with syncope and was doubled among patients with cardiac syncope, compared to those without syncope.

Precise estimates of the number of people in Australia who would be eligible for implantation with the ILR are unavailable. In the absence of Australian epidemiological studies that have measured the prevalence of unexplained recurrent syncope, varying estimates of the prevalence were derived from three sources. Applying the prevalence and incidence measured from the US-based Framingham Study to the Australian population in 2002 provided an estimate of the number of people with recurrent syncope of unknown origin of 9,638. The Applicant estimated that 3,304 patients would be eligible for the ILR based on a prevalence of syncope derived from unpublished US numbers of patients evaluated and treated for syncope. Applying statistics from the Health Insurance Commission of Australia of the number of services provided for ambulatory ECG monitoring (the comparator diagnostic device), gave an estimate of 3,134 patients with syncope. The wide range of estimates implies considerable uncertainty in the prevalence of unexplained recurrent syncope. Furthermore, it is difficult to estimate the number of people with symptoms who present for diagnosis and treatment and, consequently, the size of the subgroup of them considered suitable for implantation with the loop recorder.

## Safety

While the nature of risks associated with use of the ILR has been reported in case series, it is difficult to estimate the incidence of these events due to the lack of large, well-conducted studies. Two case series reported adverse events associated with the use of the first generation ILR (Reveal®) in patients with unexplained syncope. No studies were identified that reported adverse events associated with use of the second generation ILR (Reveal® Plus). Adverse events reported were infection in approximately two to three per cent of patients and pain in one per cent of patients. These events resolved with explantation of the device and appropriate treatment. The reported rate of infection is comparable to the acceptable rate of local infection (2%) associated with pacemaker implantation as recommended in public hospitals in Australia. No reports of injury were identified in the literature, but there is a theoretical risk of ILR malfunction and injury due to interference from external and static electromagnetic fields such as those in magnetic resonance imaging (MRI) devices. Interference caused by radiofrequency or MRI was reported in two studies.

## Effectiveness

Limitations associated with the available evidence preclude evaluation of the incremental effectiveness of the ILR compared to the external loop recorder (ELR) or standard tests in terms of diagnostic accuracy or patient-relevant outcomes such as quality of life. No studies of the most appropriate design to determine the diagnostic characteristics of the ILR or the incremental effectiveness on patient outcomes following diagnosis such as recurrence of syncope, other morbidity, mortality or quality of life were identified. Although randomised controlled trial (RCT) evidence was identified, this evidence was

not optimally designed to compare the ILR with conventional monitoring (including the ELR), primarily due to a longer follow-up for patients in the ILR arm.

### Diagnostic accuracy

In the absence of the most rigorous study design for assessing the validity of diagnostic tests, that is a prospective blind comparison of the test and a reference standard in a consecutive series of patients, the sensitivity and specificity (and related derivative characteristics) of the ILR could not be determined. Thus, evidence of the diagnostic yield of the ILR was extracted from two reports of one RCT (level II evidence) and 16 case series (level IV evidence). The RCT compared the diagnostic yield of a prolonged monitoring strategy with an ILR and conventional monitoring in 60 patients with recurrent unexplained syncope or a single episode of syncope that warranted cardiovascular investigation. Application of relevant validity criteria commonly used to assess the susceptibility of bias of RCTs revealed the likelihood of some unappraisable bias in the study design due to failure to report concealment of randomisation or blinding, and the exclusion of three participants assigned to the ILR group in calculating the diagnostic yield of the two groups. The longer follow-up in the ILR monitoring group compared to the conventional strategy group is likely to have biased the results in favour of the ILR monitoring strategy. The outcome assessed in the trial was diagnosis of the causes of syncope, defined as a symptom-rhythm correlation recorded during a spontaneous event that resembled the symptoms prior to enrollment in the trial in those assigned to the ILR strategy. In contrast, diagnosis in the conventional strategy was defined as standard published criteria for positive tilt test and positive electro-physiological testing. Use of the ILR resulted in a greater number of patients being given a diagnosis compared to those assigned to conventional testing (47% versus 20% before crossover).

Further evidence of the diagnostic yield of the ILR was provided from case series. Overall, the series reported recording of arrhythmias by the ILR device in 57–100 per cent of patients who activated the device during recurrence and up to 60.3 per cent recorded sinus rhythms. However, the lack of comparison groups makes it difficult to determine diagnostic accuracy and prevents the estimation of the incremental effectiveness of the ILR in the presence of prior investigations.

### Patient outcomes following diagnosis

There was a lack of evidence to assess the effectiveness of ILR on patient outcomes such as recurrence of syncopal symptoms and changes in quality of life and mortality following diagnosis. Two reports of the RCT (level II evidence) included in the assessment of diagnostic yield provided evidence of the treatments patients received after a diagnosis was made. Treatments were consistent with those recommended in clinical practice guidelines. The trial also reported that symptoms resolved in almost all patients following the establishment of a diagnosis, however, follow up was insufficient to determine if this effect was maintained in the longer term. In addition, as outcomes for patients with an undiagnosed cause of syncope were not reported, the incremental effectiveness of the ILR compared to conventional monitoring could not be determined.

### Comparative effectiveness

There is currently a lack of evidence to determine the effectiveness of the ILR compared to the ELR or standard tests in terms of diagnostic accuracy or patient-relevant

outcomes including quality of life. The available evidence does allow the conclusion that use of the ILR results in a higher diagnostic yield than conventional testing (including the ELR). The place of the ILR in the diagnostic pathway of patients with recurrent unexplained syncope is uncertain. As the ILR is invasive, its use may not be appropriate until diagnosis has failed with the use of conventional monitoring. Crossover data from the available trial evidence suggest that additional diagnoses may be obtained with the use of the ILR if conventional testing fails to result in a diagnosis.

## Cost-effectiveness

An economic analysis was conducted comparing ILR with standard care (which is assumed to consist of no further ECG monitoring in the majority of cases) in patients with recurrent syncopal episodes occurring at intervals greater than a week apart in whom diagnosis has not been achieved through history, physical examination, monitoring of blood pressure and ECG, and who are determined either to have no structural heart disease or to be at low risk of sudden cardiac death, and in whom ELR is inappropriate or has failed to elicit a diagnosis.

The analysis was performed over a three-year time horizon. The key assumptions in the analysis were:

- total incremental costs associated with an ILR are $4,419;
- an additional 33 per cent of patients achieved a diagnosis through ILR;
- the average cost to treat a diagnosis (bradyarrhythmia or tachyarrhythmia) over three years is $696;
- 74 per cent of patients diagnosed were successfully treated;
- successfully treated patients avoided 0.583 hospitalisations per year for treatment of injuries sustained as a result of recurrent syncope;
- the average cost of hospitalisation for treatment of injuries sustained as a result of syncope is $2,383; and
- successfully treated patients have a 0.132 improvement in utility that is sustained in years subsequent to diagnosis.

Costs and benefits occurring in years two and three of the model are discounted at 5 per cent per annum. The key results of the analysis are summarised in the following table.

| Intervention | Incremental |
|---|---|
| **Incremental costs:** | |
| . Incremental costs associated with ILR | $4,419.03 |
| . Treatment costs | $695.90 |
| . Cost offsets from hospitalisations avoided | –$970.10 |
| Total incremental costs | $4,144.83 |
| **Benefits** | |
| . Patients diagnosed | 33% |
| . Proportion of patients diagnosed who are successfully treated | 74% |
| . If each successfully treated patients has a 0.132 utility gain each year, then a total of 0.377 discounted QALYs is gained by each successfully treated patient over 3 years. Thus, the average QALY gained per patient is: | 0.09 QALYs |
| Incremental cost of ILR (over standard care) over 3 years per: | |
| additional patient diagnosed | $12,560 |
| additional patient successfully treated | $16,973 |
| additional QALY gained | $44,969 |

Abbreviations: QALYS, quality adjusted life years

Sensitivity analyses demonstrated that the estimates of incremental cost-effectiveness of ILR over standard care are most sensitive to the time horizon of the model (eg increasing the time horizon from three to five years results in an incremental cost of ILR per QALY of $25,392), the incremental efficiency of ILR in diagnosing patients (eg reducing the incremental effectiveness from 33 per cent to 20 per cent results in an incremental cost of ILR per QALY of $76,132), the proportion of patients successfully treated following diagnosis (eg decreasing the proportion of successfully treated patients from 74 per cent to 60 per cent results in an incremental cost of ILR per QALY of $57,917) and the utility estimated to be gained by successfully treated patients (eg increasing the estimate of utility gain from 0.132 to 0.242 results in an incremental cost of ILR per QALY of $23,555). Treatment costs and cost offsets from reduced hospitalisation of successfully treated patients are approximately equivalent in the analysis. Thus, exclusion of these variables has only a marginal effect on the results of the analysis.

## Recommendation

MSAC recommended that on the strength of evidence pertaining to the safety, effectiveness and cost-effectiveness of implantable loop recorder for unexplained recurrent syncope – Reveal Plus®, public funding should be supported for this procedure in patients with recurrent syncope who have had appropriate prior investigations.

The Minister for Health and Ageing accepted this recommendation on 24 June 2004.

## Implementation

It is recommended that the ILR be implanted by specialists with adequate training and experience in implanting pacemakers, in patients who have unexplained recurrent syncope:

- after initial medical history, physical examination, blood pressure measurement, surface ECG testing, conventional monitoring with the ELR, and other tests as indicated;
- are suspected of having arrhythmia cause or unexplained recurrent syncope;
- are not suspected of having a neurogenic cause or underlying structural heart disease associated with a high risk of sudden cardiac death.

# Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of the implantable loop recorder (ILR), a diagnostic procedure for unexplained recurrent syncope. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. The MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

The MSAC's terms of reference and membership are at Appendix A. The MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for the implantable loop recorder in patients with unexplained syncope:

- after initial medical history, physical examination, blood pressure measurement, surface electrocardiogram (ECG) testing, and other tests;
- who are suspected of having arrhythmia cause or unexplained recurrent syncope; and
- who are not suspected of having a neurogenic cause or underlying structural heart disease associated with a high risk of sudden cardiac death.

# Background

## Syncope

Syncope is the sudden, transient loss of consciousness with spontaneous recovery that is associated with a loss of postural tone (Soteriades et al 2002). A review (Linzer et al 1997) reports that in 45 per cent of patients whose primary disorder can by diagnosed, a potential cause of syncope is established after a history and physical examination including an ECG. However, in a proportion of patients, diagnosis of the underlying cause of recurrent syncope can be problematic as symptoms may occur sporadically and infrequently (Krahn et al 2003b).

The causes of syncope can be broadly grouped into five main categories: neurally mediated (also known as vasovagal or neurocardiogenic, describing syncope associated with inappropriate vasodilation, bradycardia or both), orthostatic hypotensive, psychiatric, neurologic (eg associated with seizures and secondary to migraines, transient ischaemic attacks and subclavian steal) and cardiac. Table 1 describes the characteristics and severity of the different types of syncope.

Soteriades et al (2002) examined the incidence and causes of syncope and the prognosis of those with syncope in the Framingham Heart Study, a large epidemiological study based in the US. The most frequently identified cause of syncope was neurally mediated (21.2%), but in 36.6 per cent of participants, the cause of syncope was unknown (Soteriades et al 2002). The prognosis of patients depends on the type of syncope diagnosed. Although overall the risk of death was increased by 31 per cent for participants with syncope and was doubled among patients with cardiac syncope compared to those without syncope, participants with neurally mediated syncope were found to have a benign prognosis with no increase in the risk of death compared to persons who did not have syncope (Soteriades et al 2002).

Clinical guidelines (Linzer et al 1997) report that history, physical examination and recording of the ECG are at the core of the work up. Linzer et al (1997) reported data from six studies of hospitalised patients that showed history and physical examination helped to identify a potential cause of syncope in 45 per cent of patients whose primary disorder could be diagnosed. Other tests that may help to determine the cause of syncope include echocardiography, carotid sinus massage, tilt table testing and Holter monitors. An ECG recording during syncope is needed to include or exclude arrhythmias as a cause (Kapoor 2000).

**Table 1 Characteristics and severity of syncope (Linzer et al 1997)**

| Type or cause of syncope | Characteristics | Severity |
|---|---|---|
| **Neurally mediated reflex** | | |
| . Vasovagal | Warmth, nausea | Benign |
| . Vasodepressor | Occurs after daily activity | Benign |
| . Situational | | |
| Cough | | |
| Micturition | | |
| Defecation | | |
| Swallow | | |
| . Other | | |
| Carotid sinus | After neck pressure or head turning | Benign |
| Neuralgia | | |
| **Orthostatic hypotension** | Symptoms upon standing upright | Benign |
| **Medications** | Symptoms associated with drug use | Benign to severe |
| **Psychiatric** | Frequent symptoms, lack of injury | Benign |
| **Neurologic** | Seizure activity, headache, diplopia, hemiparesis | Moderate |
| Migraines | | |
| Transient ischemic attacks | | |
| Seizures | | |
| Subclavian steal | | |
| **Cardiac** | | |
| . Organic heart disease | Chest pain, dyspnea, exertional, postoperative | Severe |
| Aortic stenosis | | |
| Pulmonary embolism, pulmonary hypertension | | |
| Myxoma | | |
| Myocardial infarction, coronary spasm | | |
| Tamponade, aortic dissection | | |
| **Arrhythmias** | Sudden syncope, injury | Moderate |
| . Bradyarrhythmias | | |
| Sinus node disease | | |
| 2nd or 3rd degree heart block | | |
| Pacemaker malfunction | | |
| Drug-induced | | |
| . Tachyarrhythmia**s** | Palpitations | Severe |
| Ventricular tachycardia | | |
| Torsades de pointes | | |
| Supraventricular tachycardia | | |
| **Unknown** | Negative workup | Usually benign to moderate |

Echocardiography screens the patient for the presence of structural cardiac abnormalities. Some examples of such defects include cardiomyopathy, cardiac tumours, right ventricular dysplasia, pulmonary embolism and aortic dissection (Brignole et al 2001).

Pressure at the site where the common carotid artery bifurcates produces a reflex slowing in heart rate and a fall in blood pressure. In some patients with syncope, especially those aged greater than 40 years, an abnormal response to carotid massage can be observed (Brignole et al 2001). The response to carotid sinus massage is generally classified as cardioinhibitory (ie asystolic), vasodepressive (fall in systolic blood pressure) or mixed (Brignole et al 2001).

Tilt table testing can be used to determine a predisposition to neurally mediated forms of syncope. Two general types of testing procedures include upright tilt testing alone

(passive testing) and tilt testing in conjunction with a chemical agent such as isoproterenol (Kapoor 1998). Tilt table testing is thought to work by introducing a potent orthostatic stimulus, such as prolonged upright posture, to produce a maximal state of venous pooling, thus provoking vagal reactions (Grubb 1998).

Electrophysiologic testing is an invasive diagnostic method used to initiate an arrhythmia by stimulation of the atria and ventricles (Olshansky 1998). Electrophysiological studies use endocardial and (in the coronary sinus) epicardial electrical stimulation and recording to disclose abnormalities that suggest a primary arrhythmia as the cause of syncope (Brignole et al 2001).

Most ambulatory ECG monitoring in syncope is undertaken with an external 24-hour recorder connected to the patient via external wiring and adhesive ECG patches known as a Holter monitor (Brignole et al 2001). Longer term event monitoring can also be undertaken with external loop recorders (ELRs). Loop event recorders can be activated after a syncopal episode and can record two to five minutes of rhythm strip prior to the activation and 30 to 60 seconds of the rhythm after activation (Kapoor 1998). Tracings can be transmitted by telephone and monitors can be worn for weeks to months (Kapoor 1998).

## The procedure

The implantable loop recorder is an eight cubic centimetre device, which is 61 millimetres long, 19 millimetres wide, 8 millimetres thick and weighs 17 grams (Mieszczanska et al 2001). The device is implanted under local anaesthetic via a small (two centimetre) incision into a subcutaneous pocket, most frequently in the left pectoral region. Other sites that may be used include the left submammary, right pectoral and intercostal spaces (Kenny & Krahn 1999). The ILR is fastened to underlying tissues with non-absorbable sutures. The incision is then closed with absorbable sutures and a satisfactory electrogram verified after wound closure (Kenny 1999).

The ILR has a programmable memory feature that allows the recording of up to three episodes totalling 42 minutes of single lead electrocardiographic tracings (Luria & Shen 2001). The rhythm monitored before, during and after a symptomatic episode can be stored for later recall using an external activator (Bloemers & Sreeram 2002). Newer versions of the device can be set to activate automatically when the patient's intrinsic heart rate goes above or below the preset limits (Bloemers & Sreeram 2002).

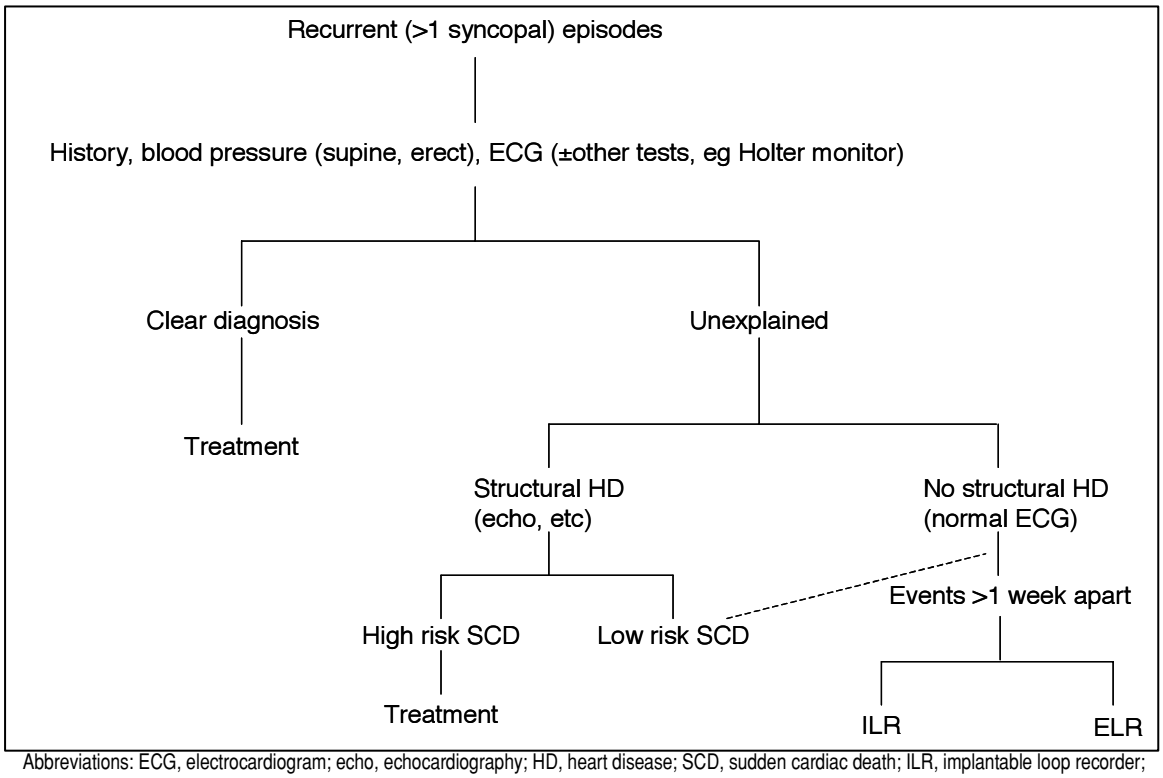
## Intended purpose

This assessment reviews the use of the implantable loop recorder (ILR) for patients with unexplained syncope:

- after initial medical history, physical examination, blood pressure measurement, surface ECG testing, and other tests;
- who are suspected of having arrhythmia cause or unexplained recurrent syncope; and

- who are not suspected of having a neurogenic cause or underlying structural heart disease associated with a high risk of sudden cardiac death.

Clinical expertise suggests that the most appropriate approach for the evaluation of patients in Australia with unexplained recurrent syncope can be represented by the flow diagram depicted in Figure 1.




Abbreviations: ECG, electrocardiogram; echo, echocardiography; HD, heart disease; SCD, sudden cardiac death; ILR, implantable loop recorder; ELR, external loop recorder

**Figure 1 Flow diagram of the proposed approach to the evaluation of syncope in Australia**

Patients who have unexplained recurrent syncope following initial investigations including medical history, physical examination, blood pressure measurement, surface ECG and possibly other tests and who have or are suspected of having underlying structural heart disease would undergo appropriate investigation including echocardiography. Patients without structural heart disease, or with structural heart disease and a low risk of sudden cardiac death, and syncopal events occurring greater than a week apart, are considered likely candidates for implantation with an ILR, or use of an ELR, for the diagnosis of the underlying cause of the syncope. Conventional monitoring with continuous ambulatory ECG monitoring (eg with the ELR) is available to this patient group, thus use of the invasive ILR may not be appropriate until diagnosis has failed with the use of conventional monitoring. Clinical expertise suggests that in most patients, ILR would be used after the failure of ELR to establish a diagnosis, but in some patients, the ELR may not be appropriate.

## Clinical need

Syncope may be associated with substantial morbidity. Studies frequently cite that syncope accounts for one to six per cent of hospital admissions and three per cent of

emergency department visits (Kapoor 1992). As it is unlikely that all patients with episodes of syncope will present to hospital or emergency departments, applying these figures would not give an accurate estimate of the burden of disease of syncope.

No Australian epidemiological studies reporting the prevalence or incidence of syncope or the associated burden of disease were identified. Precise estimates of the number of people in Australia who would be eligible for implantation with the ILR are unavailable. In the absence of Australian epidemiological studies that have measured the prevalence of unexplained recurrent syncope, varying estimates of prevalence were derived from the following sources: primary population based studies measuring the prevalence and incidence of syncope in the US, statistics from the Health Insurance Commission of Australia of the number of services provided for ambulatory ECG monitoring with the ELR and figures cited by the Applicant.

Population based studies provide the most appropriate estimates of the number potentially eligible for implantation with the ILR. One population based study, the Framingham Heart Study conducted in the US, was identified (Soteriades et al 2002). The study enrolled 7,814 people aged 20 to 96 years and conducted surveillance over an average of 17 years. This study investigated the prevalence, incidence and causes of syncope. Table 2 presents relevant estimates from the study.

**Table 2 Incidence and prevalence of syncope from the Framingham Heart Study**

| At least one syncopal episode in their lifetime | Incidence rate of syncope | Number of cases of syncope (period prevalence) | Proportion with syncope of unknown origin | Proportion with recurrent syncope[a] |
|---|---|---|---|---|
| Male: 71/2,336 (3.0%)<br>Female: 101/2,873 (3.5%) | 6.2 per 1,000 person years | 822/7,814 (10.5%) over an average of 17 years (follow up available for 727) | 36.6% | 157/727 (21.6%) |

[a] One or more recurrence

Application of the Framingham Heart Study figures to the Australian population (Australian Bureau of Statistics 2003) provides an estimate of the number of people with recurrent unexplained syncope as follows:

- The estimated percentage of people with syncope per year is assumed to be the average number of cases per year based on the 17-year period prevalence follow up data (ie 10.5%/17= 0.62%) or 121,909 people per year.
- The estimated number of people with syncope of unknown origin in the Framingham study (36.6%) applied to the number of expected people with syncope per year (121,909) in the Australian population is 44,619.
- Assuming that recurrence of syncope is the same across all types of syncope (ie vasovagal, cardiac, unknown origin), the estimated number of people with recurrent syncope of unknown origin is 9,638 (21.6% of 44,619).
- The estimated number of people with recurrent syncope of unknown origin who would be suitable for ILR in Australian clinical practice is currently unknown.

The major limitation of estimating the number of patients likely to be using the ILR in Australia based on the Framingham Study is the uncertainty about how well the

Framingham Heart Study figures will generalise to the Australian population. In addition, it is difficult to estimate the number of people with symptoms who present for treatment, and, consequently, the size of the subgroup of them considered suitable for the ILR.

The approach in the Application to estimate the number of patients eligible for the ILR was also based on applying proportions drawn from the literature to the Australian population. However, the figures applied in the Application are not derived from the Framingham Study and suggest that a total of 3,304 patients would be eligible for the ILR. Appendix H, Tables H1 and H2 present the estimates provided in the Application and comments on the sources of the estimates. The estimate provided in the Application may be unreliable for the following reasons:

- The Applicant divided the population eligible for ILR into those likely to use the ILR in early diagnosis and those likely to use it in later diagnosis. Expert clinical opinion suggests that this diagnosis management pathway is unlikely in the Australian setting and that the pathway in the Australian setting is more likely to follow that outlined in Figure 1.

- The Applicant's estimate of the prevalence of syncope was apparently derived from unpublished US numbers of patients evaluated and treated for syncope rather than from published epidemiological studies.

- Other estimates could not be verified from the Application as citations used to support some estimates were not provided or were unclear.

An alternative estimate of the number of patients with syncope likely to be eligible for the ILR can be derived from the number of patients who currently use ambulatory ECG monitoring with ELRs, a diagnostic procedure that may be considered an alternative to the ILR in some patients. The number of services provided for ambulatory ECG monitoring is available from the Health Insurance Commission of Australia. (Table 3) for the following services:

- Item 11710- AMBULATORY ECG MONITORING, patient activated, single or multiple event recording, utilising a looping memory recording device which is connected continuously to the patient for 12 hours or more and is capable of recording for at least 20 seconds prior to each activation and for 15 seconds after each activation, including transmission, analysis, interpretation and report (Medicare Benefits Schedule Book 1 Nov 2002).

- Item 11711- AMBULATORY ECG MONITORING for 12 hours or more, patient activated, single or multiple event recording, utilising a memory recording device which is capable of recording for at least 30 seconds after each activation, including transmission, analysis, interpretation and report (Medicare Benefits Schedule Book 1 Nov 2002).

**Table 3 Requested Medicare items processed from January 1999 to December 2002**

| Item number | 1999 | 2000 | 2001 | 2002 |
|---|---|---|---|---|
| 11710 | 2,324 | 2,731 | 2,637 | 2,806 |
| 11711 | 263 | 330 | 315 | 328 |
| Combined total | 2,587 | 3,061 | 2,952 | 3,134 |

Source: www.hic.gov.au

Thus, in 2002, a total of 3,134 services for ambulatory ECG monitoring were funded under Medicare. The proportion of patients receiving services for ambulatory monitoring who would be suitable for the ILR in Australian clinical practice is currently unknown. Clinical opinion suggests that the proportion of patients with recurrent syncope of unknown cause who would be eligible for the ILR is approximately 15 per cent and that use of this technology would depend on current specialist practice and the uptake rate. Precise estimates of the number of people in Australia who would be eligible for implantation with the ILR are unavailable.

In summary, three estimates of usage data have been proposed. Assuming that population based estimates of the incidence and prevalence of syncope are similar between Australian and the US, using the Framingham study the estimated number of patients with recurrent unexplained syncope would be 9, 638, although the proportion of these considered eligible for the ILR is unknown. The estimate of the proposed number of patients eligible for the ILR provided in the Application is 3,304. Australian usage figures of ambulatory ECG monitoring as reported to the Health Insurance Commission in 2002 as an estimate of the number of patients is 3,134.

## Existing procedures and comparator

The ideal means for determining the diagnostic accuracy of the ILR would be a prospective blind comparison with reference standard in a consecutive series of patients from a relevant clinical population. However, as syncope is a symptom of multiple disease states, there is no single reference standard available to verify its cause. In the absence of a suitable reference test, diagnostic yield may be assessed indirectly by measurement of the reduction in recurrence of syncope following diagnosis and treatment (Brignole et al 2001).

Clinical expertise suggests that the ELR is the most appropriate comparator for patients:

- with unexplained recurrent syncope after initial medical history, physical examination, blood pressure measurement, surface ECG and other tests if indicated;
- suspected of having an arrhythmia cause or unexplained recurrent syncope; and
- not suspected of having a neurogenic cause or underlying structural heart disease associated with a high risk of sudden cardiac death.

However, the place of the ILR in the diagnostic pathway of patients with recurrent unexplained syncope is uncertain as use of ILR is invasive and may not be appropriate until diagnosis has failed with the use of conventional monitoring with the ELR. Clinical expertise suggests that the clinical decision as to which diagnostic tool to use should be at the discretion of the treating practitioner on a case-by-case basis. Although the non-invasive ELR may generally be chosen over the ILR, the ELR may not be appropriate for some patients, including those in rural areas.

The use of the ELR is currently funded under the existing item numbers for ambulatory ECG monitoring shown in Table 3.

## Marketing status of the device

The implanted components of the Reveal® Plus ILR system have been registered by the Therapeutic Goods Administration (TGA), AUST R 75496, as an implantable ECG recorder. The Reveal® Plus activator has also been registered by the TGA, AUST R 81758. The Reveal® Plus is currently the only implantable ECG recorder available on the Australian market.

An earlier version of this device, Reveal®, was previously listed by the TGA but is no longer used in Australia.

## Current reimbursement arrangement

Use of the device is not currently funded under an existing Medicare item number.

The use of the device is listed on Schedule 5 Benefits payable in respect of surgically implanted prostheses and human tissue items and other medical devices list (Department of Health and Ageing 2003). This is a list of those items that health funds must fund for privately insured patients. Usage data is not currently available for the ILR.

# Approach to assessment

## Review of literature

Several search strategies were used to cover all the aspects needed for this topic, focusing on the three areas of safety, effectiveness and cost-effectiveness. Within effectiveness, the search was designed to identify studies reporting diagnostic characteristics and health outcomes of patient who had undergone the test.

In order to identify all of the relevant information published in journal articles, several separate strategies were performed as detailed in Appendix D.

Test terms were identified to describe the test or intervention and included 'implantable loop recorder', or 'ILR', and trade names. The test terms formed the core of the searching (Appendix D; Tables D1–D8) and were combined with the terms for safety, diagnostic characteristics, patient health outcomes following test and cost-effectiveness as follows:

- Safety: terms for safety, morbidity, mortality, complications and adverse events were combined with the test terms (Appendix D, Table D5, using the Boolean operator "AND").
- Diagnostic characteristics: terms for sensitivity and specificity or diagnosis were combined with the test terms (Appendix D, Tables D1 and D2).
- Patient health outcomes after undergoing the test: disease terms for syncope, fainting, arrhythmia and unconsciousness were combined with the test terms (Appendix D, Tables D3 and D4).
- Cost-effectiveness: terms for economics, costs, pricing and QALYs were combined with the test terms (Appendix D, Tables D6 and D7).

### Electronic resources

Table 4 lists the electronic databases accessed to identify relevant literature.

**Table 4 Electronic databases accessed during the literature search**

| Database | Period covered |
|---|---|
| Cochrane Library | Issue 1, 2003 |
| Medline (OVID) | November 1996 to June Week 1 2003 |
| PreMedline (OVID) | June 10, 2003 |
| EMBASE (OVID) | June 15, 2003 |
| CINAHL (OVID) | 1982 to June Week 1 2003 |
| Biological Abstracts (OVID) | 1980 to April 2003 |

### Health Technology Assessment, clinical trial registries and other relevant websites

Relevant Health Technology Assessment agency websites were searched to identify completed reviews or economic evaluations of ILR for unexplained recurrent syncope. A list of these sites is provided in Appendix C. Relevant clinical trial register and other websites were searched to identify clinical trials currently under way. A list of these sites is provided in Appendix C.

### Other search strategies

The search of electronic databases and websites was supplemented by a hand search of reference lists of relevant citations and a search of key authors in the Medline database (Appendix D, Table D8). Key authors were defined as those who have published relevant citations and were identified after the initial search. Contact was also made with the authors of a relevant publication considered to be the best available evidence in order to clarify issues relating to patient follow-up. This resulted in the identification of a second publication reporting other outcomes from a single trial, published after completion of the literature search.

## Selection criteria

The following criteria were developed *a priori* in consultation with the supporting committee of experts to determine the eligibility of relevant studies to assess the effectiveness of the ILR. The list of articles potentially eligible for further assessment after application of the selection criteria was forwarded to the supporting committee for review. Table 5 details the characteristics of the selection criteria for studies included in the review of effectiveness.

**Table 5 Selection criteria for studies**

| Characteristic | Inclusion | Exclusion |
|---|---|---|
| Patients | Patients with unexplained syncope after initial medical history, physical examination, blood pressure measurement (supine and erect) surface ECG testing, and other tests (according to potential indication eg Holter monitor, echocardiography), and suspected of having arrhythmia cause or unexplained recurrent syncope (events occurring more than one week apart) | Patients suspected of having a neurogenic cause of syncope, or underlying structural heart disease associated with a high risk of sudden cardiac death |
| Intervention | Implantable loop recorder (ILR) | |
| Comparator | External loop recorder (ELR) | |
| Outcome | . diagnostic accuracy of the ILR (sensitivity, specificity and derivatives, or other accuracy outcomes) in detecting arrhythmia causes of syncope<br>. patient outcomes following diagnosis and treatment, eg morbidity, mortality, quality of life<br>. safety | Outcomes in patients with presyncope and not syncope |
| Study design | . Accuracy: studies that report the diagnostic characteristics in an independent blind comparison of ILR and an appropriate reference standard in a consecutive group of patients were initially sought as such designs provide the most rigorous evidence to assess accuracy of the device.<br>As no such studies were identified, studies reporting diagnostic characteristics in an independent blind or objective comparison in non-consecutively selected patients or studies that report diagnostic characteristics in which the reference standard was not applied to all patients were sought. As no studies with the designs described above were identified, studies that reported indices of diagnostic accuracy in any design were included for assessment.<br>Included study designs were those that compared the ILR and comparator tests on randomly allocated individuals, and studies without a comparator reference standard in a consecutively selected case series.<br>. Patient outcomes following diagnosis: Systematic reviews, RCTs or comparative studies of health outcomes after patients have undergone implantation with a loop recorder, and following diagnosis | . Accuracy: narrative reviews, editorials and other opinion pieces, articles identified as preliminary reports when results are published in later versions, articles in abstract form only, case reports.<br>. Patient outcomes following diagnosis: as publications reporting outcomes from a RCT were identified, evidence from other study designs was excluded from assessment. Narrative reviews, editorials and other opinion pieces, articles identified as preliminary reports when results are published in later versions, articles in abstract form only, case reports |
| Publication | English-language articles, or well-designed RCTs published in any language.<br>1995 onwards. Clinical expertise suggested that clinical studies of the ILR were unlikely to appear in the published literature until 1995, the year that the device became available | Non-English publications that were of more bias-prone study designs.<br>Pre-1995 publications of any study design |

# Assessment of validity

Articles meeting the inclusion criteria for assessment of effectiveness underwent critical appraisal to evaluate the potential for bias of their study designs. Critical appraisal was performed using the methods described below.

## Effectiveness

Two factors are considered in the determination of the effectiveness of a diagnostic procedure:

- accuracy of the procedure, ie diagnostic characteristics; and

- patient management and outcomes following diagnosis, ie the usefulness of the test in improving outcomes for patients.

### Accuracy

The most rigorous study design for assessing the validity of diagnostic procedures is considered to be a prospective blind comparison of the test and a reference, or gold standard in a consecutive series of patients from a relevant clinical population (Jaeschke et al 1994, Sackett et al 2000). The publication by the Cochrane Methods Working Group on Systematic Review of Screening and Diagnostic Tests (1996) expands on this definition and recommends the following criteria for assessment of validity of evidence pertaining to diagnostic tests:

- test being evaluated (study test) is compared with a reference standard (gold standard);
- study test and reference test are measured independently (blind) of each other;
- choice of patients who were assessed by the reference standard was independent of the study test's results;
- study test was measured independently of all other clinical information;
- reference standard was measured before any interventions were started with knowledge of test results;
- tests were compared in a valid study design:
  - tests done independently on each person (most valid);
  - different tests done on randomly allocated individuals;
  - all tests done on each person but not assessed independently; and
  - different tests on different individuals, not randomly allocated (least valid).

Based on these criteria, the validity of the methodology of included articles was assessed against the checklist presented in Table 6. Studies meeting all of the criteria described are considered the most rigorous and least susceptible to bias.

**Table 6 Criteria and definitions for assessing validity of diagnostic studies**

| Validity criterion | Definition |
|---|---|
| Test is compared with a reference standard (gold standard) | Patients in the study should have undergone both the diagnostic test in question and a reference test that would provide confirmatory proof that they do or do not have the target disorder |
| Appropriate spectrum of consecutive patients | Study should included patients that the test would normally be used on in clinical practice, ie patients covering the spectrum of mild to severe cases of the target disorder, early and late cases, and patients with other, commonly confused, diagnoses. An inappropriate spectrum compares patients already known to have the disorder with a group of normal non-diseased patients or with patients diagnosed with another condition |
| Masked assessment of study and reference tests results | The study test and the reference test should be interpreted separately by persons unaware of the results of the other (avoidance of review bias) |
| All study subjects tested with both study and reference tests | The reference test should be applied regardless of a positive or negative result from the study test (avoidance of work-up/verification bias) |
| Study test measured independently of clinical information | The person interpreting the test should be masked to clinical history and results of any other tests performed previously |
| Reference test measured prior to any interventions | No treatment interventions should be initiated prior to the application of the reference (or study) test |

Included studies were also classified according to a hierarchy of evidence (Table 7). At present there is no National Health and Medical Research Council (NHMRC) of Australia system for assigning a hierarchy of evidence to studies of diagnostic tests. Thus, the system developed by the Centre for Evidence Based Medicine, National Health Service Research and Development, United Kingdom (1999) was adapted for use (Table 7). The levels of evidence reflect the methodological rigour of the studies. A study assigned as level I evidence is considered the most rigorous and least susceptible to bias, while a study deemed to contain level IV evidence is considered the least rigorous and most susceptible to bias. It should be noted that these levels exclude categorisation of systematic reviews of level I studies of diagnostic tests (which would be considered level I evidence).

**Table 7 Levels of evidence for diagnostic tests**

| Level of Evidence | Criteria |
|---|---|
| I | Independent blind comparison of an appropriate spectrum[a] of consecutive patients, all of whom have undergone both the diagnostic test and the reference standard |
| II | Independent, blind or objective comparison but in a set of non-consecutive patients, or confined to a narrow spectrum of study individuals (or both), all of whom have undergone both the diagnostic test and the reference standard |
| III | Independent blind comparison of an appropriate spectrum, but the reference standard was not applied to all study patients |
| IV | Any of:<br>. Reference standard was not applied blinded or not applied independently<br>. No reference test applied (case series) |

[a]An appropriate spectrum is a cohort of patients who would normally be tested for the target disorder.

## Reporting accuracy

The accuracy of a diagnostic test is primarily determined by its ability to identify the target disorder compared to the recognised reference standard test. Accuracy is measured by diagnostic characteristics such as sensitivity and specificity. The diagnostic characteristics of each test were reviewed, subject to the availability of studies in which subjects are tested with at least two of the diagnostic tests under investigation and the

reporting of sufficient data. Minimum requirements for computing sensitivity are sufficient data to compute the proportion of subjects with the disorder whose tests were correctly identified as positive. For specificity, data are required to compute the proportion of patients without the disorder whose tests were correctly identified as negative.

Diagnostic test results are summarised in two-by-two tables as in Table 8. Individuals who test positive for the disease in both the study test under investigation and the reference test are represented in cell 'a' and are called true positives (TP). Individuals without the disease who test negative in both tests (the 'd' cell) are called true negatives (TN).

A diagnostic test may produce discordance between the test result and the true disease status of the subject. A false result is reported when this occurs. Cells 'b' and 'c' in Table 8 illustrate these situations. In the former, the test is positive in individuals without the disease. In the latter, the test is negative in diseased individuals. These two sets of false results are called false positives (FP) and false negatives (FN), respectively.

**Table 8 The generic relationship between results of the diagnostic test and disease status**

| | True Disease Status (Reference test) | | |
|---|---|---|---|
| Study Test Results | Diseased | Not Diseased | Total |
| Positive | a | b | a+b |
| Negative | c | d | c+d |
| Total | a+c | b+d | a+b+c+d |

Abbreviations: a = number of diseased individuals detected by the test; b = number of individuals without disease detected by the test; c = number of diseased individuals not detected by the test; d = number of individuals without disease not detected by the test; a+b = total number of individuals testing positive; c+d = total number of individuals testing negative; a+c = total number of diseased individuals; b+d = total number of individuals without disease; a+b+c+d = total number of individuals studied

Sensitivity is the proportion of diseased individuals who test positive. It is a measure of the probability of correctly diagnosing a case, or the probability that any given case will be identified by the test. Referring to Table 8,

$$Sen = \frac{a}{a+c} = \frac{TP}{TP+FN}$$

Specificity is the proportion of individuals without disease who test negative. It is the probability of correctly identifying a non-diseased person with the study test.

$$Spe = \frac{d}{b+d} = \frac{TN}{TN+FP}$$

Although the above method is the ideal for determining test accuracy, its application to conditions such as syncope may be limited. It is argued that as syncope is an episodic symptom rather than a disease, the opportunity to capture the episodic symptoms may be rare and most tests evaluate the presence of physiological states that lead to syncope. Thus, establishing a cause may be presumptive (Brignole et al 2001). Furthermore, it is argued that there is no reference standard for most tests, thus diagnostic yield of many tests can be assessed indirectly by measurement of the reduction in syncope recurrence following diagnosis and treatment (Brignole et al 2001).

### Patient outcomes following diagnosis

Detection of the pathology of the diagnostic procedure under consideration is not the only indicator of the usefulness of the test. Unless application of the procedure improves patient management options, and ultimately patient health outcomes, its usefulness is considered limited (Sackett et al 2000). The ideal method for assessing patient outcomes following use of the diagnostic test is an RCT that compares outcomes of patients who have had the test with outcomes for those patients who have not had the test, and are followed up for an appropriate length of time to measure patient-relevant morbidity, quality of life and mortality. For example, an RCT measuring recurrence of syncopal episodes in patients with recurrent unexplained syncope following diagnosis and treatment would be a rigorous method for assessing the usefulness of a diagnostic procedure such as the ILR compared to another diagnostic procedure.

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the NHMRC (NHMRC 2000).

These dimensions (Table 9) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

**Table 9 Evidence dimensions**

| Type of evidence | Definition |
|---|---|
| Strength of the evidence | |
| . Level | The study design used, as an indicator of the degree to which bias has been eliminated by design[a] |
| . Quality | The methods used by investigators to minimise bias within a study design |
| . Statistical precision | The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect |
| Size of effect | The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval |
| Relevance of evidence | The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used |

[a]See Table 10

The three sub-domains level, quality and statistical precision are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 10.

**Table 10 Designations of levels of evidence**

| Level of evidence[a] | Study design |
|---|---|
| I | Evidence obtained from a systematic review of all relevant randomised controlled trials |
| II | Evidence obtained from at least one properly-designed randomised controlled trial |
| III-1 | Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method) |
| III-2 | Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group |
| III-3 | Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group |
| IV | Evidence obtained from case series, either post-test or pre-test/post-test |

[a]Modified from NHMRC (1999)

Included articles underwent critical appraisal to evaluate aspects of the study design for susceptibility to bias. A list of criteria used to evaluate the validity of the primary research evidence included in this report is outlined in Table 11. These criteria are based on a list assembled by the NHS Centre for Reviews and Dissemination (2001) to evaluate the validity of evidence from various study designs.

**Table 11 Validity criteria according to study design**

| Study design | Validity criteria[a] |
|---|---|
| Randomised controlled trial | Randomised method; allocation concealment; blinding of patients, investigators and outcome assessors; proportion lost to follow-up; intention to treat analysis |
| Cohort | Prospective/retrospective; comparable groups at inception; identification and adjustment for confounding factors; blind outcome assessment; sufficient duration of follow-up; proportion lost to follow-up |
| Case-control | Explicit definition of cases; adequate details of selection of controls; comparable groups with respect to confounding factors; interventions and other exposures assessed in same way for cases and controls; appropriate statistical analysis |
| Case series | Indication was comparable across patients; disease severity was comparable across patients; explicit entry criteria; outcome assessed in all patients; follow-up time uniform; outcomes assessed objectively; outcomes assessed in a blinded manner; outcome measures quantified |

[a]Modified from NHS Centre for Reviews and Dissemination (2001)

## Data extraction

Data were extracted using standardised instruments created for the assessment. Two reviewers examined each article and any discrepancies in evaluation were discussed and resolved through consensus. Contact with corresponding authors was attempted to clarify specific issues relating to validity or results.

## Expert advice

An Advisory Panel with expertise in general medicine, cardiology, electrophysiology, and consumer issues was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for Advisory Panel's, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations, and consumer bodies for nominees. Membership of the Advisory Panel is provided at Appendix B.

# Results of assessment

## Search results

Figure 2 outlines the process of article selection for assessment of the effectiveness of the ILR in the current report. The search strategies designed to identify articles on diagnostic accuracy and patient outcomes following diagnosis initially identified a total of 352 and 95 articles, respectively (although there was extensive overlap). Examination of the abstracts of all identified citations resulted in exclusion of 296 and 40 articles, respectively, that did not meet inclusion criteria for accuracy and patients outcomes. Assessment of the full text of the remaining articles resulted in the inclusion of 18 articles – two reports of one RCT (level II evidence) and 16 case series (level IV evidence) – for critical appraisal of diagnostic accuracy and two articles (two reports of one RCT) for critical appraisal of patient outcomes. The two reports of a single RCT included for assessment of patient outcomes following diagnosis was also included for assessment of diagnostic accuracy.

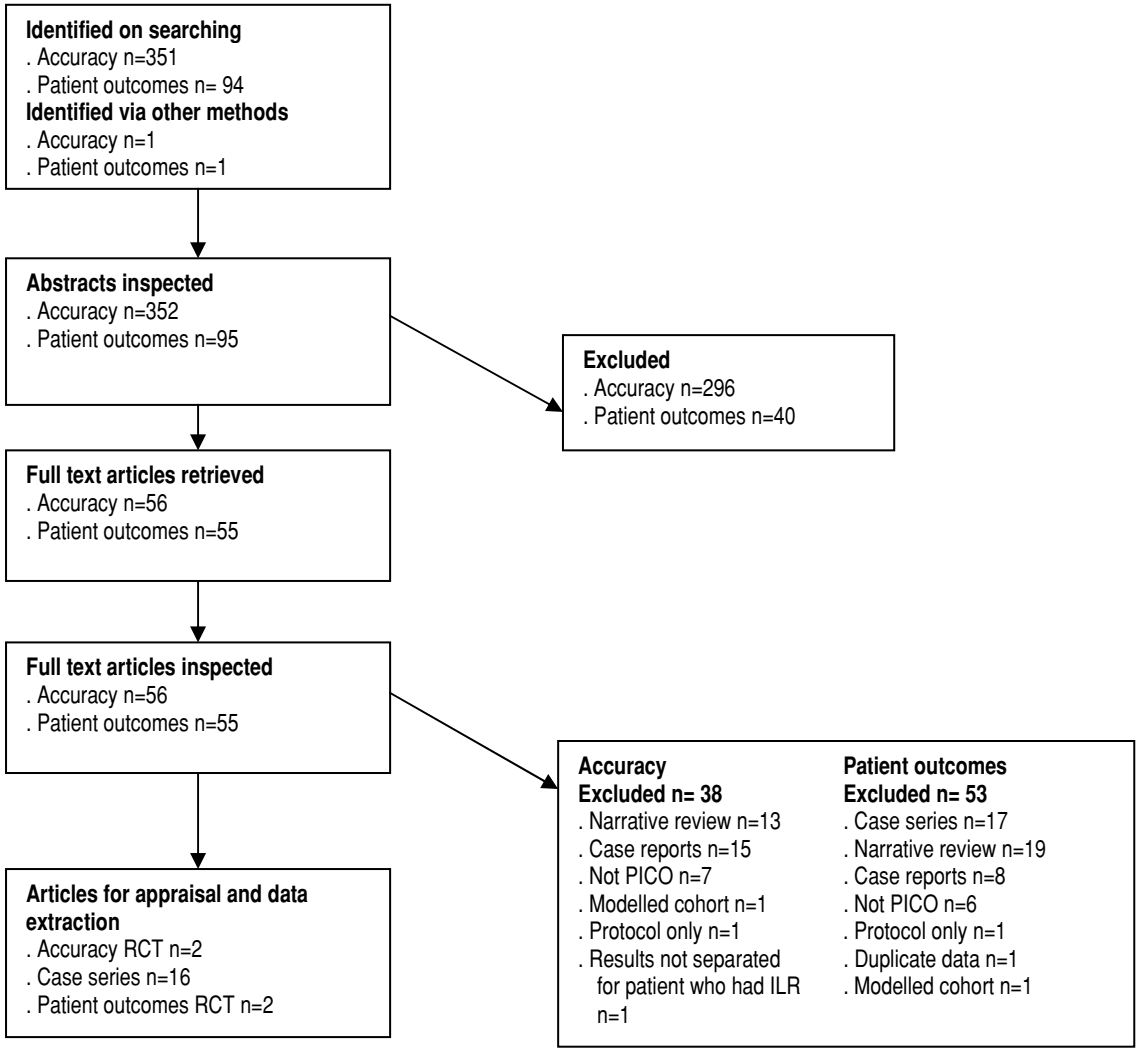



**Figure 2 Flowchart demonstrating selection process for articles of the implantable loop recorder**

## Is it safe?

Use of the ILR is associated with potential adverse events. While the nature of such risks has been reported in case series (Krahn et al 1999, Seidl et al 2000), it is difficult to estimate the incidence of these events due to the lack of large, well-conducted studies. In addition, it is established that external and static electromagnetic fields such as those in magnetic resonance imaging (MRI) devices can interfere with appropriate function of pacemakers and implantable defibrillators, and even result in serious injury. Although no reports of injury were identified in the literature, there is a theoretical risk of ILR malfunction and injury associated with interference from magnetic fields. Interference caused by radiofrequency or MRI was reported in two studies (De Cock et al 2000, Gimbel & Wilkoff 2003).

### Adverse events

Two case series (Krahn et al 1999, Seidl et al 2000) report adverse events associated with the use of the first generation ILR (Reveal®) in patients with unexplained syncope. No studies were identified that reported adverse events associated with use of the second generation ILR (Reveal® Plus). Krahn et al (1999) and Seidl et al (2000) reported infection in two to three per cent of patients and Krahn et al (1999) reported pain in one per cent of patients (Table 12). Pacemaker implantation is associated with a comparable rate of local infections. Expert opinion suggests that the consensus of public hospitals in Australia for the acceptable upper limit of local infections associated with pacemaker implantation is two per cent.

**Table 12 Adverse events associated with Reveal® implantable loop recorders in two case series**

| Study | Number of patients | Pertinent patient characteristics | Site of implantation | Adverse events | Outcomes |
|---|---|---|---|---|---|
| Krahn et al (1999) | 85 | Mean (SD) age: 59 (18)<br>Male: 52%<br>Concomitant cardiovascular disease: 62% | Left pectoral (64%)<br>Left inframammary (32%)<br>Left intercostal (2%)<br>Right parasternal (2%) | Local infection: 2 (2.4%)<br><br>Persistent pain: 1 (1.2%)<br><br>Local erosion with infection: 1 (1.2%) | Device removal and oral antibiotics. Re-implantation (n=1)<br><br>Device moved from left inframammary to left pectoral region, pain resolved<br><br>Device explanted without incident |
| Seidl et al (2000) | 133 | Mean age: 56<br>Male: 50%<br>Concomitant cardiovascular disease: 40% | Left pectoral (66%)<br>Left submammary (30%)<br>Parasternal or intercostal (4%) | Local infection: 3 (2.3%);<br>Persistent pain: 1 (0.8%) | Device explanted and local antibiotics |

Abbreviations: SD, standard deviation

# Is it effective?

## Technical problems

Use of the ILR may be associated with a number of technical problems. Technical problems were reported in one RCT (Krahn et al 2001a), seven case series (Krahn et al 1995, De Cock et al 2000, Hartog et al 2000, Seidl et al 2000, Armstrong et al 2002, Chrysostomakis et al 2003, Huikuri et al 2003) and two case reports (Chrysostomakis 2002, Gimbel & Wilkoff 2003). Problems in the first- and second-generation devices included undersensing, device interrogation problems, device migration, activator failure, false events and interference (Tables 13 and 14).

### Undersensing and interference

Undersensing was reported in three studies using the second generation ILR (Chrysostomakis et al 2002, 2003, Hartog et al 2000). Interference caused by radiofrequency or MRI was reported in two studies (De Cock et al 2000, Gimbel & Wilkoff 2003). These events may lead to problems with accurately capturing syncopal episodes and interpreting results correctly.

### Activator failure

Three studies (Krahn et al 1995, 2001a, Armstrong et al 2003) reported failure in activation of the first-generation ILR. The second-generation ILR includes an automatic activation function that was meant to resolve these issues. However, three studies of Reveal® Plus reported problems with inappropriate triggering or activation (Hartog et al 2000, Chrysostomakis et al 2002, Huikuri et al 2003).

**Table 13 Technical problems associated with the first generation (Reveal®) implantable loop recorder**

| Study | Study design | Number of patients | Indication | Site of implantation | Technical problems |
|---|---|---|---|---|---|
| Krahn et al (1995) | Case series | 16 (9 implantations) | Recurrent unexplained syncope | Left pectoral region | Inappropriate 'freezing' of data: 7 (77.8%). |
| De Cock et al (2000) | Case series (*in vitro* and *in vivo*) | 2 patients, 3 non-implanted devices<br>15 *in vitro* and 24 *in vivo* measurements | Not stated | Not stated | *In vitro*<br>Radiofrequency interference (no events stored): 1 (6.7%)<br>MRI interference: 1 (6.7%);<br>False events: 2 (13.3%);<br>*In vivo*:<br>No events stored: 1 (4.2%) |
| Seidl et al (2000) | Case series | 133 | Recurrent unexplained syncope | Left pectoral (66%), left submammary (30%), parasternal or intercostal (4%) | Problems interrogating device: 4 (3.0%)<br>Device migration: 5 (3.8%) |
| Krahn et al (2001a) | RCT | 30 | Recurrent unexplained syncope or single episode with injury | Left chest region | Activator failure: 1 (3.3%) |
| Armstrong et al (2003) | Case series | 15 | Syncope or unexplained falls | Not stated | Stiffness of activator button: 1 (6.7%) |

**Table 14 Technical problems associated with the second generation (Reveal® Plus) implantable loop recorder**

| Study | Study design | Number of patients | Indications | Site of implantation | Technical problems |
|---|---|---|---|---|---|
| Hartog et al (2000) | Case series | 40 | Unexplained syncope | Between 1st and 4th ribs, extending from sternum to mid clavicular line | Inappropriate autoactivation: 36 (90.0%)<br>Mean events per week: 15.9<br>Loss of signal: 9 (25%)<br>Undersensing: 21 (58.3%);<br>Oversensing of T-waves: 5 (13.9%)<br>Noise: 1 (2.8%) |
| Chrysostomakis et al (2002) | Case report | 1 | Presyncopal and syncopal episodes | Left parasternal area | Inappropriate automatic activation |
| Chrysostomakis et al (2003) | Case series | 32 | Undiagnosed syncopal episodes | Left parasternal zone (13), heart apex zone (19) | Undersensed episodes: 15 (36%) |
| Gimbel & Wilkoff (2003) | Case report | 1 | Recurrent injurious syncope | Left parasternal area | Artefact mimicking tachycardia recorded during shoulder MRI |
| Huikuri et al (2003) | Case series | 30 | Acute myocardial infarction | Not stated | False event rate: 1.4 per week when sutured in the pocket versus 4.3 per week when not sutured<br>Inappropriate triggering: 2.3 events per patient |

## Diagnostic characteristics

No studies were identified in which the diagnostic characteristics of the ILR were subjected to an independent, blind comparison with a reference standard. Thus the sensitivity and specificity (and related derivative characteristics) of the ILR could not be determined. In the absence of such studies, two reports of one RCT (Krahn et al 2001a, 2003a) and 16 case series (Krahn et al 1995, 1998, 1999, Neirop et al 2000, Seidl et al 2000, Krahn et al 2001b, Mieszczanska et al 2001, Moya et al 2001, Ashby et al 2002, Bloemers & Sreeram 2002, Brignole et al 2002, Krahn et al 2002, Menozzi et al 2002, Armstrong et al 2003, Donateo et al 2003, Garcia-Civera et al 2003) which reported diagnostic yield were critically appraised.

### Randomised controlled trials

Two reports (Krahn et al 2001a, 2003a) of one RCT (Level II evidence) were identified. Krahn et al (2001a) reported the diagnostic yield of two strategies used in the evaluation of recurrent unexplained syncope, while Krahn et al (2003a) reported the diagnostic yield and cost implications. Patients were randomised to a prolonged monitoring strategy with an ILR or a conventional strategy that included a two- to four-week period of monitoring with an ELR followed by tilt table and electrophysiological testing. However, due to differing lengths of follow-up in the two strategies (as discussed in 'Validity' below), a valid comparison between the diagnostic yields of the ILR group and the conventional group could not be easily made. Patients included in the ILR arm had the first generation ILR device (Reveal®) placed in the left chest region under local anaesthetic. The authors reported that the device was capable of recording up to 42 minutes of single-lead ECG. Patients were offered the alternative strategy if the assigned strategy did not provide a diagnosis.

The study was conducted in Canada. Patients with recurrent unexplained syncope or a single episode of syncope that warranted cardiovascular investigation were invited to participate. Patients excluded were those with left ventricular ejection fraction of less than 35 per cent who were unlikely to survive for one year, those who were unable to provide follow-up or to give informed consent, or those with typical neurally mediated syncope.

A total of 60 patients (33 males) were enrolled in the trial. The mean (SD) age of patients randomised to the ILR strategy was 68 (14) years compared to 64 (14) years for those randomised to the conventional strategy.

Prior to enrollment, all patients underwent clinical assessment consisting of postural blood pressure testing, a minimum of 24 hours of baseline ambulatory monitoring or in-patient telemetry, and a transthoracic echocardiogram. In addition, selected patients also underwent neurological or cardiovascular tests at the discretion of their referring physician. These investigations appear to be consistent with the current approach to evaluation of unexplained recurrent syncope in Australian clinical practice (Figure 1).

The clinical characteristics of patients enrolled in the trial are reported in Table 15. Patients assigned to the ILR and conventional testing groups appeared to be similar in their baseline characteristics. Characteristics of syncope appeared similar in both groups, as did the proportion of patients with a structural heart disease and normal baseline ECG recordings and the left ventricular ejection fraction.

**Table 15 Clinical characteristics of patients in the randomised controlled trial**

| Clinical characteristics | ILR strategy (n = 30) | Conventional strategy (n = 30) |
|---|---|---|
| **Baseline ECG, n (%)** | | |
| . Normal | 20 (67) | 22 (73) |
| . Conduction disturbance | 5 (27) | 7 (23) |
| . Sinus bradycardia | 3 (10) | 0 (0) |
| . Atrial fibrillation | 2 (7) | 1 (3) |
| **Structural heart disease, n (%)** | 13 (43) | 10 (33) |
| . Ischemic heart disease | 9 (30) | 5 (17) |
| . Valvular heart disease | 1 (3) | 5 (17) |
| . Cardiomyopathy | 3 (10) | 0 (0) |
| **LVEF, %, mean (SD)** | 55 (8) | 55(6) |
| **Number of syncopal episodes, mean (SD)** | | |
| . Previous year | 2.3 (1.3) | 2.8 (2.7) |
| . Lifetime | 4.1 (3.3) | 5.8 (6.6) |
| **Duration of syncope, years, mean (SD)** | 6.6 (12.1) | 8.7 (26.6) |

Abbreviations: LVEF, lung volume ejection fraction; SD, standard deviation

## Validity

Krahn et al (2001a, 2003a) did not report the method of randomisation, if the allocation sequence was concealed from investigators entering patients into the trial or blinding of patients, investigators or outcome assessors. Due to the nature of the diagnostic strategies used, it would have been difficult to blind patients or investigators, but not outcome assessors, to group assignment. There were no losses to follow up, but the study excluded three participants assigned to the prolonged monitoring arm in calculating the diagnostic yield of the two groups.

The outcome assessed in the trial was diagnosis of the causes of syncope. This was defined differently in the two monitoring strategies. For patients assigned to the ILR strategy, diagnosis was defined as a symptom-rhythm correlation recorded during a spontaneous event that resembled the symptoms prior to enrollment in the trial. In contrast, diagnosis in the conventional strategy was defined as standard published criteria for positive tilt test (the occurrence of syncope or presyncope accompanied by a fall in blood pressure of more than 30 mmHg) and positive electrophysiological testing (induction of ventricular tachycardia for more than a 30-second duration or requiring urgent intervention, sustained supraventricular tachycardia, a corrected sinus node recovery time of more than 550 milliseconds or a His-ventricle [HV] interval of more than 75 milliseconds).

Patients allocated to the ILR strategy were followed for one year. The exact length of follow-up of patients allocated to the conventional strategy is uncertain but is assumed to be shorter than the ILR strategy since Krahn et al (2001a, 2003a) reported that monitoring with the ELR occurred over a two- to four-week period followed by tilt table and electrophysiological monitoring. The longer follow-up in the ILR monitoring arm in the RCT is likely to have biased the results in favour of the ILR monitoring strategy.

### Summary of findings

A diagnosis was obtained before crossover in 14 (47%) patients allocated to the ILR strategy and six (20%) allocated to the conventional strategy (Table 16). The incremental difference between diagnostic yields was 27% (95% CI: 4, 50%). Of the 14 patients who had an arrhythmic event recorded by the ILR at the time of syncope, 10 were diagnosed with bradycardia, one with tachycardia and three with vasovagal syncope.

**Table 16 Outcomes reported in the randomised controlled trial**

| Outcome | ILR strategy (n = 30) | Conventional strategy (n = 30) |
|---|---|---|
| Length of follow-up | 1 year | Unclear. 2 to 4 weeks |
| Symptom recurrence:<br>. Captured<br>. Non-captured | <br>14<br>1 | Not reported |
| Diagnosis established:<br>. Arrhythmia<br>. Other | 14<br>Bradycardia: 10; tachycardia: 1<br>Vasovagal syncope: 3[a] | 6<br>AV block: 1; poor AV node function: 2; tachycardia: 1<br>Positive tilt test: 2 |

Source: Krahn et al (2001a, 2003a]
[a]Confirmed on tilt table testing in one patient
Abbreviations: AV, atrioventricular

Table 17 describes the flow of patients after crossover following non-diagnosis with the original strategy. Krahn et al (2001a, 2003a) reported that 21 patients of 24 who remained undiagnosed after conventional monitoring chose to cross over to monitoring with the ILR. Of these patients, 15 had a recurrence in symptoms that was captured on the ILR and a diagnosis, defined as recording a symptom-rhythm correlation, was obtained in eight (33%) patients.

**Table 17 Results of randomised controlled trial following crossover**

| Outcome | Crossover to ILR strategy (n = 21) | Crossover to conventional strategy (n = 6) |
|---|---|---|
| Symptom recurrence:<br>. Captured<br>. Non-captured | <br>8<br>3 | Not reported |
| Diagnosis established:<br>. Arrhythmia<br>. Other | 8<br>Bradycardia [a]: 4; tachycardia: 2<br>Sinus rhythm with seizure-like activity: 2 | 1<br>Sustained AV node re-entrant tachycardia: 1 |

Source: Krahn et al (2001a, 2003a]
[a]Reported as 6 patients in Krahn et al (2001a), but 5 patients in Krahn et al (2003a)

Krahn et al (2001a) reported that six patients of 16 who remained undiagnosed after ILR monitoring, or were in follow-up, chose to cross over to conventional monitoring without the use of an ELR. This differs from Krahn et al (2003a) in which the number crossing over was stated as five. The tilt test was negative in all six patients (Krahn et al 2001a) and all five patients (Krahn et al 2003a). One diagnosis was obtained via a positive electrophysiological test – the patient had a sustained AV node re-entrant tachycardia associated with hypotension (Krahn et al 2001a, 2003a).

### Case series

As no studies comparing the accuracy of the ILR against a reference test were identified and the RCT did not estimate diagnostic characteristics, the review was expanded to include evidence from case series (level IV evidence). A total of 16 case series was critically appraised (Appendix F).

### Study characteristics

Studies took place in Australia, North America and Europe. Four studies (Seidl et al 2000, Brignole et al 2001, Moya et al 2001, Krahn et al 2002) recruited patients from two or more countries. Fifteen of the 16 studies (Krahn et al 1995, 1998, 1999, Neirop et al 2000, Seidl 2000, Krahn et al 2001b, Mieszczanska et al 2001, Moya et al 2001, Ashby et al 2002, Brignole et al 2002, Krahn et al 2002, Menozzi et al 2002, Armstrong et al 2003, Donateo et al 2003, Garcia-Civera et al 2003) enrolled adult patients with a mean age ranging from 59 to 73 years across these studies. One case series (Bloemers & Sreeram 2002) enrolled a younger group of patients, including paediatric patients, with an age range of 9 months to 26 years.

The first generation ILR was used in nine studies (Krahn et al 1999, 2001b, Moya et al 2001, Ashby et al 2002, Brignole et al 2002, Menozzi et al 2002, Armstrong et al 2003, Donateo et al 2003, Garcia-Civera et al 2003). Krahn et al (1995, 1998) used a prototypic version of the device and a subset of patients used the second generation ILR, Reveal® Plus, in two studies (Meiszczanda et al 2001, Bloemers & Sreeram 2002).

In all studies, patients underwent thorough clinical assessment prior to implantation with the loop recorder. This included at least a medical history, physical examination and electrocardiogram. Varying proportions of patients also underwent further testing using ELRs, echocardiography, and electrophysiological and tilt table tests. In these case series, the ILR was used to investigate long-term unexplained syncope, single episodes of syncope warranting further investigation, presyncope or unexplained falls.

### Validity

None of the studies met all validity criteria for assessing the methodological quality of case series (Appendix F, Table F4). Only four of 16 studies (Neirop et al 2000, Armstrong et al 2003, Donateo et al 2003, Garcia-Civera et al 2003) were likely to have minimised selection bias by reporting that consecutively selected patients were enrolled in the study and including all patients in reporting outcomes. The study endpoints were generally objective and reported as recording of an event during syncope or diagnosis of the underlying cause of syncope. None of the studies reported blinding of outcome assessors to the patients' history and results of previous investigations, which would have minimised the potential for measurement bias.

### Results

Studies ranged in size from seven (Bloemers & Sreeram 2002) to 206 patients (Krahn et al 2002). Duration of follow-up was not stated in a number of studies. Where reported, it ranged from five (Armstrong et al 2003) to 16 months (Menozzi et al 2002). Recurrence of syncope during the study period was highly variable, ranging from 17.1 per cent (Menozzi et al 2002) to 100 per cent (Donateo et al 2002).

The ILR device recorded arrhythmias in 57 per cent (Armstrong et al 2003) to 100 per cent (Bloemers & Sreeram 2002, Menozzi et al 2002) of patients who activated the device during recurrence. Up to 60.3 per cent (Krahn et al 2001b) recorded sinus rhythms. In 6.7 per cent (Garcia-Civera et al 2003) to 73.3 per cent (Armstrong et al 2003) of cases, no diagnosis was made.

## Patient outcomes following diagnosis

### Randomised controlled trial

Two reports (Krahn et al 2001a, 2003a) of one RCT (level II evidence) were included for critical appraisal. The descriptive characteristics and validity of the trial have been described in the previous section. Whilst the publications reported the treatments that patients received after diagnosis (Table 18), no information was available concerning the long-term health outcomes of patients.

**Table 18 Treatments following diagnosis reported in the randomised controlled trial of ILR**

| Diagnosis | Treatment |
|---|---|
| **ILR** | |
| . Bradycardia (n=14) | Pacemaker therapy |
| . Tachycardia (n=3) | Anti-arrhythmic drug therapy |
| . Vasovagal syncope (n=3) | Increased salt and water intake |
| **Conventional monitoring** | |
| . Bradycardia | |
| 3rd degree AV block (n=1) | |
| AV block (n=2) | Pacemaker implantation |
| . Sustained monomorphic ventricular tachycardia (n=1) | Implantable defibrillator |
| . Sustained AV node re-entrant tachycardia (n=1) | Ablation |
| . Positive tilt test (n=2) | |

Source: Krahn et al (2001a, 2003a)
Abbreviations: AV, atrioventricular

Treatments following diagnosis reported in the trial were consistent with those recommended in clinical practice guidelines (Brignole et al 2001). All seven patients diagnosed using the conventional strategy (Table 18) experienced a resolution of symptoms following treatment. One patient with monomorphic ventricular tachycardia associated with hypotension was treated with an implantable defibrillator. A patient with inducible sustained AV node re-entrant tachycardia underwent ablation. Three patients were diagnosed with bradycardia of whom two were treated with pacemaker implantation. Treatment was not reported in three patients.

Fourteen patients assigned to the ILR strategy were diagnosed with bradycardia and treated with a pacemaker (Table 18). Patients diagnosed with regular narrow complex tachycardia associated with atrial flutter or narrow complex tachycardias were treated with antiarrhythmic drug therapy. Three patients had symptoms and a history suggestive of vasovagal syncope that was confirmed by tilt table testing for one patient. These patients were advised to increase salt and water intake. Two patients were diagnosed with a seizure disorder and treated accordingly.

There was a report of one death due to a cerebrovascular accident in the group that underwent monitoring with the ILR. It is unclear whether this patient had been diagnosed with an arrhythmic cause of syncope, had a recurrence of symptoms prior to death, or if the death was related to the underlying condition that led to syncope.

Krahn et al (2001a) reported that syncope resolved in 27 (93.1%) patients of 29 that were followed up for a mean (SD) of 19.3 (8.9) months after a diagnosis was made. One patient required implantation with a pacemaker and one was diagnosed with partial complex seizures and treated with anticonvulsant therapy. As follow-up was not reported according to the monitoring strategy originally received by the patient, no comparison of the effectiveness of the ILR and conventional monitoring could be made.

## Discussion

The evidence in support of the effectiveness of ILR for recurrent unexplained syncope is preliminary. In the assessment of the effectiveness of diagnostic tests, not only is it desirable to establish the diagnostic accuracy of the test compared to an established standard, but it is also considered important to determine whether the use of the new test results in clinically important gains in patient-relevant outcomes such as quality of life. Although RCT evidence was identified, a valid comparison between the ILR monitoring strategy and the conventional monitoring strategy was difficult, primarily due to a longer follow-up for patients in the ILR arm. There is currently a lack of evidence for determining the comparative effectiveness of ILR.

### Diagnostic accuracy

None of the studies allowed the estimation of standard measures of diagnostic accuracy such as sensitivity, specificity and their derivatives. No studies were identified for which the design was appropriate to allow these estimations. Thus the search was expanded to include case series as supporting evidence. The lack of a comparison group makes it difficult to determine diagnostic accuracy and other outcomes in the presence of other tests. It also prevents the estimation of the incremental effectiveness of the test in the presence of prior investigations. Finally, it is difficult to rule out substantial clinical heterogeneity given the wide variations in the way the studies were conducted.

### Diagnostic yield

The RCT may have allowed measurement of the comparative accuracy of the device, but the study was not conducted in such a way as to allow the estimation of sensitivity, specificity or their derivatives. Instead, the number of patients randomised to a testing strategy who received a diagnosis under that strategy was compared. Using this outcome, the study reported that use of the ILR resulted in a greater number of patients being given a diagnosis compared to those assigned to conventional testing (47% versus 20% prior to crossover). However, the contribution of the longer follow up in the ILR strategy to this difference cannot be determined. In the absence of a suitable reference test, diagnostic yield may be assessed indirectly by measurement of the reduction in syncope recurrence following diagnosis and treatment (Brignole et al 2001), although this was not performed in the RCT.

### Patient outcomes following diagnosis

It is unclear whether use of the ILR resulted in improvements in patient-relevant outcomes stemming from changes in management. Treatments following diagnosis were reported on the available evidence but the more patient-relevant and longer-term outcomes, including recurrence of syncopal symptoms, other morbidities, changes in quality of life and mortality, were not. Although the trial reported that resolution of symptoms occurred in almost all patients following the establishment of a diagnosis,

follow-up was insufficient to determine if this effect was maintained in the longer term. In addition, outcomes for patients whose cause of syncope was not diagnosed were not reported, thus the incremental effectiveness of the ILR compared to conventional monitoring could not be determined.

### Comparative effectiveness

The available evidence allows conclusions about the diagnostic yield of the ILR compared to conventional testing including the ELR. The ILR resulted in a higher diagnostic yield than conventional testing (47% versus 20%; difference = 27%; 95% CI: 4, 50%). After conventional testing had failed to result in a diagnosis in 24 patients, eight extra patients obtained a diagnosis with subsequent use of the ILR.

There is currently a lack of evidence to allow determination of the diagnostic accuracy in terms of sensitivity, specificity and their derivatives, of the ILR, or the effectiveness of ILR compared to ELR or standard tests on long-term patient-relevant outcomes such as quality of life. In addition, as conventional monitoring with the continuous ambulatory ECG monitoring (eg with the ELR) is available to this patient group, use of the invasive ILR for most patients may not be appropriate until diagnosis has failed with the use of conventional monitoring.

## What are the economic considerations?

Determination of the setting in which ILR would be used in practice allows definition of both the characteristics of the patients who would benefit from the use of ILR and the appropriate comparator that should be included in an economic evaluation. Figure 3 summarises the diagnostic cascade considered appropriate for the investigation of patients with recurrent syncopal episodes. According to data provided in this report:

- there is insufficient evidence to determine the comparative effectiveness and safety of ILR versus ELR; and
- ILR involves an invasive procedure and has some risk of adverse events.

Expert opinion suggests that it is unrealistic to expect patients to wear an ELR for more than a few weeks. Given all of these details, this section of the report assumes that ILR would not be used in place of ELR in practice but that it is likely to be used only where ELR is inappropriate or where ELR has failed to elicit a diagnosis.

Given the details outlined above, the population in whom ILR would be appropriate consists of patients with recurrent syncopal episodes occurring at intervals greater than a week apart in whom diagnosis has not been achieved through history, physical examination, monitoring of blood pressure and ECG, and who are determined to either have no structural heart disease or be at low risk of sudden cardiac death, and in whom ELR is inappropriate or has failed to elicit a diagnosis.

The appropriate comparator in an economic evaluation is therefore standard management where use of ELR is inappropriate or has failed. Standard management may consist of repeat ELR in some patients but no further ECG monitoring in the majority of patients. Costs and effectiveness of ILR and standard management are the primary considerations in an economic evaluation.

## Literature review

The approach used to identify any literature analysing the cost-effectiveness of ILR is outlined in the 'Approach to assessment'. No economic evaluations analysing the incremental cost-effectiveness of ILR over any comparators were located. Two articles reporting the results of cost analyses were identified (Krahn et al 1999, Simpson et al 1999) but both of these analyses were conducted for the Canadian setting. The analyses are based on the average diagnostic yields reported in Krahn et al (1998). No incremental analyses are provided and the analyses assume yields to be the same in any patient population irrespective of the order and results of any previous tests. The results of the analyses are not directly generalisable to the Australian context.

An Application was submitted to the MSAC requesting a review for possible MBS listing of ILR in the diagnosis of recurrent unexplained syncope in patients who experience transient symptoms suggestive of cardiac arrhythmia. The Application includes the results of two economic evaluations comparing ILR with other technologies.

## Review of submitted model

The following assessment is based on a consideration of the economic analyses provided in the Application to the MSAC. Note that all $ values refer to Australian dollars.

The Application uses one fundamental model (constructed using Data Pro software) to conduct two economic evaluations.

Figure 3 summarises the diagnostic algorithm assumed in the Application and the places where it is proposed that ILR be used. As evident in Figure 3, the Application proposes that ILR could be used in two groups of patients. An economic evaluation is performed for each setting.

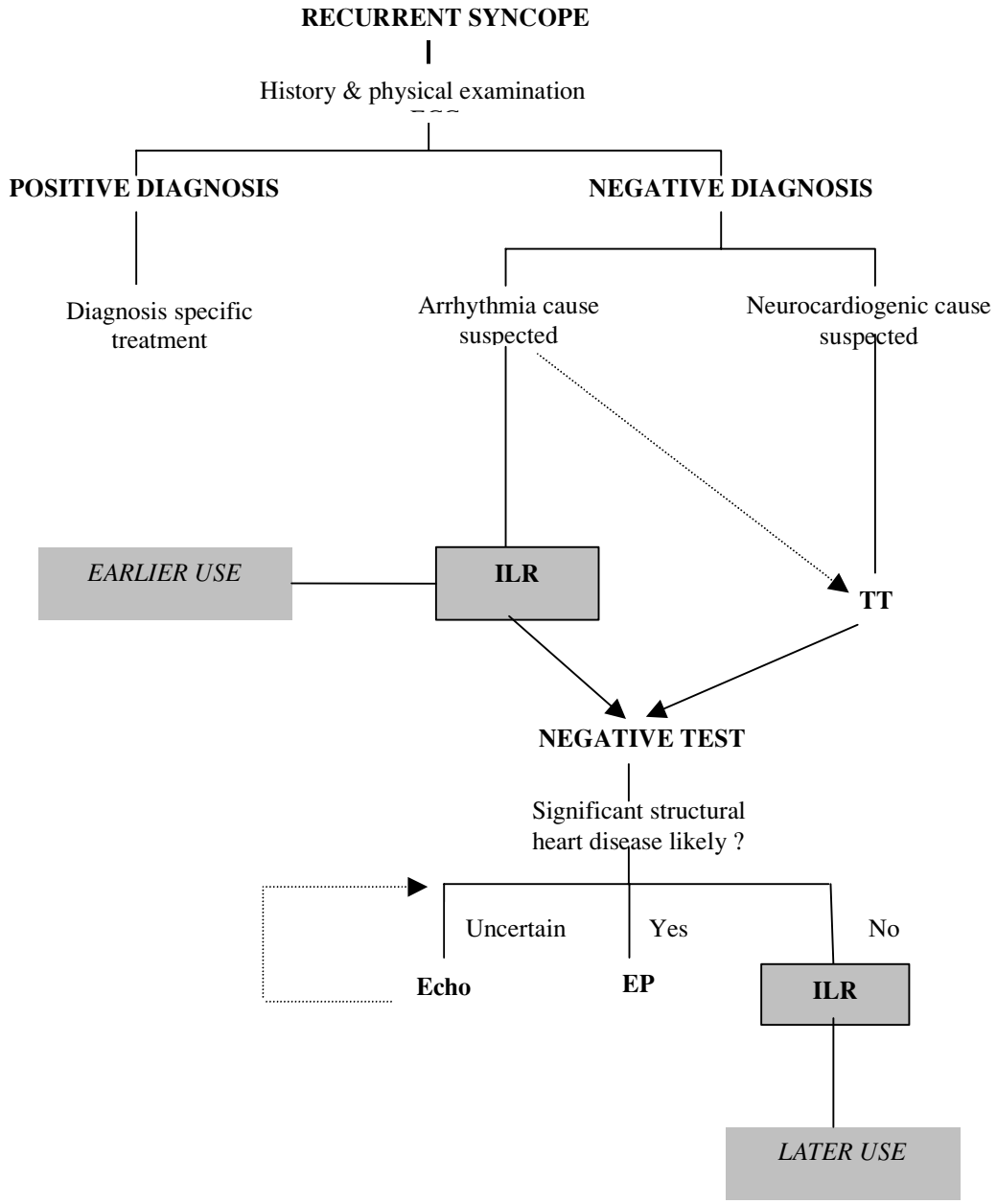
- In the first economic evaluation, ILR is used early in the diagnostic cascade. As discussed in 'Background', expert opinion did not concur with the Applicant's proposed diagnostic algorithm for evaluation of patients with unexplained, recurrent syncope or the proposed clinical setting in which ILR is used early in the diagnostic cascade. In particular, it was considered that the possibility of structural heart disease should be investigated earlier. This evaluation assumes that ILR will be used in place of ELR plus tilt table testing in 50 per cent of patients. The inclusion of tilt table testing as part of the comparator in the early setting is inappropriate. Tilt table testing is used in addition to ambulatory ECG monitoring (by ELR) rather than as a substitute, as it is used to diagnose conditions other than those that can be diagnosed by ECG (eg failure of compensatory mechanisms in response to orthostatic stress). As discussed above, data provided in this report suggest that:

  - there is insufficient evidence to determine the comparative effectiveness and safety of ILR versus ELR; and

  - ILR involves an invasive procedure and has some risks of adverse events.

  Expert opinion considered that ILR would not be used in place of ELR but is likely to be used only where ELR is inappropriate or where ELR has failed to elicit a diagnosis.

- In the second economic evaluation, ILR is used late in the diagnostic cascade. The Applicant's proposed algorithm in which ILR is used late in the diagnostic cascade is approximately consistent with the algorithm considered appropriate according to expert opinion (see Figure 3). This evaluation assumes that ILR will not replace existing technology but will be used in addition to existing technologies. Standard management is the appropriate comparator. As discussed above, standard management may consist of repeat ELR in some patients, but no further ECG monitoring in the majority of patients.




Abbreviations: Echo, echocardiography; EP, electrophysiology; TT, tilt table test

**Figure 3 Diagnostic algorithm for patients with recurrent unexplained syncope as assumed in the application in the case where ILR is available**

## Structure of submitted model (including transition probabilities)

The structure of the submitted model used to conduct the economic evaluations and the transition probabilities assumed in the submitted model is summarised in Figure 4. The model compares costs and benefits of ILR with those of:

- ELR with or without tilt table testing for patients where ILR is used early in the diagnostic cascade; and
- standard care for patients where ILR is used late in the diagnostic cascade.

The model examines costs and benefits over a three-year time horizon. Examination of costs and benefits over time horizons longer than one year will result in lower estimates of the incremental cost-effectiveness of ILR than an examination over one year. This is because costs associated with diagnosis, which all occur in the first year of the model, become diluted with extension of the time horizon examined. It is appropriate to consider an extended time horizon such as 3–5 years as benefits continue to accrue to patients who are diagnosed and successfully treated in the years subsequent to diagnosis.

Costs and benefits occurring in the second and third years of the model are appropriately discounted at five per cent per annum.

In each arm of the model, patients either achieve a diagnosis or fail to achieve a diagnosis. Early in the diagnostic cascade, a diagnosis is assumed to be achieved in 48.57 per cent of patients using ILR and 14.71 per cent of patients using ELR.

Thus, the incremental proportion of patients achieving diagnosis is 33.86 per cent. The source of these probabilities is Krahn et al (2001a). As discussed in 'Results of assessment', these estimates may not be reliable for several reasons.

- It does not appear that results reported by Krahn et al (2001a) are at the same time point for patients in each arm of the trial. Patients randomised to ILR were followed-up for a year whereas those randomised to conventional methods of diagnosis were not. As the likelihood of diagnosis increases with time (especially given that syncopal episodes are relatively infrequent, with a median of between two and three syncopal episodes per year), the results presented are likely to be biased in favour of ILR. Furthermore, the model makes no adjustments to proportions of patients achieving a diagnosis despite extension of the time horizon in the model to three years.
- Krahn et al (2001a) do not categorise patients in the comparator arm according to the reason diagnosis was not achieved. For example, the case where a patient experiences a spontaneous resolution of the condition and experiences no further episodes of syncope cannot be distinguished from the case where a syncopal episode is not captured to permit diagnosis. These two outcomes should be valued differently. The reasons for failure to diagnose need to be differentiated to permit an accurate assessment of the comparative performance and cost-effectiveness of the two technologies.
- Outcomes were defined differently in the two arms of the trial. Diagnosis for patients randomised to ILR was defined as symptom-rhythm correlation recorded during a spontaneous event that resembled the symptoms prior to

enrolment. In contrast, diagnosis was defined as standard published criteria for positive tilt test (the occurrence of syncope or presyncope accompanied by a fall in blood pressure of more than 30 mmHg) and positive electrophysiological testing (induction of ventricular tachycardia for more than 30-seconds duration or requiring urgent intervention, sustained supraventricular tachycardia, a corrected sinus node recovery time of more than 550 milliseconds or an His-ventricle [HV] interval of more than 75 milliseconds) for patients randomised to the comparator arm.

Late in the diagnostic cascade, a diagnosis is assumed to be achieved in 37.5 per cent of patients using ILR and zero per cent of patients using standard care.

Thus, the incremental proportion of patients achieving diagnosis is 37.5 per cent. The source of the probability of diagnosis following ILR is the combined results from Krahn et al (1998), Krahn et al (1999) and Seidl et al (2000).

Issues arising in relation to these studies include:

- they were non-comparative studies examining effectiveness of the early versions of ILR (ie prototypes of Reveal® Plus);
- results from the three studies appear to have been arbitrarily, rather than appropriately, pooled; and
- the combined results presented are not based on the intention-to-treat results from the individual studies.

Results from Krahn et al (2001a) should also have been considered. The additional number of patients diagnosed by ILR after crossover from the comparator arm would be an indication of the number of additional diagnoses that can be achieved by ILR in patients who have failed to achieve a diagnosis with ELR. Table 17 describes the flow of patients after crossover following non-diagnosis with the originally assigned strategy. Krahn et al (2001a, 2003a) reported that 21 of 24 patients who remained undiagnosed after conventional monitoring chose to crossover to monitoring with the ILR. These 24 patients are representative of the patients for whom it is proposed ILR be made available. Of these patients, 15 had a recurrence in symptoms that was captured on the ILR and a diagnosis, defined as recording a symptom-rhythm correlation, was obtained in eight of them (33%). This estimate is used in the re-analysis presented below.

The justification given for the assumption of a zero per cent diagnostic yield for the comparator is that the results of a study of undiagnosed syncopal patients with no clinical evidence of heart disease by history, physical examination or ECG suggest that the diagnostic yield of the echocardiogram is zero per cent (Recchia et al 1995). This justification is not convincing. An ECG is recommended in patients with syncope when cardiac disease is suspected yet the patients recruited to the study were not suspected of having heart disease. While there are no studies reporting such a value, the diagnostic yield associated with standard care (which may involve repeat ELR in some patients) may be a more appropriate value to assume for the comparator arm.

It would be appropriate to conduct a sensitivity analysis around the incremental proportion of patients diagnosed taking into account uncertainty beyond stochastic uncertainty (which is reflected in 95 per cent CIs). A sensitivity analysis around the re-

analysis is presented that assumes the incremental proportion of patients diagnosed is 20 per cent.

In both arms of the model, patients who have a diagnosis made are diagnosed with either bradyarrhythmia or tachyarrhythmia. Approximately 77 per cent of patients diagnosed are assumed to have bradyarrhythmia and the remainder tachycardia, roughly consistent with the data reported in Krahn et al (1998, 1999, 2001a) and Seidl et al (2000).

- Of the patients with bradyarrhythmia:
  - 25 per cent are assumed to be treated by insertion of a pacemaker. It is assumed that 94.65 per cent of patients having a pacemaker inserted will experience no further syncopal episodes.
  - 75 per cent are assumed to be treated with beta-blockers (atenolol is selected as being representative of this class). However the group of patients likely to receive treatment with beta-blockers are those with bradycardia secondary to neurocardiogenic syncope. It is assumed that 71.03 per cent of patients treated with a beta-blocker will experience no further syncopal episodes.
- Of the patients with tachyarrhythmia:
  - all are assumed to be treated by cardioversion followed by flecainide to prevent further tachycardia. It is assumed that 64.2 per cent of patients will experience no further syncopal episodes.

The assumption that all patients will be actively treated may not be valid. It is possible that some patients will have a condition diagnosed that is not clinically important enough to require treatment. Furthermore, it is inappropriate to assume that patients with tachyarrhythmia would be treated by cardioversion. Cardioversion is generally used in the treatment of sustained rhythm disorder. Patients being diagnosed by means of ILR typically have episodic rhythm disorders. It is rare for patients with episodic syncope to require cardioversion. Patients with episodic tachyarrhythmia may be treated with a variety of pharmaceutical agents. It is reasonable to choose flecainide as a representative agent.

Overall, the model assumes that 74 per cent of patients are successfully treated ((0.7667 × ((0.9465 × 0.25) +(0.7103 × 0.75)))+ (0.2333 × 0.643)). It would be appropriate to conduct a sensitivity analysis assuming, for example, that only 60 per cent of patients were successfully treated.

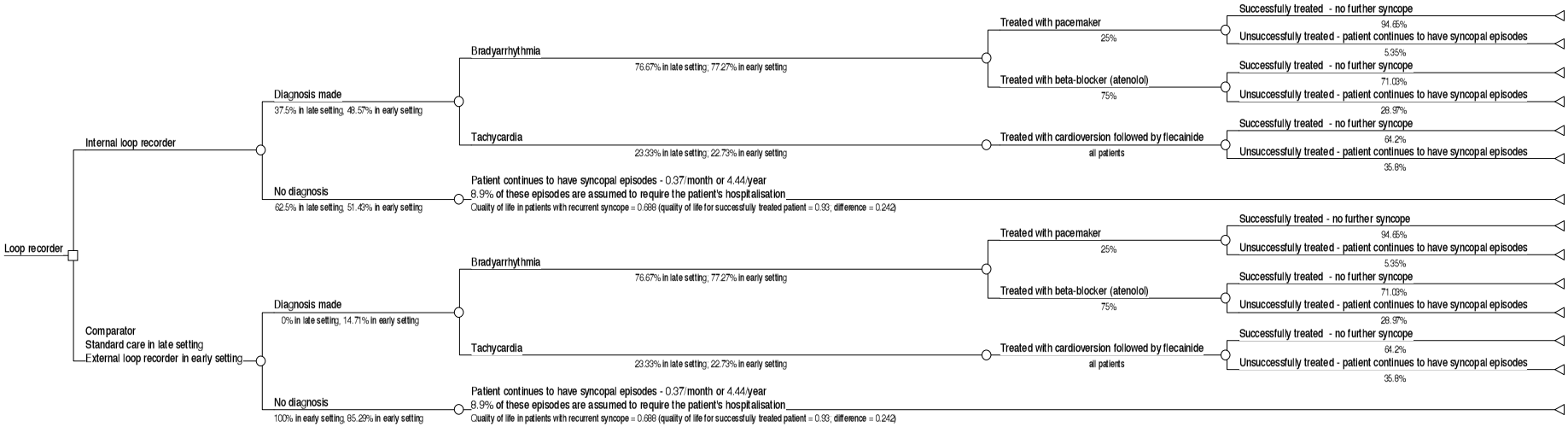



**Figure 4 Structure of submitted model including transition probabilities**

The overall structure of the model is inadequate for two main reasons:

- The model does not differentiate between the reasons why patients fail to achieve a diagnosis. Patients experiencing a spontaneous resolution of the condition who experience no further episodes of syncope are not distinguished from patients who fail to be diagnosed because syncopal episodes are not captured by a monitoring. Outcomes (eg utility estimates) for patients in these two groups are likely to be different, therefore it is important that a model differentiates between them.

- The model does not differentiate between patients diagnosed by means of ambulatory ECG monitoring and those diagnosed through other means (eg tilt table testing, electrophysiological testing). Thus, the model compounds diagnostic efficiency of other technologies with those from loop recording. Thus, the calculation of incremental cost-effectiveness does not relate to loop recording alone, but to that of combined strategies for achieving diagnosis.

A more appropriate structure for a model to compare ILR with other management techniques is presented in Figure 5. The composite outcome valued by the model is patients with either a diagnosed condition or spontaneous resolution of recurrent syncope. Assumptions about the likely success of treatment following diagnosis, and valuation of the outcomes of no further syncope, diagnosed but unsuccessfully treated, and recurrent undiagnosed syncope, would permit outcomes to be extrapolated further (eg to QALYs gained) if necessary. The time horizon for both arms of the model must be identical, however it is acknowledged that data to populate such a model are not currently available. In the absence of such data, the structure of the model presented in the Application permits the estimation of indicative incremental cost-effectiveness ratios.

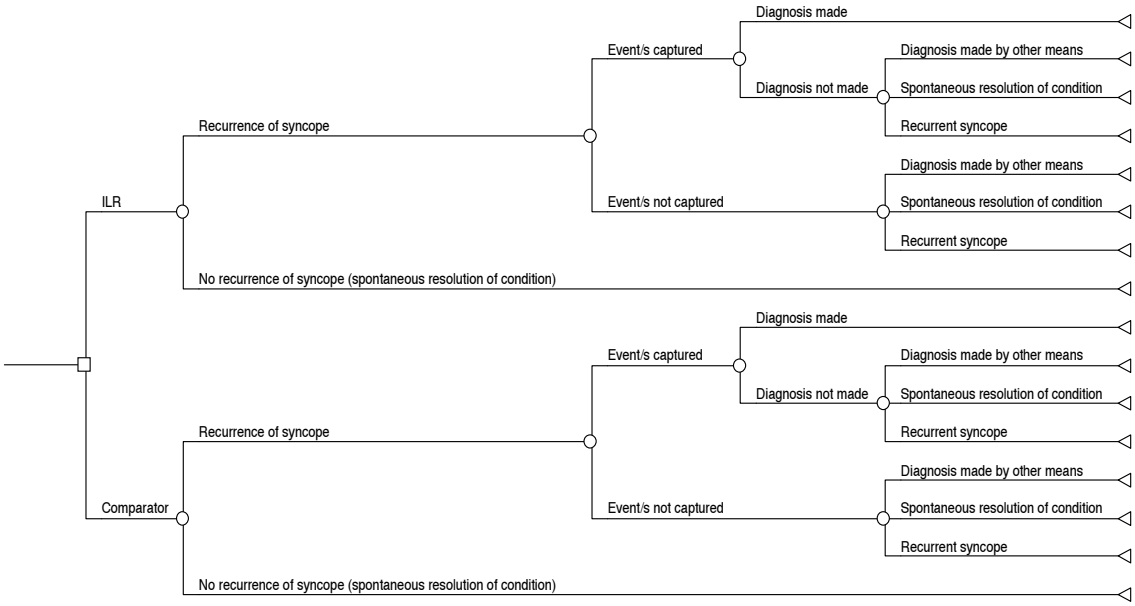



**Figure 5 Suggested structure for a model for comparing ILR and a comparator**

### Resource variables

The unit costs assumed in the model for various resources and comment on the appropriateness of the unit costs are summarised in Table 19.

Many of the unit costs assumed in the analyses, especially those for MBS services, PBS items and DRGs, are now out of date as the May 2001 MBS, the May 2002 PBS and Round 4 (1999/2000) DRG cost weights are used as references.

Overall, costs for implant and explant of the ILR are overestimated but costs of interpretation of output from the ILR are underestimated. Costs of treatment following diagnosis (eg costs associated with implantation of a pacemaker and costs associated with treatment of tachycardia) appear to be overestimated in the analyses.

Costs not included in the economic evaluations are those associated with the screening procedure before implant of the ILR, antibiotic prophylaxis following implant of the ILR, treatment of adverse events and follow-up visits to a physician for monitoring after implant of the ILR.

The re-analysis presented below includes updated and adjusted costs and the addition of costs excluded from the Application.

Costs of hospitalisation for the treatment of injuries associated with syncope are assumed to be avoided in successfully treated patients. These cost-offsets that are assumed may be underestimates of cost-offsets that would occur in practice. It is likely that patients who experience a syncopal episode but who are not injured will also present to hospital (or at least to a doctor or specialist) for reasons other than injury. These patients frequently present simply because they are anxious and alarmed and seek further investigations to diagnose the cause of syncope. The number of tests that are likely to be associated with a low diagnostic yield in such a group of patients, such as EEG and MRI, will increase the longer a patient with recurrent syncope remains undiagnosed. As there is no reliable means of estimating these costs, particularly as there is no DRG category for a hospital stay for admission for syncope, these costs are also excluded from the following re-analysis.

**Table 19 Unit costs assumed in the submitted model**

| Resource | Unit cost ($) | Source | Comment |
|---|---|---|---|
| **Costs of ILR** | | | |
| . Device | 3,048.00 | Medtronic | This is the discounted price for multiple unit purchases. A single unit costs $3,560.00 |
| . Implant | 651.95 | MBS Item No 38284 | This MBS item number relates to the insertion, removal or replacement of pacemaker electrodes. The procedure involved in implanting the ILR appears to be less complex and quicker than insertion of electrodes (15 to 20 minutes compared to about 1.75 hours). There is no direct comparator on the MBS for the insertion of an ILR. However, based on the American Medical Association's relative value of implantation of a recorder to insertion of a pacemaker, the appropriate MBS fee for implantation of an ILR should be approximately $155. (RVU of insertion of an ILR is 4.17; RVU of insertion of pacemaker is 5.52. The current MBS fee for insertion of a pacemaker (item 38281) is $207.10. Costs to implant an ILR are overestimated |
| . Explant | 651.95 | MBS Item No 38284 | Costs to explant ILR are overestimated. MBS item 30064 (removal of subcutaneous foreign body) could be considered as equivalent in terms of the nature and complexity of the process to explant an ILR |
| . Interpretation of output | 27.00 | MBS Item No 11718 | The evaluations assume that only one interpretation of output will be conducted per patient. This is an inappropriate assumption. It is likely that interpretation of output will be performed more than once, especially if patients experience more than one syncopal episode. Overall, costs for interpretation of output are underestimated |
| Total: | 4,378.90 | | |
| **Cost of comparator** | | | |
| . Early setting | | | |
| ELR | 40.35 | MBS Item 11710 | |
| Tilt table testing | 131.50 × 50% | MBS Item 11724<br>Proportion of patients having tilt table test[a] | The inclusion of costs for tilt table testing in the comparator arm is inappropriate because ILR would not be used instead of tilt table testing. The two technologies are used to diagnose different conditions |
| Total: | 106.10 | | |
| . Late setting | 0.00 | | |
| **Cost of pacemaker insertion** | | | |
| . Cost of device | 6,000.00 | Medtronic | The estimate for the cost of the pacemaker device could not be verified. The DRG figure includes costs for implanting the pacemaker and the costs of the prosthesis itself. The evaluations therefore double-count some costs for insertion of the pacemaker. Overall, costs associated with pacemaker insertion are overestimated |
| . Hospitalisation | 7,343.00 | DRG F17Z | |
| . Cost of implant | 651.95 | MBS Item No 38284 | |
| Total: | 13,994.95 | | |

**Table 19 (cont'd) Unit costs assumed in the submitted model**

| Resource | Unit cost ($) | Source | Comment |
|---|---|---|---|
| Annual cost of treatment with a beta-blocker | 9.81 ÷ | PBS cost of 30 × atenolol 50 mg | Patients may be treated with a range of pharmaceutical agents. The selection of atenolol as a representative agent is reasonable. The approach to calculation of unit cost for atenolol is correct. The assumed daily dose is within the recommended range |
| | 15 × | Days of therapy provided by 30 atenolol 50 mg tablets at 100 mg/day | |
| | 365 | Days in a year | |
| Total: | 238.71 | | |
| Cost of injury from recurrent syncope over 3 years | 2,878.00 × | DRG X06A-B | The application assumes that all injuries will require procedures and therefore estimates costs using DRG X06 – other procedures for other injuries. No justification is presented to support this assumption. Many more patients with injuries are admitted to hospital under DRG X60 – injury. Costs associated with this DRG are lower than those for DRGX06.<br>Ammirati et al (2001) propose a relationship between the number of syncopal episodes and the number of syncope-related injuries. From the data provided the proportion of injuries requiring hospitalisation is also estimated. The derivation of the figures in relation to the number of injuries estimated appears appropriate |
| | 5.3 × | No of injuries from syncope over 3 years[b] | |
| | 31/94 ÷ | Proportion of injuries requiring hospitalisation | |
| | 1.05[2] | Discounting of future costs | |
| Total: | 4,562.70 | | |
| Cost of cardioversion | 2,013.00 | DRG F71A & DRG F71B | The application assumes that cardioversion is conducted as part of DRG71 (non-major arrhythmia & conduction disorders). The application presents no justification to support its estimation of costs. It is inappropriate to assume all patients with tachyarrhythmia would be treated by cardioversion. Cardioversion is generally used in the treatment of sustained rhythm disorder. Patients being diagnosed by means of ILR typically have episodic rhythm disorders. It is rare for patients with episodic syncope to require cardioversion. No justification is presented to support the assumption that all patients diagnosed with tachycardia would require hospitalisation. Costs for treatment of tachycardia are likely to have been overestimated in the analyses |
| Annual cost of maintenance treatment with flecainide | 47.05 ÷ | PBS cost of 60 × flecainide 100 mg | Patients with episodic tachyarrhythmia may be treated with a variety of pharmaceutical agents. The choice of flecainide as a representative agent is reasonable. The approach to calculation of unit cost for flecainide is correct. The assumed daily dose is within the recommended range |
| | 30 × | Days of therapy provided by 60 flecainide 100 mg tablets at 200 mg/day | |
| | 365 | Days in a year | |
| Total: | 572.44 | | |

[a] From Krahn et al (1999)
[b]From Ammirati et al (2001)

Seven final health states are possible in each arm of the model. Table 20 summarises the costs accruing for each of these.

**Table 20 Costs accruing for each health state included in each of the models**

| Health state | No of units | Unit cost ($) | Total cost ($) |
|---|---|---|---|
| Diagnosed with bradyarrhythmia, successfully treated with pacemaker | | | 17,721.90 (ILR) or 14,101.05 (comparator arm in the early setting) or 13,994.95 (comparator arm in the late setting) |
| . Cost of diagnostic intervention (ILR or comparator) | 1 | 3,726.95[a] (ILR) or 106.10 (comparator in the early setting) or 0.00 (comparator in the late setting) | |
| . Costs associated with pacemaker insertion | 1 | 13,994.95 | |
| Diagnosed with bradyarrhythmia, unsuccessfully treated with pacemaker | | | 22,284.60 (ILR) or 18,663.75 (comparator arm in the early setting) or 18,557.65 (comparator arm in the late setting) |
| . Cost of diagnostic intervention (ILR or comparator) | 1 | 3,726.95[a] (ILR) or 106.10 (comparator in the early setting) or 0.00 (comparator in the late setting) | |
| . Costs associated with pacemaker insertion | 1 | 13,994.95 | |
| . Costs of injury from recurrent syncope over 3 years | 1 | 4,562.70 | |
| Diagnosed with bradyarrhythmia, successfully treated with beta-blockers | | | 5,061.47 (ILR) or 788.67 (comparator arm in the early setting) or 682.57 (comparator arm in the late setting) |
| . Cost of diagnostic intervention (ILR or comparator) | 1 | 4,378.90 (ILR) or 106.10 (comparator in the early setting) or 0.00 (comparator in the late setting) | |
| . Annual costs of treatment with beta-blocker | 3 | 238.71[b] | |
| Diagnosed with bradyarrhythmia, unsuccessfully treated with beta-blockers | | | 9,624.17 (ILR) or 5,351.37 (comparator arm in the early setting) or 5,245.27 (comparator arm in the late setting) |
| . Cost of diagnostic intervention (ILR or comparator) | 1 | 4,378.90 (ILR) or 106.10 (comparator in the early setting) or 0.00 (comparator in the late setting) | |
| . Annual costs of treatment with beta-blocker | 3 | 238.71[b] | |
| . Costs of injury from recurrent syncope over 3 years | 1 | 4,562.70 | |
| Diagnosed with tachycardia, successfully treated with flecainide after cardioversion | | | 8,028.74 (ILR) or 3,755.94 (comparator arm in the early setting) or 3,649.84 (comparator arm in the late setting) |
| . Cost of diagnostic intervention (ILR or comparator) | 1 | 4,378.90 (ILR) or 106.10 (comparator in the early setting) or 0.00 (comparator in the late setting) | |
| . Cost of cardioversion | 1 | 2,013.00 | |
| . Annual costs of treatment with flecainide | 3 | 572.44 [b] | |

**Table 20 (cont'd) Costs accruing for each health state included in each of the models**

| Health state | No of units | Unit cost ($) | Total cost ($) |
|---|---|---|---|
| Diagnosed with tachycardia, unsuccessfully treated with flecainide after cardioversion | | | 12,591.44 (ILR) or 8,318.64 (comparator arm in early setting) or 8,212.54 (comparator arm in the late setting) |
| . Cost of diagnostic intervention (ILR or comparator) | 1 | 4,378.90 (ILR) or $106.10 (comparator in the early setting) or 0.00 (comparator in the late setting) | |
| . Cost of cardioversion | 1 | 2,013.00 | |
| . Annual costs of treatment with flecainide | 3 | 572.44[b] | |
| . Costs of injury from recurrent syncope over 3 years | 1 | 4,562.70 | |
| Undiagnosed | | | 8,941.60 (ILR) or 4,668.80 (comparator arm in early setting) or 4,562.70 (comparator arm in the late setting) |
| . Cost of diagnostic intervention (ILR or comparator) | 1 | 4,378.90 (ILR) or 106.10 (comparator in the early setting) or 0.00 (comparator in the late setting) | |
| . Costs of injury from recurrent syncope over 3 years | 1 | 4,562.70 | |

[a] Costs of explanting the device are excluded as it is assumed that the device will be removed at the same time as the pacemaker is implanted
[b]Costs of drugs in second and third years of the model are discounted by 5% pa

Tables 21 and 22 summarise the calculation of total costs over three years for each arm in the evaluations.

**Table 21 Total costs for each arm of the submitted model over three years when ILR is used in the early setting**

| Health state | Proportion of patients in various health states (%) | Total cost ($) | Weighted cost ($) |
|---|---|---|---|
| **ILR arm** | | | |
| . Diagnosed with bradyarrhythmia, successfully treated with pacemaker | 8.9 | 17,721.90 | |
| . Diagnosed with bradyarrhythmia, unsuccessfully treated with pacemaker | 0.5 | 22,284.60 | |
| . Diagnosed with bradyarrhythmia, successfully treated with beta-blockers | 20.0 | 5,061.47 | |
| . Diagnosed with bradyarrhythmia, unsuccessfully treated with beta blockers | 8.2 | 9,624.17 | |
| . Diagnosed with tachycardia, successfully treated with flecainide after cardioversion | 7.1 | 8,028.74 | |
| . Diagnosed with tachycardia, unsuccessfully treated with flecainide after cardioversion | 4.0 | 12,591.44 | |
| . Undiagnosed | 51.4 | 8,941.60 | |
| **Total:** | **100.0** | | **9,147.77** |
| **ELR arm** | | | |
| . Diagnosed with bradyarrhythmia, successfully treated with pacemaker | 2.7 | 14,101.05 | |
| . Diagnosed with bradyarrhythmia, unsuccessfully treated with pacemaker | 0.2 | 18,663.75 | |
| . Diagnosed with bradyarrhythmia, successfully treated with beta-blockers | 6.1 | 788.67 | |
| . Diagnosed with bradyarrhythmia, unsuccessfully treated with beta blockers | 2.5 | 5,351.37 | |
| . Diagnosed with tachycardia, successfully treated with flecainide after cardioversion | 2.1 | 3,755.94 | |
| . Diagnosed with tachycardia, unsuccessfully treated with flecainide after cardioversion | 1.2 | 8,318.64 | |
| . Undiagnosed | 85.3 | 4,668.80 | |
| **Total:** | **100.0** | | **4,749.71** |

**Table 22 Total costs for each arm of the submitted model over three years when ILR is used in the late setting**

| Health state | Proportion of patients in various health states (%) | Total cost ($) | Weighted cost ($) |
|---|---|---|---|
| **ILR arm** | | | |
| . Diagnosed with bradyarrhythmia, successfully treated with pacemaker | 6.8 | 17,721.90 | |
| . Diagnosed with bradyarrhythmia, unsuccessfully treated with pacemaker | 0.4 | 22,284.60 | |
| . Diagnosed with bradyarrhythmia, successfully treated with beta-blockers | 15.3 | 5,061.47 | |
| . Diagnosed with bradyarrhythmia, unsuccessfully treated with beta blockers | 6.2 | 9,624.17 | |
| . Diagnosed with tachycardia, successfully treated with flecainide after cardioversion | 5.6 | 8,028.74 | |
| . Diagnosed with tachycardia, unsuccessfully treated with flecainide after cardioversion | 3.1 | 12,591.44 | |
| . Undiagnosed | 62.5 | 8,941.60 | |
| **Total:** | 100.0 | | **9,101.64** |
| **ELR arm** | | | |
| . Diagnosed with bradyarrhythmia, successfully treated with pacemaker | 0.0 | 13.994.95 | |
| . Diagnosed with bradyarrhythmia, unsuccessfully treated with pacemaker | 0.0 | 18,557.65 | |
| . Diagnosed with bradyarrhythmia, successfully treated with beta-blockers | 0.0 | 682.57 | |
| . Diagnosed with bradyarrhythmia, unsuccessfully treated with beta blockers | 0.0 | 5,245.27 | |
| . Diagnosed with tachycardia; successfully treated with flecainide after cardioversion | 0.0 | 3,649.84 | |
| . Diagnosed with tachycardia, unsuccessfully treated with flecainide after cardioversion | 0.0 | 8,212.54 | |
| . Undiagnosed | 100.0 | 4,562.70 | |
| **Total:** | 100.0 | | **4,562.70** |

### Outcome variables

The outcome valued by the model is patients successfully treated following diagnosis of the condition. Quality of life is estimated assuming differential utilities for patients successfully treated following diagnosis and for patients not diagnosed or unsuccessfully treated following diagnosis. Successfully treated patients are assumed to have utility scores of 0.93. Patients not achieving diagnosis or unsuccessfully treated following diagnosis are assumed to experience further syncopal episodes and are assumed to have utility scores of 0.688. Thus, a utility gain of 0.242 is estimated for successfully treated patients. These estimates were derived from Rose et al (2000) in which the EuroQol EQ-5D thermometer was completed by 136 patients with varying numbers of lifetime syncopal episodes. The relationship between the overall perception of health as measured by the EQ-5D and the log frequency of lifetime syncopal spells was investigated. It was

found that there was a significant negative relationship between the frequency of spells and overall perception of health in patients with six or more lifetime syncopal spell. This relationship was not evident in patients who had a history of less than six lifetime spells. The results are summarised in Figure 6. The Application estimated the average utility score for patients experiencing 4.4 syncopal episodes per year from the second of these figures. However, patients recruited to Krahn et al (2001a) experienced between 2.3 and 2.8 syncopal episodes per year rather than 4.4, and not all patients had experienced six syncopal spells in their lifetime (Table 15). Thus, utility gain is likely to be an overestimate of the mean utility gain that would be seen in practice. The Application appropriately presents the results of a sensitivity analysis assuming the utility gain for successfully treated patients will be 0.132 rather than 0.242.

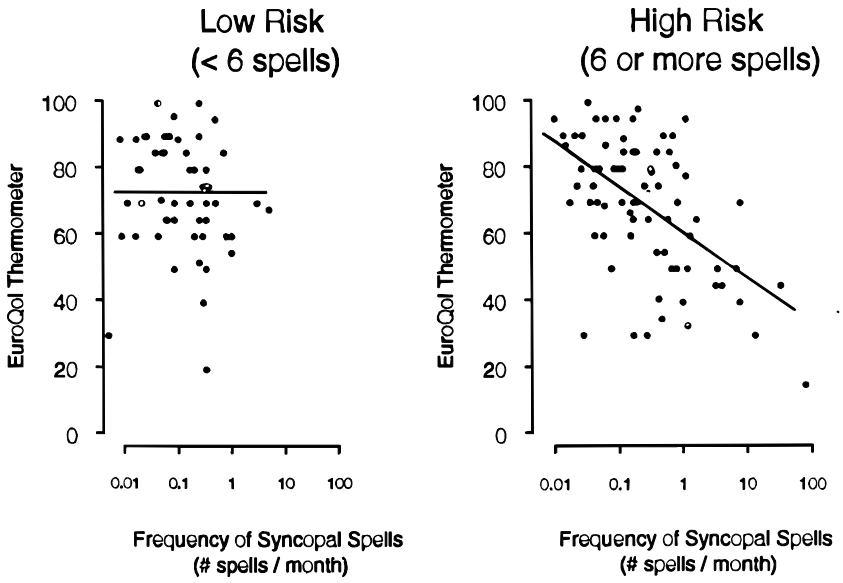



**Figure 6 The relationship between health-related quality of life (measured by the EQ-5D thermometer) and the frequency of symptoms (syncopal spells per month) within two risk groups (patients with less than six syncopal spells in their lifetime and patients with more than six syncopal spells in their lifetime.**

Tables 23 and 24 summarise the calculation of QALYs accruing over three years for each arm of the model.

**Table 23 Total QALYs for each arm of the submitted model over three years when ILR is used in the early setting**

| Health state | Proportion of patients in various health states (%) | Total QALYs | Weighted QALYs |
|---|---|---|---|
| **ILR arm** | | | |
| . Diagnosed with bradyarrhythmia, successfully treated with pacemaker | 8.9 | 2.6593 | |
| . Diagnosed with bradyarrhythmia, unsuccessfully treated with pacemaker | 0.5 | 1.9673 | |
| . Diagnosed with bradyarrhythmia, successfully treated with beta-blockers | 20.0 | 2.6593 | |
| . Diagnosed with bradyarrhythmia, unsuccessfully treated with beta blockers | 8.2 | 1.9673 | |
| . Diagnosed with tachycardia, successfully treated with flecainide after cardioversion | 7.1 | 2.6593 | |
| . Diagnosed with tachycardia, unsuccessfully treated with flecainide after cardioversion | 4.0 | 1.9673 | |
| . Undiagnosed | 51.4 | 1.9673 | |
| **Total:** | 100.0 | | **2.2161** |
| **ELR arm** | | | |
| . Diagnosed with bradyarrhythmia, successfully treated with pacemaker | 2.7 | 2.6593 | |
| . Diagnosed with bradyarrhythmia, unsuccessfully treated with pacemaker | 0.2 | 1.9673 | |
| . Diagnosed with bradyarrhythmia, successfully treated with beta-blockers | 6.1 | 2.6593 | |
| . Diagnosed with bradyarrhythmia, unsuccessfully treated with beta blockers | 2.5 | 1.9673 | |
| . Diagnosed with tachycardia, successfully treated with flecainide after cardioversion | 2.1 | 2.6593 | |
| . Diagnosed with tachycardia, unsuccessfully treated with flecainide after cardioversion | 1.2 | 1.9673 | |
| . Undiagnosed | 85.3 | 1.9673 | |
| **Total:** | 100.0 | | **2.0426** |

**Table 24 Total QALYs for each arm of the submitted model over three years when ILR is used in the late setting**

| Health state | Proportion of patients in various health states (%) | Total QALYs | Weighted QALYs |
|---|---|---|---|
| **ILR arm** | | | |
| . Diagnosed with bradyarrhythmia, successfully treated with pacemaker | 6.8 | 2.6593 | |
| . Diagnosed with bradyarrhythmia, unsuccessfully treated with pacemaker | 0.4 | 1.9673 | |
| . Diagnosed with bradyarrhythmia, successfully treated with beta-blockers | 15.3 | 2.6593 | |
| . Diagnosed with bradyarrhythmia, unsuccessfully treated with beta blockers | 6.2 | 1.9673 | |
| . Diagnosed with tachycardia, successfully treated with flecainide after cardioversion | 5.6 | 2.6593 | |
| . Diagnosed with tachycardia, unsuccessfully treated with flecainide after cardioversion | 3.1 | 1.9673 | |
| . Undiagnosed | 62.5 | 1.9673 | |
| **Total:** | 100.0 | | **2.1592** |
| **ELR arm** | | | |
| . Diagnosed with bradyarrhythmia, successfully treated with pacemaker | 0.0 | 2.6593 | |
| . Diagnosed with bradyarrhythmia, unsuccessfully treated with pacemaker | 0.0 | 1.9673 | |
| . Diagnosed with bradyarrhythmia, successfully treated with beta-blockers | 0.0 | 2.6593 | |
| . Diagnosed with bradyarrhythmia, unsuccessfully treated with beta blockers | 0.0 | 1.9673 | |
| . Diagnosed with tachycardia, successfully treated with flecainide after cardioversion | 0.0 | 2.6593 | |
| . Diagnosed with tachycardia, unsuccessfully treated with flecainide after cardioversion | 0.0 | 1.9673 | |
| . Undiagnosed | 100.0 | 1.9673 | |
| **Total:** | 100.0 | | **1.9673** |

### Results generated by submitted model

Results of the economic evaluations presented in the application are summarised in Table 25.

**Table 25 Summary of results of economic analyses presented in the application**

| Intervention | ILR | Comparator | Increment |
|---|---|---|---|
| **Early setting** | | | |
| . Costs | $9,147.77 | $4,749.71 | $4,398.06 |
| . Benefits | | | |
| Patients diagnosed | 48.57% | 14.71% | 33.86% |
| QALYs | 2.2161 QALYs | 2.0426 QALYs | 0.1735 QALYs |
| Incremental cost of ILR (over ELR plus tilt table testing in 50% of patients) per: | | | |
| . additional patient diagnosed | | | $12,989 |
| . additional QALY gained over 3 years | | | $25,349 |
| **Late setting** | | | |
| . Costs | $9,101.64 | $4,562.70 | $4,538.94 |
| . Benefits | | | |
| Patients diagnosed | 37.5% | 0.0% | 37.5% |
| QALYs | 2.1592 QALYs | 1.9673 QALYs | 0.1919 QALYs |
| Incremental cost of ILR (over standard care) per: | | | |
| . additional patient diagnosed | | | $12,104 |
| . additional QALY gained over 3 years | | | $23,652 |

## Revised analysis

A re-analysis was conducted, using the basic model presented in the Application and incorporating corrected costs and benefits as per the comments made above. Figure 7 summarises the structure of the model used for the re-analysis and Table 26 summarises the results of this re-analysis. Costs and benefits occurring in years 2 and 3 of the model are discounted at 5 per cent per annum.

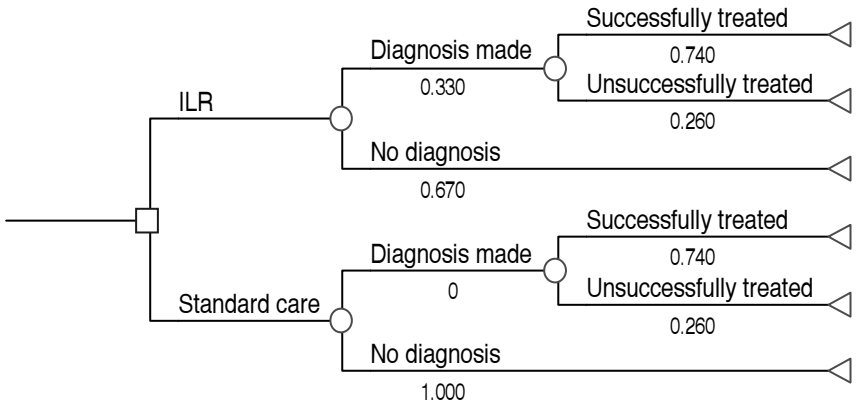



**Figure 7 Structure of model used to conduct re-analysis**

**Table 26 Results of revised economic analysis**

| Intervention | Increment |
|---|---|
| **Costs:** | |
| **Incremental costs from ILR** | |
| . Screening test (estimated assuming MBS item numbers 110 & 11718 provide equivalent services) | $150.50 |
| . Device (estimated from application) | $3,560.00 |
| . Implant procedure (estimated assuming: RVU of insertion of ILR is 4.17; RVU of insertion of pacemaker is 5.52; MBS fee (May 2003) for insertion of pacemaker (item 38281) is $207.10. | $156.45 |
| . Antibiotic cover (estimated assuming one course of cephalexin 500 mg, the most commonly prescribed antibiotic in 1999–2000 according to the Australian Statistics on Medicine, will be used. The price is according to the August 2003 PBS. | $11.22 |
| . 3 × follow-up visits (estimated assuming MBS item numbers 110 & 11718 provide equivalent services and assuming that follow up will be required approximately every 3 months during the implanted period) | $451.50 |
| . Treatment of adverse events (estimated assuming 2.3% of patients will have a local infection that will be treated with one course of cephalexin 500 mg. | $0.26 |
| . Explant procedure (estimated assuming procedure is equivalent to MBS item 30064 (removal of subcutaneous foreign body) | $89.10 |
| **Total incremental diagnostic costs:** | $4,419.03 |
| **Treatment costs** | |
| Assumptions: | |
| An additional 33% of patients achieve a diagnosis through use of ILR. | 0.33 × |
| For these additional patients diagnosed, it is assumed that 77% are diagnosed with bradyarrythmia and 23% are diagnosed with tachyarrhythmia (as per the application). | |
| . 25% of patients diagnosed with bradyarrhythima are assumed to be treated by insertion of pacemaker (which is costed by weighted private and public sector Round 5 DRG F17Z - $7,000) and 75% are assumed to be treated pharmacologically with an agent equivalent in cost to atenolol, 50 mg twice daily (costed at $236.76 pa as per August 2003 PBS). | 0.77 × (0.25 × $7,000 + 0.75 × $676.99 |
| . All patients with tachyarrhythmia are assumed to be treated by an anti-arrhythmic agent equivalent in cost to flecainide 100 mg bd (costed at $563.07 pa as per August 2003 PBS). | 0.23 × $1,610.05 |
| **Total incremental treatment costs**: | $695.90 |
| **Cost offsets** | |
| Cost offsets for successfully treated patients from avoidance of costs associated with treatment of injuries resulting from recurrent syncopal episodes are deducted. It is assumed that 74% of patients are successfully treated. It is assumed patients would have experienced, on average, 5.3 injuries from syncopal episodes evenly over 3 years (as per the application) and that 33% of these injuries would require hospitalisation (as per the application). This equates to 0.583 hospitalisations per successfully-treated patient per year. Costs of hospitalisation is estimated by taking weighted average public and private sector Round 5 DRGs X60A & X60B costs - $2,383. Thus, annual costs of hospitalisation are estimated at $1,389.30 per year. | 0.33 × 0.74 × 3972.55 |
| **Total incremental cost offsets** | –$970.10 |
| **Total incremental costs** | $4,144.83 |

**Table 26 (cont'd) Results of revised economic analysis**

| Intervention | Increment |
|---|---|
| **Benefits:** | |
| . Patients diagnosed: | 33% |
| Proportion of patients diagnosed who are successfully treated: | 74% |
| . If each successfully treated patients has a 0.132 utility gain each year, then a total of 0.377 discounted QALYs is gained by each successfully treated patient over 3 years. Thus, the average QALY gained per patient is: | 0.09 QALYs |
| Incremental cost of ILR (over standard care) over 3 years per: | |
| additional patient diagnosed | $12,560 |
| additional patient successfully treated | $16,973 |
| additional QALY gained | $44,969 |

## Sensitivity analyses

The results of a series of one-way sensitivity analyses are summarised in Table 27.

**Table 27 Results of one-way sensitivity analyses**

| Parameter changed (original value) | New value for parameter | New incremental cost of ILR per additional QALY gained Base case: $44,969 |
|---|---|---|
| Time horizon (3 years) | 5 years | $25,392 |
| % bradycardia/tachycardia (77%/23%) | 50%/50% | $44,343 |
| Additional proportion of patient diagnosed by ILR (33%) | 20% | $76,132 |
| Proportion of diagnosed patients who are successfully treated (74%) | 60% | $57,917 |
| Utility gain from successful treatment (0.132) | 0.242 | $23,555 |
| Excluding treatment costs and cost offsets | | $47,944 |

These analyses demonstrate that the estimates of incremental cost-effectiveness of ILR over standard care are most sensitive to the time horizon of the model (the longer the time horizon, the more favourable the cost-effectiveness), the incremental efficiency of ILR in diagnosing patients (the greater the incremental effectiveness, the more favourable the cost-effectiveness), the proportion of patients assumed to be successfully treated (the greater the proportion, the more favourable the cost-effectiveness), and the utility estimated to be gained by successfully treated patients (the greater the utility gain, the more favourable the cost-effectiveness). Treatment costs and cost offsets from reduced hospitalisation of successfully treated patients are approximately equivalent in the analysis. Thus, exclusion of these variables has only a marginal effect on the results of the analysis.

# Conclusions

## Safety

Evidence of the nature of adverse events associated with the use of the ILR was available in the literature, but estimates of the incidence of these events could not be determined due to the lack of large well-conducted studies. Adverse events associated with the use of the ILR were infection, reported in two to three per cent of patients, and pain, reported in one per cent of patients. These events resolved with explantation of the device and appropriate treatment.

## Effectiveness

Technical problems associated with use of the device were reported in case series and case reports. These technical difficulties included undersensing, problems with device interrogation, device migration, activator failure, false events and interference. Such technical events may interfere with the accurate capturing of syncopal episodes and interpretation of results.

Studies of the most appropriate design to determine the diagnostic characteristics of the ILR (such as sensitivity and specificity and related derivative characteristics) or the incremental effectiveness of the ILR on patient outcomes (such as recurrence of syncope, other morbidity, mortality or quality of life following diagnosis) were not identified. Evidence of the diagnostic yield of the ILR was extracted from two reports of one RCT and 16 case series. The RCT compared the diagnostic yield of a prolonged monitoring strategy with an ILR and conventional monitoring in 60 patients with recurrent unexplained syncope or a single episode of syncope that warranted cardiovascular investigation. Use of the ILR resulted in a greater number of patients being given a diagnosis compared to those assigned to conventional testing (47 per cent versus 20 per cent prior to crossover). However, the contribution of the longer follow up in the ILR strategy to this difference cannot be determined. Further limited evidence of the diagnostic yield of the ILR was provided from case series. Overall, the series reported recording of arrhythmias by the ILR device in 57–100 per cent of patients who activated the device during recurrence and recording of sinus rhythms in up to 60.3 per cent. However, the lack of comparison groups makes it difficult to determine diagnostic accuracy and the estimation of the incremental effectiveness of the ILR in the presence of prior investigations.

In addition to reporting the diagnostic yield of the ILR compared to conventional testing, the RCT provided evidence of the treatments patients received after a diagnosis was made. The trial also reported that resolution of symptoms occurred in almost all patients following the establishment of a diagnosis, but follow up was insufficient to determine if this effect was maintained in the longer term. As outcomes were not reported in patients whose cause of syncope was not diagnosed, the incremental effectiveness of the ILR compared to conventional monitoring could not be determined.

## Cost-effectiveness

An economic analysis was conducted that compared ILR with standard care (which is assumed to consist of no further ECG monitoring in the majority of patients) in patients with recurrent syncopal episodes occurring at intervals greater than a week apart in whom diagnosis has not been achieved through history, physical examination, monitoring of blood pressure and ECG, and who are determined to have either no structural heart disease or be at low risk of sudden cardiac death, and in whom ELR is inappropriate or has failed to elicit a diagnosis. The key results of the analysis were an incremental cost of ILR (over standard care) over three years per additional QALY gained of $44,969.

Sensitivity analyses demonstrate that the estimates are most sensitive to the time horizon of the model, the incremental efficiency of ILR in diagnosing patients, the proportion of patients successfully treated following diagnosis and the utility estimated to be gained by successfully treated patients. In sensitivity analyses the incremental cost per QALY ranged from $23,555 to $76,132.

# Recommendation

MSAC recommended that on the strength of evidence pertaining to the safety, effectiveness and cost-effectiveness of implantable loop recorder for unexplained recurrent syncope – Reveal Plus®, public funding should be supported for this procedure in patients with recurrent syncope who have had appropriate prior investigations.

The Minister for Health and Ageing accepted this recommendation on 24 June 2004.

# Appendix A MSAC terms of reference and membership

The MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and existing medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to the AHMAC.

The membership of the MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

| Member | Expertise or affiliation |
|---|---|
| Dr Stephen Blamey (Chair) | general surgery |
| Associate Professor John Atherton | cardiology |
| Professor Bruce Barraclough | general surgery |
| Professor Syd Bell | pathology |
| Dr Michael Cleary | emergency medicine |
| Dr Paul Craft | clinical epidemiology and oncology |
| Dr. Kwun Fong | thoracic medicine |
| Professor Jane Hall | health economics |
| Dr Terri Jackson | health economics |
| Ms Rebecca James | consumer health issues |
| Professor Brendon Kearney | health administration and planning |
| Associate Professor Richard King | internal medicine |
| Dr Ray Kirk | health research |
| Dr Michael Kitchener | nuclear medicine |
| Dr Ewa Piejko | general practice |
| Mrs Sheila Rimmer | consumer representative |
| Professor Jeffrey Robinson | obstetrics and gynaecology |

| | |
|---|---|
| Professor John Simes | clinical epidemiology and clinical trials |
| Professor Bryant Stokes | neurological surgery |
| Dr Doug Travis | urology |
| Professor Ken Thomson | radiology |

# Appendix B Advisory Panel

**Advisory Panel for MSAC application 1061 - Implantable loop recorder for unexplained syncope.**

| | |
|---|---|
| **Mr Lou McCallum** (Chair)<br>RN BSocSci<br>Consultant | Member of MSAC |
| **Dr John Hill**<br>MBBS, FRACP, DDU<br>Staff senior consultant Cardiologist and Electrophysiologist<br>Princess Alexandra Hospital, Brisbane | Nominated by the Cardiac Society of Australia and New Zealand |
| **Associate Professor Anthony C Keech**<br>MBBS, MScEpid, FRACP<br>Deputy Director, NHMRC Clinical Trials Centre<br>Academic Consultant Cardiologist<br>Royal Prince Alfred Hospital | Co-opted cardiologist |
| **Professor Richard King**<br>MBBS, FRACP<br>Programme Director Medicine<br>Southern Health | Member of MSAC |
| **Associate Professor Terry O'Brien**<br>MD FRACP<br>Royal Melbourne Hospital<br>Department of Medicine<br>University of Melbourne | Nominated by the Australian Association of Neurologists |

# Appendix C Internet sites searched

Agence d'évaluation des technologies et des modes d'intervention en santé (AÉTMIS). http://www.cets.gouv.qc.ca/en/index.htm [Accessed 19 February 2003].

Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES). http://www.anaes.fr/ANAES/anaesparametrage.nsf/HomePage?ReadForm [Accessed 19 February 2003].

Agency for Healthcare Research & Quality (AHRQ). http://www.ahrq.gov [Accessed 19 February 2003].

Alberta Heritage Foundation for Medical Research (AHFMR). http://www.ahfmr.ab.ca/index.html [Accessed 19 February 2003].

American College of Cardiology. http://www.acc.org [Accessed 19 February 2003].

American Heart Association (AHA). www.americanheart.org [Accessed 19 February 2003].

Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S). http://www.racs.edu.au/open/asernip-s.htm [Accessed 19 February 2003].

Canadian Coordinating Office for Health Technology Assessment (CCOHTA). http://www.ccohta.ca [Accessed 19 February 2003].

Cardiac Society of Australia and New Zealand. http://www.acc.org [Accessed 19 February 2003].

CardioSource. http://www.cardiosource.com/trials [Accessed 19 February 2003].

Center for Medical Technology Assessment (CMT). http://www.imt.liu.se/cmt [Accessed 19 February 2003].

CenterWatch Clinical Trials Listing Service. http://www.centerwatch.com [Accessed 19 February 2003].

Controlled Clinical Trials in Cardiovascular Medicine. http://cvm.controlled-trials.com [Accessed 19 February 2003].

Current Controlled Trials. http://www.controlled-trials.com [Accessed 19 February 2003].

Danish Institute for Health Services Research (DSI). http://www.dsi.dk [Accessed 19 February 2003].

Danish Institute for Health Technology Assessment (DIHTA). http://www.dihta.dk [Accessed 19 February 2003].

European Society of Cardiology. http://www.escardio.org/ [Accessed 19 February 2003].

Finnish Office for Health Technology Assessment (FinOHTA).
http://www.stakes.fi/finohta/e [Accessed 19 February 2003].

Institute of Technology Assessment of the Austrian Academy of Science (ITA).
http://www.oeaw.ac.at/ita/hta [Accessed 19 February 2003].

International Network of Agencies for Health Technology Assessment (INAHTA).
http://www.inahta.org [Accessed 19 February 2003].

Minnesota Health Technology Advisory Committee.
http://www.health.state.mn.us/htac [Accessed 19 February 2003].

National Co-ordinating Centre for Health Technology Assessment (NCCHTA).
http://www.hta.nhsweb.nhs.uk [Accessed 19 February 2003].

National Health & Medical Research Council of Australia Clinical Trials Centre.
http://www.ctc.usyd.edu.au [Accessed 19 February 2003].

National Heart Foundation of Australia. http://www.heartfoundation.com.au
[Accessed 19 February 2003].

National Horizon Scanning Centre (NHSC).
http://www.bham.ac.uk/PublicHealth/horizon [Accessed 19 February 2003].

National Institute for Clinical Excellence (NICE). http://www.nice.org.uk
[Accessed 19 February 2003].

National Research Register. http://www.update-software.com/National
[Accessed 19 February 2003].

New Zealand Health Technology Assessment (NZHTA). http://nzhta.chmeds.ac.nz
[Accessed 19 February 2003].

The Centre for Health Services and Policy Research (CHSPR). http://www.chspr.ubc.ca
[Accessed 19 February 2003].

The Norwegian Centre for Health Technology Assessment, SINTEF Unimed.
http://www.oslo.sintef.no/smm/News/FramesetNews.htm
[Accessed 19 February 2003].

The Swedish Council on Technology Assessment in Health care (SBU).
http://www.sbu.se/sbu-site/index.html
[Accessed 19 February 2003].

Veterans Affairs Technology Assessment Program (VATAP).
http://www.va.gov/resdev/ps/pshsrd/mdrc.htm#HealthCareTechnologyAssessment
[Accessed 19 February 2003].

# Appendix D Search Strategies

## Search terms: diagnostic accuracy

**Table D1 Diagnostic search strategy terms (Medline, Premedline, CINAHL and Biological Abstracts)**

| | |
|---|---|
| 1 | "sensitivity and specificity" |
| 2 | sensitivity.tw |
| 3 | di.fs |
| 4 | du.fs |
| 5 | specificity.tw |
| 6 | or/1-5 |
| 7 | reveal plus.mp |
| 8 | ILR$.mp |
| 9 | (record$ or monitor$).mp |
| 10 | insert$.mp |
| 11 | implant$.mp |
| 12 | intern$.mp |
| 13 | loop$.mp |
| 14 | or/10-12 |
| 15 | 14 and 9 and 13 |
| 16 | 15 or 7 or 8 |
| 17 | 16 and 6 |
| 18 | limit 17 to yr=2003 |

Glossary of terms:
.tw/textword = keyword in the text of the title, abstract or subject heading fields
.mp/textword = keyword in the text of the title, abstract or subject heading fields
/=MeSH- Medical Subject Headings, Medline's subject descriptors
$=truncation symbol to represent a series of letters at the end of a word segment
.fs/floating subheading=enables a search for the general trend of an article without designating any particular MeSH Subject Heading to which the subheading has to be attached
() nested terms to be searched together
and/or=Boolean operators "AND" and "OR"

**Table D2 Diagnostic search terms (EMBASE)**

| | |
|---|---|
| 1 | (reveal or (reveal and plus):dn |
| 2 | ilr* |
| 3 | ((record* or monitor*) and (insert* or implant* or intern*) and (loop)) |
| 4 | (('sensitivity and specificity':de) or sensitivity or specificity or ('diagnosis':de or (diagnostic and 'accuracy': de ))), between 1995 and 2003. |
| 5 | 1 and 2 and 3 and 4 |

*=truncation symbol to represent a maximum of 3 letters at the end of a word segment.
dn=device trade name
de=Drug/Medical index terms (EMTREE, Embase's subject descriptors)
() nested terms to be searched together
and/or=Boolean operators "AND" and "OR"

# Search terms: patient outcomes following diagnosis

**Table D3 Patient outcomes following diagnosis (Medline, Premedline, CINAHL and Biological Abstracts)**

| | |
|---|---|
| 1 | syncope/ |
| 2 | arrhythmia/ |
| 3 | bradycardia/ |
| 4 | tachycardia/ |
| 5 | bradyarrhythmia/ |
| 6 | tachyarrhythmia/ |
| 7 | or/1-6 |
| 8 | reveal plus.mp |
| 9 | ILR$.mp |
| 10 | (record$ or monitor$).mp |
| 11 | insert$.mp |
| 12 | implant$.mp |
| 13 | intern$.mp |
| 14 | loop$.mp |
| 15 | or/11-13 |
| 16 | 15 and 10 and 14 |
| 17 | 16 or 8 or 9 |
| 18 | 7 and 17 |

**Table D4 Patient outcomes following diagnosis search strategy (EMBASE)**

| | |
|---|---|
| 1 | ((reveal or (reveal plus)):dn or ilr* or ((record* or monitor*) and (insert* or implant* or intern*) and (loop))) and ((‘heart arrhythmia’:de) |
| 2 | between 1995 and 2003 |

# Search terms: safety

**Table D5 Safety search strategy (Medline, Premedline, CINAHL and Biological Abstracts)**

| | |
|---|---|
| 1 | Safety/ |
| 2 | Mortality/ |
| 3 | Morbidity/ |
| 4 | complicat$.mp |
| 5 | adver$.mp |
| 6 | side effect$.mp |
| 7 | co.xs |
| 8 | ae.xs |
| 9 | et.xs |
| 10 | or/1-9 |
| 11 | reveal plus.mp |
| 12 | ILR$.mp |
| 13 | (record$ or monitor$)mp |
| 14 | insert$.mp |
| 15 | implant$.mp |
| 16 | intern$.mp |
| 17 | loop$.mp |
| 18 | or/14-16 |
| 19 | 18 and 13 and 17 |
| 20 | 19 or 11 or 12 |
| 21 | 10 and 20 |

# Search terms: economics

**Table D6 Costs related to the intervention (Medline, Premedline, CINAHL and Biological Abstracts)**

| | |
|---|---|
| 1 | cost-benefit analysis/ |
| 2 | cost$.mp |
| 3 | price$.mp |
| 4 | pricing.mp |
| 5 | costs and cost analysis/ |
| 6 | economics/ |
| 7 | economic$.mp |
| 8 | (expenditure$ not energy).mp |
| 9 | (value adj 1 money).mp |
| 10 | budget$.mp or budgets/ |
| 11 | preference$.mp |
| 12 | Quality adjusted life years/ |
| 13 | qaly$.mp |
| 14 | og.xs |
| 15 | sn.xs |
| 16 | or/1-15 |
| 17 | reveal plus.mp |
| 18 | ILR$.mp |
| 19 | (record$ or monitor$)mp |
| 20 | insert$.mp |
| 21 | implant$.mp |
| 22 | intern$.mp |
| 23 | loop$.mp |
| 24 | or/20-22 |
| 25 | 24 and 19 and 23 |
| 26 | 25 or 17 and 18 |
| 27 | 16 and 26 |

**Table D7 Costs related to the intervention (Medline, Premedline, CINAHL and Biological Abstracts)**

| | |
|---|---|
| 1 | cost-benefit analysis/ |
| 2 | cost$.mp |
| 3 | price$.mp |
| 4 | pricing.mp |
| 5 | costs and cost analysis/ |
| 6 | economics/ |
| 7 | economic$.mp |
| 8 | (expenditure$ not energy).mp |
| 9 | (value adj 1 money).mp |
| 10 | budget$.mp or budgets/ |
| 11 | preference$.mp |
| 12 | Quality adjusted life years/ |
| 13 | qaly$.mp |
| 14 | or/1-13 |
| 15 | syncope |
| 16 | 14 and 15 |

# Search terms: key authors

**Table D8 Search terms for key authors (Medline)**

| | |
|---|---|
| 1 | Krahn A$.au |
| 2 | Kapoor W$.au |
| 3 | Linzer M$.au |
| 4 | Seidl K$.au |

# Appendix E Studies included in the review

## Studies assessing diagnostic accuracy

### Randomised controlled trials

Krahn, A.D., Klein, G.J., Yee, R. & Skanes, A.C. 2001a. 'Randomized assessment of syncope trial: Conventional diagnostic testing versus a prolonged monitoring strategy', *Circulation*, 104 (1), 46–51.

Krahn, A.D., Klein, G.J., Yee, R., Hoch, J.S. & Skanes, A.C. 2003a. 'Cost Implications of Testing Strategy in Patients with Syncope', *Journal of the American College of Cardiology*, 42 (3), 495–501.

### Case series

Armstrong, V.L., Lawson, J., Kamper, A.M., Newton, J. & Kenny, R.A. 2003. 'The use of an implantable loop recorder in the investigation of unexplained syncope in older people', *Age and Ageing*, 32 (2), 185–188.

Ashby, D.T., Cehic, D.A., Disney, P.J., Mahar, L.J. & Young, G.D. 2002. 'A retrospective case study to assess the value of the implantable loop recorder for the investigation of undiagnosed syncope', *Pacing & Clinical Electrophysiology*, 25 (8), 1200–1205.

Bloemers, B.L. & Sreeram, N. 2002. 'Implantable loop recorders in pediatric practice'. *Journal of Electrocardiology*, 35 (Suppl), 131–135.

Brignole M, Menozzi C, Moya A, Garcia-Civera R, Donateo P, Puggioni E, Migliorini R, Navarro X & International Study on Syncope of Uncertain Etiology I, 2002. 'Nonarrhythmic syncope documented by an implantable loop recorder (an ISSUE substudy)'. *American Journal of Cardiology.,* 90 (6), 654-7.

Donateo P, Brignole M, Menozzi C, Bottoni N, Alboni P, Dinelli M, Del Rosso A, Croci F, Oddone D, Solano A & Puggioni E, 2003. 'Mechanism of syncope in patients with positive adenosine triphosphate tests'. *Journal of the American College of Cardiology.,* 41 (1), 93-8.

Garcia-Civera R, Ruiz-Granell R, Morell-Cabedo S, Sanjuan-Manez R, Perez-Alcala F, Plancha E, Navarro A, Botella S & Llacer A, 2003. 'Selective use of diagnostic tests in patients with syncope of unknown cause'. *Journal of the American College of Cardiology,* 41 787-90.

Krahn AD, Klein GJ, Fitzpatrick A, Seidl K, Zaidi A, Skanes A & Yee R, 2002. 'Predicting the outcome of patients with unexplained syncope undergoing prolonged monitoring'. *Pacing & Clinical Electrophysiology.,* 25 (1), 37-41.

Krahn, A.D., Klein, G.J., Norris, C. & Yee, R. 1995. 'The etiology of syncope in patients with negative tilt table and electrophysiological testing', *Circulation*, 92 (7), 1819–1824.

Krahn, A.D., Klein, G.J., Yee, R. & Norris, C. 1998. 'Final results from a pilot study with an implantable loop recorder to determine the etiology of syncope in patients with negative noninvasive and invasive testing', *American Journal of Cardiology*, 82 (1), 117–119.

Krahn, A.D., Klein, G.J., Yee, R., Skanes, A.C. & The RI. 2001b. 'Predictive value of presyncope in patients monitored for assessment of syncope', *American Heart Journal*, 141 (5), 817–821.

Krahn, A.D., Klein, G.J., Yee, R., Takle-Newhouse, T. & Norris, C. 1999. 'Use of an extended monitoring strategy in patients with problematic syncope. Reveal Investigators', *Circulation*, 99 (3), 406–410.

Menozzi C, Brignole M, Garcia-Civera R, Moya A, Botto G, Tercedor L, Migliorini R, Navarro X & International Study on Syncope of Uncertain Etiology I, 2002. 'Mechanism of syncope in patients with heart disease and negative electrophysiologic test'. *Circulation.,* 105 (23), 2741-5.

Mieszczanska, H., Ibrahim, B. & Cohen, T.J. 2001. 'Initial clinical experience with implantable loop recorders', *Journal of Invasive Cardiology*, 13 (12), 802–804.

Moya A, Brignole M, Menozzi C, Garcia-Civera R, Tognarini S, Mont L, Botto G, Giada F, Cornacchia D & International Study on Syncope of Uncertain Etiology I, 2001. 'Mechanism of syncope in patients with isolated syncope and in patients with tilt-positive syncope'. *Circulation.,* 104 (11), 1261-7.

Nierop, P.R., van Mechelen, R., van Elsacker, A., Luijten, R.H. & Elhendy, A. 2000. 'Heart rhythm during syncope and presyncope: results of implantable loop recorders', *Pacing & Clinical Electrophysiology*, 23 (10 Pt 1), 1532–1538.

Seidl K, Rameken M, Breunung S, Senges J, Jung W, Andresen D, van Toor A, Krahn AD, Klein GJ & Reveal I, 2000. 'Diagnostic assessment of recurrent unexplained syncope with a new subcutaneously implantable loop recorder. Reveal-Investigators'. *Europace.,* 2 (3), 256-62.

## Patient outcomes following diagnosis

### Randomised controlled trials

Krahn, A.D., Klein, G.J., Yee, R. & Skanes, A.C. 2001a. 'Randomized assessment of syncope trial: conventional diagnostic testing versus a prolonged monitoring strategy.[comment]', *Circulation*, 104 (1), 46–51.

Krahn, A.D., Klein, G.J., Yee, R., Hoch, J.S. & Skanes, A.C. 2003a. 'Cost implications of testing strategy in patients with syncope', Journal of the American College of Cardiology, 42 (3), 495–501.

# Appendix F Summary of studies of effectiveness

**Table F1 Details of study design**

| Study | Study location | Study design | Dates of enrolment | Patient population | | |
|---|---|---|---|---|---|---|
| | | | | Sample size | No males (%) | Mean age years (SD) |
| Armstrong et al (2003) | The UK | Retrospective case series | Not reported | 15 | 2 (13.3) | 73 (range 61-89) |
| Ashby et al (2002) | Australia | Retrospective case series | Oct 1998 to Sep 2000 | 48 | 21 (43.75) | 70.6 (15.7) |
| Bloemers et al (2002) | The Netherlands | Retrospective case series | Not reported | 7 | 4 (57.1) | 12.8 (range 0.8 to 25.9) |
| Brignole et al (2001) | Italy and Spain | Case series, with sub-series comparison | Nov 1997 to Jul 2000 | 52 | 43 (82.6) | 71 (8) |
| Donateo et al (2003) | Italy | Case series, with sub-series comparison | Jan 1998 to Dec 2000 | ATP: 36<br>Control: 15 | ATP: 14 (38.8)<br>Control: 10 (66.7) | ATP: 69 (10)<br>Control: 61 (13) |
| Garcia-Civera et al (2003) | Spain | Case series, with sub-series comparison | Not reported | Group A: 72<br>Group B: 112 | Group A: 52 (72.2)<br>Group B: 61 (54.4) | Group A: 59 (14)<br>Group B: 51 (18) |
| Krahn et al (1995) | Canada | Case series | Sep 1992 to Sep 1994 | 16 | 12 (75.0) | 57 (19) |
| Krahn et al (1998) | Canada | Case series | Sep 1992 to Sep 1994 | 24 | 17 (70.8) | 59 (17) |
| Krahn et al (1999) | Canada | Case series | Not reported | 85 | 44 (51.7) | 59 (18) |
| Krahn et al (2001b) | Canada | Case series | Not reported | 85 | 44 (51.7) | 59 (18) |
| Menozzi (2002) | Italy | Case series | Mar 1998 to Nov 2002 | 35 | 31 (88.5) | 66 (13) |
| Mieszczanda et al (2001) | USA | Case series | Not reported | 12 | 6 (50.0) | 61 (22) |
| Moya et al (2001) | Italy and Spain | Case series, with sub-series comparison | Nov 1997 to Jul 2000 | Tilt –ve: 82<br>Tilt +ve: 29 | Tilt –ve 45 (54,8)<br>Tilt –ve 11 (37.9) | Tilt –ve: 63 (17)<br>Tilt +ve: 64 (15) |
| Nierop et al (2000) | The Netherlands | Case series | Feb 1997 to Sep 1999 | 35 | 15 (42.8) | 65 (17) |
| Seidl et al (2000) | Multicentre (Unclear) | Case series | Feb 1997 to Jan 1998 | 133 | 67 (50.3) | 56 |

[a]Unclear if standard error or standard deviation

**Table F2 Summary of patient characteristics**

| Study | Symptom (duration or frequency) | Co-morbidities n (%) | Clinical assessment before ILR | Entry criteria | Description of study endpoint |
|---|---|---|---|---|---|
| Armstrong et al (2003) | Mean (range) duration of symptoms prior to study (months): 48 (4-200) | Hypotension: 7 (47%)<br>History of ischemic heart disease: 5 (33%);<br>Previous cerebrovascular disease: 3 (20%) | Detailed history, full physical examination, resting 12 lead ECG, repeated morning orthostatic blood pressure measurement, erect and supine carotid sinus massage, passive head up tilt in the majority of cases and glyceryl trinitrate provocation tilt testing<br>All subjects had at least one 24 hour ECG | Inclusion: Case notes of consecutive patients over the age of 60 years who had implantation of Reveal for the investigation of syncope and unexplained falls | Unclear |
| Ashby et al (2002) | Not reported | Structural heart disease: 12 (25.8%) | History, physical examination and 12 lead ECG undertaken. At the discretion of the referring or implanting cardiologist patients also underwent echo-cardiography (68.8%), ELR (87.5%), electrophysiology study (52.1%), tilt table test (14.6%) or an electroencephalogram (6.3%). If these tests diagnosed the cause of syncope, patients were not included in the study | Inclusion: If patients were unable to be diagnosed with the tests under 'Clinical assessment prior to ILR' they were referred for further assessment and an ILR | Unclear |
| Bloemers et al (2002) | Not reported | Ebstein's anomaly: 1 (14.2%)<br>Transposition of great arteries: 2 (28.4%) | 12 lead ECG, echocardiogram and 24-hr Holter monitor (all patients), 4 week ambulatory Holter recording 3(43%), exercise test 4 (57%), electrophysiology study 3 (43%), diagnostic catheterisation 2 (29%) | Not reported | Symptomatic event |
| Brignole et al (2001) | Median (range) duration of syncope prior to study (years): 2 (1-3) | Structural heart disease: 28 (54%)<br>Bundle branch block: 52 (100%) | History, physical examination, baseline ECG, carotid sinus massage, echocardiogram, 24-hour ambulatory monitoring and electrophysiology study | Inclusion: All patients with any type of branch bundle block with QRS>100 ms, no documentation of II or III degree AV block, and a negative electrophysiology study | ILR-documented syncopal event |

**Table F2 (cont'd) Summary of patient characteristics**

| Study | Symptom (duration or frequency) | Co-morbidities n (%) | Clinical assessment before ILR | Entry criteria | Description of study endpoint |
|---|---|---|---|---|---|
| Donateo et al (2003) | Median (interquartile range) duration of syncope (years): 4 (2–10) | Structural heart disease: 10 (27.7%) Hypertensive: 8 Ischemic: 1 Congenital: 1 | History, physical examination, baseline ECG, carotid sinus massage and 24-hour ambulatory monitoring and tilt testing<br>Other tests as required | Inclusion ATP group: Patients were considered eligible if they were >40 years old, had previously had three or more syncopal episodes with an interval of >6 months between the first and last episode, and had a clinical presentation severe enough because of a high number of spells or high risk to require treatment, if any was available<br>Inclusion control group: Consecutive patients who had a negative ATP and tilt tests who had received an ILR for the diagnostic at the same period of recruitment as the ATP group | Analysis of the ECG tracing obtained during the first syncopal episode that was correctly recorded by the device |
| Garcia-Civera et al (2003) | Mean (SD) number of syncopal episodes in the previous year<br>Group A: 4.6 (7)<br>Group B: 3.9 (9) | Group A: Structural heart disease: 35 (48.6%) Heart failure: 8 (11.1%) Family history of sudden death: 1 (1.4%) | History, physical examination, ECG, a carotid sinus massage, postural blood pressure testing, and 24-hour ambulatory monitoring<br>Other tests as required | Group A: the presence of structural heart disease or family history of sudden death, an abnormal ECG, significant non-symptomatic arrhythmia on Holter monitoring (sinus pause >2 s, second degree atrioventricular block, asymptomatic supraventricular or ventricular tachycardia) and paroxysmal palpitations before or immediately after the episode of syncope<br>Group B: not reported | Diagnosis of cause of syncope |

**Table F2 (cont'd) Summary of patient characteristics**

| Study | Symptom (duration or frequency) | Co-morbidities n (%) | Clinical assessment before ILR | Entry criteria | Description of study endpoint |
|---|---|---|---|---|---|
| Krahn et al (1995) | Mean (SD) number of episodes of syncope in the previous year: 8.7 (6.1) | Angina 2 (12.5%)<br>Hypertension 1 (6.25%)<br>Previous cardiac transplant 1 (6.25%)<br>Hypertrophic cardiomyopathy 1 (6.25%)<br>Myocardial infarction 3 (18.75%)<br>Previous slow pathway ablation 1 (6.25%) | Patients underwent a minimum of 48 hours of ambulatory monitoring and TOE or radionuclide ventriculography. An exercise test or neurological investigations were also performed in selected cases. If these tests were negative electrophysiology testing were performed. | Inclusion: Patients with recurrent unexplained syncope referred to University Hospital between September 1992 and September 1994 who had negative non-invasive investigations and negative tilt table testing and electrophysiology studies were asked to participate in the trial.<br><br>Exclusion: Patients were not included in this study if only had presyncope. | Diagnosis of syncopal events |
| Krahn et al (1998) | Mean (SD) number of episodes of syncope in the previous year: 7.2 (5.4) | Structural heart disease 11 (46%)<br>Previous cardiac transplant 1 (4)<br>Coronary artery disease 6 (25%)<br>Hypertrophic cardiomyopathy 1 (4)<br>Hypertension 2 (8%)<br>Mitral stenosis 1 (2%) | Patients underwent a minimum of 48 hours of ambulatory monitoring and TOE or radionuclide ventriculography. An exercise test and neurological investigations were performed in selected cases. If these tests were negative, electrophysiology testing was performed | Inclusion: Patients with recurrent unexplained syncope referred to University Hospital between Sep 1992 and Sep 1994 who had negative non-invasive investigations and negative tilt table testing and electrophysiology studies were asked to participate in the trial (From Krahn 1995)<br>Exclusion: Patients who had presyncope | Diagnosis of syncopal events |
| Krahn et al (1999) | Mean (SD) duration of syncope (years): 5.5 (8.9)<br>Mean (SD) frequency of syncopal spells in the previous year: 5.1 (5.5) | Cardiovascular disease: 53 (62) | History, physical examination, ECG, 24-hour ambulatory monitoring and a Holter monitor. At the discretion of the investigator, patients had an ECG: 70<br>Head up tilt test: 49<br>Electrophysiology study: 43<br>ELR: 24 | Inclusion: Patients were eligible if they had had more than 2 episodes in the previous year or a single episode in addition to a history of presyncope<br>Exclusion: Patients who were unlikely to survive a year, were unable to give informed consent, had a previously implanted device, were pregnant or women of a childbearing potential not on a reliable form of contraception | Cause of syncope |

**Table F2 (cont'd) Summary of patient characteristics**

| Study | Symptom (duration or frequency) | Co-morbidities n (%) | Clinical assessment before ILR | Entry criteria | Description of study endpoint |
|---|---|---|---|---|---|
| Krahn et al (2001b) | Mean (SD) duration of syncope (years): 5.5 (8.9)<br>Mean (SD) frequency of syncopal spells in the previous year: 5.1 (5.5) | Cardiovascular disease: 53 (62%) | History, physical examination, ECG, 24-hour ambulatory monitoring and a Holter monitor<br>ECG at the discretion of the investigator :70<br>Head up tilt test: 49<br>Electrophysiology study: 43<br>ELR: 24 | Inclusion: Patients were eligible if they had had more than 2 episodes in the previous year or a single episode in addition to a history of presyncope<br>Exclusion: Patients who were unlikely to survive a year, were unable to give informed consent, had a previously implanted device, were pregnant or women of a childbearing potential not on a reliable form of contraception | Cause of syncope |
| Krahn et al (2002) | Median number of previous syncopal events: 4 | Structural heart disease: 68 (33%) | Not applied to all patients<br>Previous tilt table test: 63<br>Previous electrophysiology study: 46 | Not reported | Investigation of recurrent syncope |
| Menozzi et al (2002) | Median duration (interquartile range) of syncope, years: 1 (1–3) | Structural heart disease (100%) | Physical examination, baseline ECG, carotid sinus massage, echocardiogram, 24-hour ambulatory monitoring and complete electrophysiology study | Inclusion: All patients with heart disease at overt risk of ventricular arrhythmia, because these were patients with previous myocardial infarction or cardiomyopathy with depressed left ventricular ejection fraction or non-sustained ventricular tachycardia in whom an electrophysiologic study did not induce monomorphic ventricular tachycardia, with the exception of the patients with bundle branch block who were evaluated separately | Analysis of the electro-graphic tracing obtained during the first syncopal episode that was correctly recorded by the device |

**Table F2 (cont'd) Summary of patient characteristics**

| Study | Symptom (duration or frequency) | Co-morbidities n (%) | Clinical assessment before ILR | Entry criteria | Description of study endpoint |
|---|---|---|---|---|---|
| Mieszczanda et al (2001) | Mean (SD) number of episodes prior to ILR implantation: 6.0 (5.4) | Coronary artery disease: 3 (25%)<br>Dilated cardiomyopathy: 2 (17%) | Tilt table test, electrophysiology study and neurologic work up | Not reported | Not reported |
| Moya et al (2001) | Median duration (range) of syncope, years :<br>Tilt –ve: 4 (2–6)<br>Tilt +ve: 3 (2–10) | Any structural heart disease<br>Tilt +ve: 9 (31%)<br>Ischemic 4 (44.4)<br>Valvular 1 (11.1)<br>Hypertensive: 4 (44.4%)<br>Tilt –ve: 26 (31.7%)<br>Ischemic: 7 (26.9%)<br>Valvular: 5 (19.2%);<br>Hypertensive 12 (46.2%)<br>Other: 2 (7.7%) | History, physical examination, baseline ECG, carotid sinus massage, echocardiogram, and 24-hour ambulatory monitoring and tilt testing<br>Any other test(s) necessary for the diagnosis of syncope | Inclusion (Both groups): Patients who had had ≥3 syncopal episodes in the previous 2 years with an interval between the first and the last episode of 6 months | Analysis of the electro-graphic tracing obtained during the first syncopal episode that was correctly recorded by the device |

**Table F2 (cont'd) Summary of patient characteristics**

| Study | Symptom (duration or frequency) | Co-morbidities n (%) | Clinical assessment before ILR | Entry criteria | Description of study endpoint |
|---|---|---|---|---|---|
| Nierop et al (2000) | Mean (SD) number, of syncopal episodes in the past 12 months: 5.2 (3.3) | Previous myocardial infarction: 2 (6%) Hypertrophic cardiomyopathy: 1 (3%); Bifascicular block: 10 (29%) | History, physical examination, 12-lead ECG, echocardiography, routine lab investigation, 24-hour ambulatory ECG recording and assessment of LV ejection fraction by means of a radionuclide technique | Inclusion: Patients who had had 2 or more witnessed episodes of syncope of unknown origin within the previous 12 months or one episode of syncope with significant trauma<br>Exclusion: Previous myocardial infarction with an ejection fraction < 0.40, dilated or hypertrophic cardiomyopathy, non-sustained ventricular tachycardia of more than 16 beats on the Holter recording, aortic valvular disease, significant left ventricular outflow obstructions on the echocardiogram, proven orthostatic hypotension, explicit vasovagal syncope, and hypertensive carotid sinus syndrome. Elderly patients (>80 years) using more than three cardioactive drugs and patients with dementia or Alzheimer's disease | Not reported |
| Seidl et al (2000) | Mean (SD) number of episodes of syncope in the year prior to study: 6.3 (10.6) Years (SD) of symptoms before study: 5.7 (8.9) | Concomitant cardiovascular disease: 53 (40%) Unknown disease: 23 (17%) | Resting ECG, ambulatory monitoring or in-hospital monitoring and echocardiography at investigator's discretion<br>ELR: 19 (14%) Tilt table testing 63 (47%) Electrophysiology studies: 72 (54%) | Inclusion: Patients were included in the study if they were referred to participating centres between Feb 1997 and Jan 1998 | A correlation of symptoms and cardiac rhythm |

**Table F3 Device characteristics of included studies of ILR**

| Study | Version of device used | Programming | Electrogram sensing undertaken | Device placement n (%) |
|---|---|---|---|---|
| Armstrong et al (2003) | Reveal® | Not reported | Not reported | Not reported |
| Ashby et al (2002) | Reveal® | All patients had the rhythm recorded 40 minutes prior and minutes after activation | Yes | Left intraclavicular region |
| Bloemers et al (2002) | Reveal® /Reveal® plus | Varied from a possible 1 patient activated event to 13 or 14 auto-activated events to 3 patient activated events and 5-6 auto-activated events | Not reported | Subcutaneously in the left chest region 6 (85.7)<br>(youngest patient) abdominal region 1 (14.3) |
| Brignole et al (2001) | Reveal® | 1 event, 21 minute preactivation, and 1 minute postactivation | Not reported | Not reported |
| Donateo et al (2003) | Reveal® | 1 event, 21 minute preactivation, and 1 minute postactivation | Not reported | Not reported |
| Garcia-Civera et al (2003) | Reveal® | Not reported | Not reported | Not reported |
| Krahn et al (1995) | Prototype | Not reported | Yes | Left pectoral region |
| Krahn et al (1998) | Prototype | Not reported | Yes | Left pectoral region |
| Krahn et al (1999) | Reveal® | Not reported | Yes | Left pectoral region 54 (63.6); Left intramammary 27 (31.7); Left intercostal 2 (2.35); Right parasternal 2 (2.35) |
| Krahn et al (2001b) | Reveal® | Not reported | Yes | Left pectoral region 54 (63.6); Left intramammary 27 (31.7); Left intercostal 2 (2.35); Right parasternal 2 (2.35) |
| Krahn et al (2002) | Various (unclear) | Not reported | Not reported | Not reported |
| Menozzi et al (2002) | Reveal® | 1 event, 21 minute preactivation, and 1 minute postactivation | Not reported | Not reported |
| Mieszczanda et al (2001) | 10 (83) Reveal®<br>2 (17) Reveal® plus | Not reported | Not reported | Unclear |
| Moya et al (2001) | Reveal® | 1 event, 21 minute preactivation, and 1 minute postactivation | Not reported | Not reported |
| Nierop et al (2000) | Reveal® | Not reported | Not reported | In the majority of patients the device was implanted in the left intraclavicular region. In young female patients a left submammary implant was performed by a plastic surgeon in the operating room |
| Seidl et al (2000) | Reveal® | At the discretion of the implanting physician | Only in a subset of 8 patients | Left pectoral region 87 (66), Left submammary 40 (30) and parasternal 3 (2) and intercostal regions 3 (2) |

**Table F4 Validity of included studies**

| Study | Consecutive patients enrolled | Prospective or Retrospective design | Explicit description of patients | Explicit Inclusion/Exclusion criteria | Patients entered with similar baseline characteristics | All patients included | Outcomes assessed objectively | Blinded assessment of outcome | For subseries, description of series & prognostic factors |
|---|---|---|---|---|---|---|---|---|---|
| Armstrong et al (2003) | Yes | Retrospective | Yes | Inclusion–Yes<br>Exclusion–Not reported | No | Yes | Yes | Not reported | NA |
| Ashby et al (2002) | Not reported | Retrospective | Unclear | No | Unclear | Unclear | Not reported | Not reported | NA |
| Bloemers et al (2002) | Not reported | Retrospective | Yes | Not reported | No | Unclear | Unclear | Not reported | NA |
| Brignole et al (2001) | Not reported | Prospective | Yes | Yes | Unclear | Unclear | Unclear | Not reported | NA |
| Donateo et al (2003) | Yes | Prospective | Yes | Yes | No | Yes | Unclear | Not reported | NA |
| Garcia-Civera et al (2003) | Yes | Prospective | Yes | Yes | Yes | Yes | Unclear | Not reported | NA |
| Krahn et al (1995) | Not reported | Prospective | Yes | Yes | No | Unclear | Unclear | Not reported | NA |
| Krahn et al (1998) | Not reported | Prospective | Yes | Yes | No | Unclear | Unclear | Not reported | NA |
| Krahn et al (1999) | Not reported | Prospective | Yes | Yes | No | Unclear | Unclear | Not reported | NA |
| Krahn et al (2001b) | Not reported | Prospective | Yes | Yes | No | Unclear | Unclear | Not reported | NA |
| Krahn et al (2002) | Not reported | Prospective | Unclear | Not reported | Not reported | Unclear | Unclear | Not reported | NA |
| Menozzi et al (2002) | Not reported | Prospective | Yes | Inclusion–Yes<br>Exclusion–Not reported | Yes | Unclear | Yes | Not reported | NA |
| Mieszczanda et al (2001) | Not reported | Prospective | Yes | Not reported | No | Unclear | Unclear | Not reported | NA |
| Moya et al (2001) | Not reported | Prospective | Yes | Inclusion–Yes<br>Exclusion–Not reported | No | Unclear | Yes | Not reported | Yes |
| Nierop et al (2000) | Yes | Prospective | Yes | Yes | Unclear | Yes | Unclear | Not reported | NA |
| Seidl et al (2000) | Not reported | Prospective | Unclear | Unclear | No | Unclear | Unclear | Not reported | NA |

Abbreviations: NA, not applicable

**Table F5 Results of included studies**

| Study | Sample size | Follow up Mean (SD) months | Time to recurrence or activation Mean (SD) months | Number with recurrence | Number with event recorded at time of recurrence | Proportion with arrhythmia during recording n (%) | Proportion with sinus rhythm during recording | Proportion with other diagnosis during recording | No diagnosis |
|---|---|---|---|---|---|---|---|---|---|
| Armstrong et al (2003) | 15 | 5 | Range, weeks until recurrence of syncope: (range 1–58) | Not reported | 7 | 4 (57.1)<br>Bradycardia: 3<br>Ventricular tachycardia: 1 | 3 (42.8) | 0 | 11 (73.3%) |
| Ashby et al (2002) | 48 | 5.6 (5.7) | 2.8 (2.1) Syncope or presyncope | 25 | 25 | 10 (40.0)<br>Bradycardia: 7, treated with pacemaker<br>Tachycardia: 3, Treated with AVN blocking drugs | 15 (60.0)<br>Epileptic seizure: 2<br>Vertigo: 1<br>Current pulmonary embolism: 1<br>Non-cardiac syncope diagnosed: 11 | 0 | 23 (47.9%)<br>No recurrence of symptoms during study period |
| Bloemers et al (2002) | 7 | Mean (range): 7.5 (3–16) | Mean (range): 8 (2–14 ) | 4 | 4 | 4 (1)<br>Sinus tachycardia: 1 (Munchausen's by proxy)<br>Supraventricular tachyarrhythmia: 1, treated with ablation<br>Sustained monomorphic ventricular tachycardia: 1;to be treated with ablation<br>Asystole >3 seconds: 1, treated with pacemaker | 0 (0.0) | 0 | 3 (42.8%)<br>No recurrence of symptoms during study period |
| Brignole et al (2001) | 52 | Minimum follow up; 3 | Median (interquartile range) days: 48 (16–100) | 19 | 19 | Sinus tachycardia 1(5.2)<br>One or more prolonged asystolic pauses 17 | 1 (5.2) | 0 | 33 (63.4%) |

**Table F5 (cont'd) Results of included studies**

| Study | Sample size | Follow up Mean (SD) months | Time to recurrence or activation Mean (SD) months | Number with recurrence | Number with event recorded at time of recurrence | Proportion with arrhythmia during recording | Proportion with sinus rhythm during recording | Proportion with other diagnosis during recording | No diagnosis |
|---|---|---|---|---|---|---|---|---|---|
| Donateo et al (2003) | 36 | ATP positive group: 18 (9)<br>ATP negative group: 16 (9) | ATP positive group: Median (interquartile range): 9 (3–13)<br>ATP negative group: Not reported | ATP positive group: 18<br>ATP negative group: Not reported | ATP positive group: 16<br>ATP negative group: 9 | ATP positive group: 16<br>Tilt negative: AV block: 3, Sinus arrest: 1, Tachycardia: 2<br>Tilt positive: Sinus arrest 5, Sinus bradycardia: 2, Tachycardia: 1<br>ATP negative group: AV block: 1, Sinus arrest :4, Sinus bradycardia: 1, Tachycardia: 1<br>Treatments included pacemaker therapy: 7<br>Transcatheter ablation: 1<br>Authors did not report which patients received these therapies and no other therapies were given | ATP positive group: 0<br>Tilt negative : 2<br>ATP negative group: :2 | ATP positive group: 0<br>Tilt negative: 1<br>Rapid atrial fibrillation thought to be epilepsy, treated with anti-epileptic drugs | ATP positive group: 20<br>No recurrence in symptoms: 18<br>Unable to activate device: 2<br>ATP negative group:<br>No outcome reported: 6<br>No recurrence of symptoms: 2 |
| Garcia-Civera et al (2003) | Group A: 72, sub-group of 15 received ILR<br>Group B: 112 | Subgroup of group A: 7.8 (4.7) | 81.3 (96.4) days | 8/15 | 8 | 7<br>Paroxysmal AV block: 3 (with intraventricular conduction defect)<br>Sinus arrest: 2<br>Polymorphic ventricular tachycardia: 2 | 1 | 0 | 1 (Patient with sinus rhythm) |

**Table F5 (cont'd) Results of included studies**

| Study | Sample size | Follow up Mean (SD) months | Time to recurrence or activation Mean (SD) months | Number with recurrence | Number with event recorded at time of recurrence | Proportion with arrhythmia during recording | Proportion with sinus rhythm during recording | Proportion with other diagnosis during recording | No diagnosis |
|---|---|---|---|---|---|---|---|---|---|
| Krahn et al (1995) | 16 | Not reported | 4.4 (4.2) months | 15/16 | 15 | 9 (60.0)<br>Bradycardia: 7, treated by pacemaker implantation<br>Tachyarrhythmia: 2<br>Sustained ventricular tachycardia: 1, treated by sotalol<br>AV node re-entrant tachycardia: 1, treated by AV node modification | 6 (40.0)<br>Vasodepressor syncope: 2<br>+ve tilt test: 1, treated with β blockers<br>Hemodynamic obstruction: 1, treated with β blocker, no recurrence of symptoms<br>Cause of syncope not reported: 1, treated with psychotherapy<br>Syncope with seizure like activity and normal HR 1, undergoing neurological evaluation | 0 | 1 (6.2) no recurrence in symptoms, follow up continues |

**Table F5 (cont'd) Results of included studies**

| Study | Sample size | Follow up Mean (SD) months | Time to recurrence or activation Mean (SD) months | Number with recurrence | Number with event recorded at time of recurrence | Proportion with arrhythmia during recording | Proportion with sinus rhythm during recording | Proportion with other diagnosis during recording | No diagnosis |
|---|---|---|---|---|---|---|---|---|---|
| Krahn et al (1998) | 24 | Not reported | 5.1 (4.8) | 21 | 21 | 11 (52.3)<br>Bradycardia: 9<br>Non-sustained ventricular tachycardia: 1<br>Sustained ventricular node re-entrant tachycardia: 1 | 10 (47.6)<br>Suspected vasodepressor syncope HR>40 bpm: 5<br>Hypertrophic cardiomyopathy with sinus tachycardia: 1<br>Psychogenic syncope: 1 | 0 | 3 (12.5) no symptom recurrence during study period. Device removed, no further symptoms<br>Infrequent presyncopal episodes associated with sinus tachycardia: 1 |
| Krahn et al (2001b) | 85 | 12 months | 2.9 (3.6) months | 62 | 53<br>Syncope: 12<br>Syncope + presyncope: 16<br>Presyncope: 25 | 21 (39.6)<br>Bradycardia: 18 of whom 13 (72.7) treated with pacemaker<br>Diagnosed as neurally mediated syncope: 6<br>Tachycardia: 3 | 32 (60.3) | 0 | 9 (10.5) had recurrence but failed to activate device.<br>Completed 1 year of follow up and had device removed after no recurrence: 17<br>Died before diagnosis: 3<br>Lost to follow up before diagnosis: 2<br>Early device removal required before diagnosis: 2 |

**Table F5 (cont'd) Results of included studies**

| Study | Sample size | Follow up Mean (SD) months | Time to recurrence or activation Mean (SD) months | Number with recurrence | Number with event recorded at time of recurrence | Proportion with arrhythmia during recording | Proportion with sinus rhythm during recording | Proportion with other diagnosis during recording | No diagnosis |
|---|---|---|---|---|---|---|---|---|---|
| Krahn et al (2002) | 206 | At least 6 months | Not reported | 142 | 132 | Bradycardia: 35 (26.5) treated with pacemaker implantation<br>Tachycardia: 12<br>Supraventricular tachycardia: 5<br>Atrial fibrillation | 63 (47.7)<br>Neurally mediated syncope: 22 | 0 | Symptoms resolved, no diagnosis: 64 (30.5)<br>No recurrence of symptoms: 64<br>Failed to activate device: 10 |
| Menozzi et al (2002) | 35 | 16 (11) months | 6 (5) months | Syncope: 6 (17.1%)<br>Presyncope: 13 (37.1%) | Syncope: 6<br>Presyncope: 8 | AV block and asystole: 1<br>Atrial fibrillation and asystole: 1<br>Sinus arrest: 1<br>Sinus tachycardia: 1<br>Rapid atrial fibrillation: 2<br>Sustained ventricular tachycardia: 1<br>Paroxysmal atrial fibrillation or atrial tachycardia: 1<br>Post tachycardia pause: 1<br>Sinus tachycardia: 1 | 0<br>No rhythm variations: 4 | 0 | No recurrence of symptoms: 16 (45.7)<br>No rhythm variations: 4 (presyncope) No diagnosis reported |

**Table F5 (cont'd) Results of included studies**

| Study | Sample size | Follow up Mean (SD) months | Time to recurrence or activation Mean (SD) months | Number with recurrence | Number with event recorded at time of recurrence | Proportion with arrhythmia during recording | Proportion with sinus rhythm during recording | Proportion with other diagnosis during recording | No diagnosis |
|---|---|---|---|---|---|---|---|---|---|
| Mieszczanda et al (2001) | 12 | 7.2 (5.8) months<br>(Range 1 day to 18 months) | Not reported | 8 | 7 | 30 seconds asystole: 1<br>20 seconds asystole: 1<br>6 seconds asystole: 1<br>Junctional bradycardia 40/minute: 1 | Epilepsy: 1 (14.2) | 0 | 7 (58.3)<br>No recurrence of symptoms: 4<br>Unable t o make diagnosis: 2<br>Patient failed to activate device at time of symptom recurrence: 1<br>Patient unavailable for follow up: 1 (unclear which version of the device used) |

**Table F5 (cont'd) Results of included studies**

| Study | Sample size | Follow up Mean (SD) months | Time to recurrence or activation Mean (SD) months | Number with recurrence | Number with event recorded at time of recurrence | Proportion with arrhythmia during recording | Proportion with sinus rhythm during recording | Proportion with other diagnosis during recording | No diagnosis |
|---|---|---|---|---|---|---|---|---|---|
| Moya et al (2001) | 111<br>Tilt –ve: 82<br>Tilt +ve: 29 | Tilt –ve: 9(5)<br>Tilt +ve: 10(5) months | Median, range (days)<br>Tilt –ve: 105 (47–226)<br>Tilt +ve: 59 (22–98) | Tilt –ve: 28<br>Tilt +ve: 10 | Tilt –ve: 24<br>Tilt +ve: 8 | Tilt –ve<br>Syncope:<br>Asystolic pause: 11<br>Asystole type: sinus arrest/AV block: 9/2<br>Bradycardia <40bpm: 2<br>Sinus tachycardia: 1<br>Atrial tachycardia: 1<br>Treatment by permanent pacemaker: 10<br>Presyncope:<br>19 patients/20 episodes<br>Relative bradycardia: 4<br>Paroxysmal supraventricular tachycardia: 4<br>Sinus tachycardia: 4<br>Tilt +ve<br>Syncope:<br>Asystolic pause 5; Asystole type AV block 5; Bradycardia <40bpm: 1; Treatment by permanent pacemaker 4<br>Presyncope:<br>7 patients/13 episodes<br>Relative bradycardia: 2<br>Paroxysmal supraventricular tachycardia: 5<br>Treatment by implantable defibrillator: 1<br>Treatment by catheter ablation of atrial tachycardia: 1 (Authors did not report to which groups these 2 patients belonged) | Tilt –ve:<br>Syncope: 9<br>Presyncope: 8 episodes<br>Tilt +ve:<br>Syncope: 2<br>Presyncope: 6 episodes | 0 | Tilt –ve:<br>Unable to activate device: 2<br>No outcomes reported: 37<br>Tilt +ve:<br>Unable to activate device: 2<br>No outcomes reported: 12 |

**Table F5 (cont'd) Results of included studies**

| Study | Sample size | Follow up Mean (SD) months | Time to recurrence or activation Mean (SD) months | Number with recurrence | Number with event recorded at time of recurrence | Proportion with arrhythmia during recording | Proportion with sinus rhythm during recording | Proportion with other diagnosis during recording | No diagnosis |
|---|---|---|---|---|---|---|---|---|---|
| Nierop et al (2000) | 35 | 11 (8.3) months<br>1 week after ILR implantation then 3-monthly outpatient visits | Range 1–11 months | 24 | 20 (57)b<br>Syncope: 10<br>Syncope + presyncope: 4<br>Presyncope: 6 | 10 (50.0)<br>Tachycardia: 6, 2/6 treated with radiofrequency ablation after further testing using electrophysiology<br>Bradycardia: 4 (then had +ve tilt table test and treated with pacemaker) | 10 (50.0) | 0 | No symptom recurrence: 11 (31.4).<br>4 patients non-compliant, 3/4 died during follow up |
| Seidl et al (2000) | 133 | 10.8 (4.3) months | Not reported | 83 (62)b | 72 | 32 (44.4)<br>Bradycardia: 21 6/21 slowing heart rate which was interpreted as the cardioinhibitory component of neurally mediated syncope<br>Tachycardia: 8<br>AV nodal re-entry tachycardia treated with AV node modification (1/8)<br>Supraventricular tachycardia treated with antiarrhythmic drugs 5/8<br>Self terminating torsade-de-points tachycardia treated with high dose beta-blocker therapy1/8<br>Pacemaker dysfunction: 1, treated by replacing pacemaker 1/1<br>Ventricular premature beats: 2, treated with anti-arrhythmic drugs 2/2 | 0 | 40 (55.6)<br>Non-arrhythmic referred to other non-cardiac specialists<br>Rhythm at time of event not reported | No diagnosis 50 (37.5)<br>No events and continue to be followed: 41<br>Failed activation: 11 |

[b] Note that result is for both syncope and presyncope

# Appendix G Studies excluded from review

## Accuracy

### Case reports


Berger, T., Roithinger, F.X. & Hintringer, F. 2002. 'Images in cardiology: Diagnosis of a rare cause of arrhythmogenic syncope by means of an implantable loop recorder', *Heart*, 88 (1), 10.

Chrysostomakis, S.I., Simantirakis, E.N., Marketou, M.E. & Vardas, P.E. 2002. 'Implantable loop recorder undersensing mimicking complete heart block', *Europace*, 4 (2), 211–213.

Chugh, A., Aboufakher, R., Riba, A. & Knight, B. 2002. 'Recurrent syncope in a patient with an implantable loop recorder: what is the diagnosis?', *Journal of Cardiovascular Electrophysiology*, 13 (11,) 1176–1177.

Cohen, T.J., Ibrahim, B. & Sassower, M.J. 2000. 'Revealing data retrieved from an implantable loop recorder', *Journal of Invasive Cardiology*, 12 (3), 174–175.

Futterman, L.G. & Lemberg, L. 2000. 'A novel device in evaluating syncope', *American Journal of Critical Care*, 9 (4), 288–293.

Gimbel, J.R. & Wilkoff, B.L. 2003. 'Artefact mimicking tachycardia during magnetic resonance imaging in a patient with an implantable loop recorder', *Heart*, 89 (3), e10.

Gorenek B, Kudaiberdieva G, Cavusoglu Y, Goktekin O, Ata N, Unalir A, Birdane A & Timuralp B, 2001. 'Implantable event loop recorder prevents misdiagnosis of underlying arrhythmia in patients with unexplained palpitations--a case report'. *Angiology.*, 52 (11), 781-4.

Hadian, D., Lowe, M.R., Scott, L.R. & Groh, W.J. 2002. 'Use of an insertable loop recorder in a myotonic dystrophy patient', *Journal of Cardiovascular Electrophysiology*, 13 (1), 72–73.

Kassotis, J., Yusupova, M., Thoben, D., Stawiarski, M. & Reddy, C.V. 2001. 'Syncope masquerading as a panic disorder: role of the subcutaneous loop recorder in eliciting the appropriate diagnosis.[comment]', *Pacing & Clinical Electrophysiology*, 24 (12), 1829–1830.

Mairesse, G.H. & Marchand, B. 2003. 'Prolonged asymptomatic sinus pause indicated by implantable loop recording', *Heart*, 89 (3), 244.

Sanatani, S., Peirone, A., Chiu, C., Human, D.G., Gross, G.J. & Hamilton, R.M. 2002. 'Use of an implantable loop recorder in the evaluation of children with congenital heart disease', *American Heart Journal*, 143 (2), 366–372.

Simantirakis, E.N., Chrysostomakis, S.I., Manios, E.G. & Vardas, P.E. 2000. 'Insertable loop recorder in unmasking the cause of syncope', *Pacing & Clinical Electrophysiology*, 23 (10 Pt 1), 1573–1575.

Simpson, C.S., Barlow, M.A., Krahn, A.D., Klein, G.J., Yee, R. & Skanes, A.C. 2000.

'Recurrent seizure diagnosed by the insertable loop recorder'. *Journal of Interventional Cardiac Electrophysiology*, 4 (3), 475–479.

Vlay, S.C. & Lawson, W.E. 2000. 'Demonstration of myocardial ischemia by an internal loop recorder', *Pacing & Clinical Electrophysiology*, 23 (10 Pt 1), 1576–1578.

Zaidi, A., Clough, P., Mawer, G. & Fitzpatrick, A. 1999. 'Accurate diagnosis of convulsive syncope: role of an implantable subcutaneous ECG monitor.[comment]', *Seizure*, 8 (3), 184–186.

**Modelled cohort**

Krahn, A.D., Klein, G.J., Yee, R. & Manda, V. 1999. 'The high cost of syncope: cost implications of a new insertable loop recorder in the investigation of recurrent syncope'. *American Heart Journal*, 137 (5), 870–877.

**Narrative review**

Brignole, M., Menozzi, C., Moya, A., Garcia-Civera, R. & International Study on Syncope of Uncertain Etiology I. 2001. 'Implantable loop recorder: towards a gold standard for the diagnosis of syncope?', *Heart*, 85 (6), 610–612.

Cerino-Toth, L. 1999. 'Implantable loop monitor for detection of syncope', *Critical Care Nursing Clinics of North America*, 11 (3), 297–301.

Futterman, L.G. & Lemberg, L. 2002. 'Ambulatory electrocardiographic monitoring: use of the implantable loop recorder in the evaluation of syncope', *Journal of Cardiovascular Nursing*, 16 (3), 24–33.

Hammill, S.C. 1997. 'Value and limitations of noninvasive assessment of syncope', *Cardiology Clinics*, 15 (2), 195–218.

Heaven, D.J. & Sutton, R. 2000. 'Syncope', *Critical Care Medicine*, 28 (10 Suppl), N116–120.

Hepner, D.L. 2000. 'Anesthetic implications of a new implantable device: the loop recorder system', *Anesthesiology*, 93 (4), 1161.

Kenny, R.A. & Krahn, A.D. 1999. 'Implantable loop recorder: evaluation of unexplained syncope', *Heart*, 81 (4), 431–433.

Klein, G.J., Krahn, A., Yee, R. & Skanes, A. 2000. 'The implantable loop recorder: the herald of a new age of implantable monitors', *Pacing & Clinical Electrophysiology*, 23 (10 Pt 1), 1456.

Krahn, A.D., Klein, G.J. & Yee, R. 1996. 'Recurrent unexplained syncope: diagnostic and therapeutic approach', *Canadian Journal of Cardiology*, 12 (10), 989–994.

Krahn, A.D., Klein, G.J. & Yee, R. 1997. 'Recurrent syncope. Experience with an implantable loop recorder', *Cardiology Clinics*, 15 (2), 313–326.

Luria, D.M. & Shen, W.K. 2001. 'Syncope in the elderly: new trends in diagnostic approach and nonpharmacologic management', *American Journal of Geriatric Cardiology*, 10

(2), 91–96.

Raj, S.R. & Sheldon, R.S. 2002. 'Syncope: investigation and treatment', *Current Cardiology Reports*, 4 (5), 363–370.

Vardas, P.E. 2000. 'From the Einthoven galvanometer to the implantable loop recorder: revelations in store', *Pacing & Clinical Electrophysiology*, 23 (10 Pt 1), 1453–1455.

**Results unable to be separated for those who had the ILR**

Zaidi, A., Clough, P., Cooper, P., Scheepers, B. & Fitzpatrick, A.P. 2000. 'Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause', *Journal of the American College of Cardiology*, 36 (1), 181–184.

**Study does not meet PICO – no accuracy outcomes or not ILR**

Chrysostomakis, S.I., Klapsinos, N.C., Simantirakis, E.N., Marketou, M.E., Kambouraki, D.C. & Vardas, P.E. 2003. 'Sensing issues related to the clinical use of implantable loop recorders', *Europace*, 5 (2), 143–148.

De Cock, C.G., Spruijt, J.H., Van Campen, L.M.C., Plu, A.W. & Visser, C.A. 2000. 'Electromagnetic interference of an implantable loop recorder by commonly encountered electronic devices', *Pacing & Clinical Electrophysiology*, 23 (10 part 1), 1516–1518.

Krahn, A.D., Klein, G.J., Yee, R. & Norris, C. 1997. 'Maturation of the sensed electrogram amplitude over time in a new subcutaneous implantable loop recorder', *Pacing & Clinical Electrophysiology*, 20 (6), 1686–1690.

Krahn, A.D., Renner, S.M., Klein, G.J., Yee, R., Skanes, A. & Evans, E.M. 2000. 'The utility of holter monitoring compared to loop recorders in the evaluation of syncope and presyncope', *Annals of Noninvasive Electrocardiology*, 5 (3), 284–289.

Simpson, C.S., Krahn, A.D., Klein, G.J., Yee, R. & Skanes, A.C. 1999. 'A cost effective approach to the investigation of syncope: relative merit of different diagnostic strategies', *Canadian Journal of Cardiology*, 15 (5), 579–584.

Zimetbaum, P., Kim, K.Y., Ho, K.K.L., Zebede, J., Josephson, M.E. & Goldberger, A.L. 1997. 'Utility of patient-activated cardiac event recorders in general clinical practice', *American Journal of Cardiology*, 79 (3), 371–372.

Zimetbaum, P.J. & Josephson, M.E. 1999. 'The evolving role of ambulatory arrhythmia monitoring in general clinical practice', *Annals of Internal Medicine*, 130 (10), 848–856.

**Study protocol only**

Kenny, R.A. 1999. 'SAFE PACE 2: Syncope and Falls in the Elderly--Pacing and Carotid Sinus Evaluation: a randomized controlled trial of cardiac pacing in older patients with falls and carotid sinus hypersensitivity', *Europace*, 1 (1), 69–72.

## Patient outcomes following diagnosis

### Case reports

Berger, T., Roithinger, F.X. & Hintringer, F. 2002. 'Images in cardiology: Diagnosis of a rare cause of arrhythmogenic syncope by means of an implantable loop recorder', *Heart*, 88 (1), 10.

Chrysostomakis, S.I., Simantirakis, E.N., Marketou, M.E. & Vardas, P.E. 2002. 'Implantable loop recorder undersensing mimicking complete heart block', *Europace*, 4 (2), 211–213.

Chugh, A., Aboufakher, R., Riba, A. & Knight, B. 2002. 'Recurrent syncope in a patient with an implantable loop recorder: what is the diagnosis?', *Journal of Cardiovascular Electrophysiology*, 13 (11), 1176–1177.

Cohen, T.J., Ibrahim, B. & Sassower, M.J. 2000. 'Revealing data retrieved from an implantable loop recorder', *Journal of Invasive Cardiolog*, 12 (3), 174–175.

Mairesse, G.H. & Marchand, B. 2003. 'Prolonged asymptomatic sinus pause indicated by implantable loop recording', *Heart*, 89 (3), 244.

Shellock, F.G., Tkach, J.A., Ruggieri, P.M. & Masaryk, T.J. 2003. 'Cardiac pacemakers, ICDs, and loop recorder: Evaluation of translational attraction using conventional ("long-bore") and "short-bore" 1.5- and 3.0-Tesla MR systems', *Journal of Cardiovascular Magnetic Resonance*, 5 (2), 387–397.

Steely, D., Ozdemir, A., Antalki, T., Bissett, J.K., Formicola, T. & Talley, J.D. 1998. 'It fits! (intelligence transfer: From images to solutions): The implantable syncope monitor', *Journal of Interventional Cardiology*, 11 (5 I), 511–512.

Vlay, S.C. & Lawson, W.E. 2000. 'Demonstration of myocardial ischemia by an internal loop recorder', *Pacing & Clinical Electrophysiology*, 23 (10 Pt 1), 1576–1578.

### Case series

Armstrong, V.L., Lawson, J., Kamper, A.M., Newton, J. & Kenny, R.A. 2003. 'The use of an implantable loop recorder in the investigation of unexplained syncope in older people', *Age and Ageing*, 32 (2), 185–188.

Ashby, D.T., Cehic, D.A., Disney, P.J.S., Mahar, L.J. & Young, G.D. 2002. 'A retrospective case study to assess the value of the implantable loop recorder for the investigation of undiagnosed syncope', *Pacing and Clinical Electrophysiology*, 25 (8), 1200–1205.

Bloemers, B.L. & Sreeram, N. 2002. 'Implantable loop recorders in pediatric practice', *Journal of Electrocardiology*, 35 (Suppl), 131–135.

Brignole M, Menozzi C, Moya A, Garcia-Civera R, Mont L, Alvarez M, Errazquin F, Beiras J, Bottoni N, Donateo P & International Study on Syncope of Uncertain Etiology I, 2001. 'Mechanism of syncope in patients with bundle branch block and negative electrophysiological test'. *Circulation.,* 104 (17), 2045-50.

Brignole M, Menozzi C, Moya A, Garcia-Civera R, Donateo P, Puggioni E, Migliorini R, Navarro X & International Study on Syncope of Uncertain Etiology I, 2002. 'Nonarrhythmic syncope documented by an implantable loop recorder (an ISSUE substudy)'. *American Journal of Cardiology.,* 90 (6), 654-7.

Donateo P, Brignole M, Menozzi C, Bottoni N, Alboni P, Dinelli M, Del Rosso A, Croci F, Oddone D, Solano A & Puggioni E, 2003. 'Mechanism of syncope in patients with positive adenosine triphosphate tests'. *Journal of the American College of Cardiology,* 41 (1), 93-98.

Garcia-Civera R, Ruiz-Granell R, Morell-Cabedo S, Sanjuan-Manez R, Perez-Alcala F, Plancha E, Navarro A, Botella S & Llacer A, 2003. 'Selective use of diagnostic tests in patients with syncope of unknown cause'. *Journal of the American College of Cardiology,* 41 787-90.

Krahn AD, Klein GJ, Fitzpatrick A, Seidl K, Zaidi A, Skanes A & Yee R, 2002. 'Predicting the outcome of patients with unexplained syncope undergoing prolonged monitoring'. *PACE - Pacing and Clinical Electrophysiology,* 25 (1), 37-41.

Krahn, A.D., Klein, G.J., Yee, R. & Norris, C. 1998. 'Final results from a pilot study with an implantable loop recorder to determine the etiology of syncope in patients with negative noninvasive and invasive testing', *American Journal of Cardiology*, 82 (1), 117–119.

Krahn, A.D., Klein, G.J., Yee, R., Skanes, A.C. & Investigators R. 2001. 'Predictive value of presyncope in patients monitored for assessment of syncope', *American Heart Journal*, 141 (5), 817–821.

Krahn, A.D., Klein, G.J., Yee, R., Takle-Newhouse, T. & Norris, C. 1999. 'Use of an extended monitoring strategy in patients with problematic syncope. Reveal Investigators', *Circulation*, 99 (3), 406–410.

Menozzi C, Brignole M, Garcia-Civera R, Moya A, Botto G, Tercedor L, Migliorini R, Navarro X & International Study on Syncope of Uncertain Etiology I, 2002. 'Mechanism of syncope in patients with heart disease and negative electrophysiologic test'. *Circulation.,* 105 (23), 2741-5.

Mieszczanska, H., Ibrahim, B. & Cohen, T.J. 2001. 'Initial clinical experience with implantable loop recorders', *The Journal of Invasive Cardiology*, 13 (12), 802–804.

Moya A, Brignole M, Menozzi C, Garcia-Civera R, Tognarini S, Mont L, Botto G, Giada F, Cornacchia D & International Study on Syncope of Uncertain Etiology I, 2001. 'Mechanism of syncope in patients with isolated syncope and in patients with tilt-positive syncope'. *Circulation.,* 104 (11), 1261-7.

Nierop, P.R., van Mechelen, R., van Elsacker, A., Luijten, R.H. & Elhendy, A. 2000. 'Heart rhythm during syncope and presyncope: results of implantable loop recorders', *Pacing & Clinical Electrophysiology*, 23 (10 Pt 1), 1532–1538.

Seidl K, Rameken M, Breunung S, Senges J, Jung W, Andresen D, van Toor A, Krahn AD, Klein GJ & Reveal I, 2000. 'Diagnostic assessment of recurrent unexplained syncope with a new subcutaneously implantable loop recorder. Reveal-Investigators'. *Europace.,* 2 (3), 256-62.

Zaidi, A.., Clough, P., Cooper, P., Scheepers, B. & Fitzpatrick, A.P. 2000. 'Misdiagnosis of epilepsy: Many seizure-like attacks have a cardiovascular cause', *Journal of the American College of Cardiology*, 36 (1), 181–184.

#### Duplicated study data

Brignole, M. & Menozzi, C. 2002. 'Diagnosing arrhythmias as a mechanism of syncope', *Cardiology Review*, 19 (8), 18–22.

#### Modelled cohort

Krahn, A.D., Klein, G.J., Yee, R. & Manda, V. 1999. 'The high cost of syncope: Cost implications of a new insertable loop recorder in the investigation of recurrent syncope', *American Heart Journal*, 137 (5), 870–877.

#### Narrative review

Brignole, M., Menozzi, C., Moya, A., Garcia-Civera, R. & International Study on Syncope of Uncertain Etiology I. 2001. 'Implantable loop recorder: towards a gold standard for the diagnosis of syncope?', *Heart*, 85 (6), 610–612.

Cerino-Toth, L. 1999. 'Implantable loop monitor for detection of syncope', *Critical Care Nursing Clinics of North America*, 11 (3), 297–301.

Hepner, D.L. 2000. 'Anesthetic implications of a new implantable device: the loop recorder system', *Anesthesiology*, 93 (4), 1161.

Kenny, R.A. & Krahn, A.D. 1999. 'Implantable loop recorder: evaluation of unexplained syncope', *Heart*, 81 (4), 431–433.

Klein, G.J., Krahn, A., Yee, R. & Skanes, A. 2000. 'The implantable loop recorder: the herald of a new age of implantable monitors', *Pacing & Clinical Electrophysiology*, 23 (10 Pt 1), 1456.

Krahn, A.D., Klein, G.J. & Yee R. 1996. 'Recurrent unexplained syncope: Diagnostic and therapeutic approach', *Canadian Journal of Cardiology*, 12 (10), 989–994.

Krahn, A.D., Klein, G.J. & Yee, R. 1997. 'Recurrent syncope: Experience with an implantable loop recorder', *Cardiology Clinics*, 15 (2), 313–326.

Krahn, A.D., Klein, G.J., Yee, R. & Skanes, A.C. 2003. 'Use of the implantable loop recorder in patients with unexplained syncope', *Minerva Cardioangiologica*, 51 (1), 21–27.

Krahn, A.D., Yee, R., Klein, G.J. & Skanes, A.C. 1999. 'Syncope: Experience with the implantable loop recorder', *ACC Current Journal Review*, 8 (1), 80–84.

Linzer, M., Yang, E.H., Estes, III, N.A.M., Wang, P., Vorperian, V.R. & Kapoor, W.N. 1997. 'Diagnosing syncope: Part 1: Value of history, physical examination, and electrocardiography', *Annals of Internal Medicine*, 126 (12), 989–996.

Linzer, M., Yang, E.H., Estes, III, N.A.M., Wang, P., Vorperian, V.R. & Kapoor, W.N. 1997. 'Diagnosing syncope. Part 2: Unexplained syncope', *Annals of Internal Medicine*, 127 (1), 76–86.

Luria, D.M. & Shen, W.K. 2001. 'Syncope in the elderly: New trends in diagnostic approach and nonpharmacologic management', *American Journal of Geriatric Cardiology*, 10 (2), 91–96.

Maurer, M.S. & Bloomfield, D.M. 2002. 'Atrial fibrillation and falls in the elderly', *Clinics in Geriatric Medicine*, 18 (2), 323–337.

McLeod, K.A. 2001. 'Dizziness and syncope in adolescence', *Heart*, 86 (3) 350–354.

Olshansky, B. 2001. 'Syncope evaluation at a crossroad: For which patients?', *Circulation*, 104 (1), 7–8.

Raj, S.R. & Sheldon, R.S. 2002. 'Syncope: investigation and treatment', *Current Cardiology Reports*, 4 (5), 363–370.

Vardas, P.E. 2000. 'From the Einthoven galvanometer to the implantable loop recorder: revelations in store', *Pacing & Clinical Electrophysiology*, 23 (10 Pt 1), 1453–1455.

Zaidi, A. & Fitzpatrick, A.P. 2000. 'Misdiagnosis of convulsive syncope as epilepsy', *Cardiovascular Reviews and Reports*, 21 (7), 359–364.

Zimetbaum, P.J. & Josephson, M.E. 1999. 'The evolving role of ambulatory arrhythmia monitoring in general clinical practice', *Annals of Internal Medicine*, 130 (10), 848–856.

**Study does not meet PICO – no accuracy outcomes or not ILR or patients did not have syncope**

Chrysostomakis, S.I., Klapsinos, N.C., Simantirakis, E.N., Marketou, M.E., Kambouraki, D.C. & Vardas, P.E. 2003. 'Sensing issues related to the clinical use of implantable loop recorders', *Europace*, 5 (2), 143–148.

De Cock, C.G., Spruijt, J.H., Van Campen, L.M.C., Plu, A.W. & Visser, C.A. 2000. 'Electromagnetic interference of an implantable loop recorder by commonly encountered electronic devices', *Pacing & Clinical Electrophysiology*, 23 (10 part 1), 1516–1518.

Huikuri, H.V., Mahaux, V. & Bloch-Thomsen, P.E. 2003. 'Cardiac arrhythmias and risk stratification after myocardial infarction: results of the CARISMA pilot study', *Pacing & Clinical Electrophysiology*, 26 (1 Pt 2), 416–419.

Krahn, A.D., Klein, G.J., Yee, R. & Norris, C. 1997. 'Maturation of the sensed electrogram amplitude over time in a new subcutaneous implantable loop recorder', *Pacing and Clinical Electrophysiology*, 20 (6), 1686–1690.

Sarasin FP, Louis-Simonet M, Carballo D, Slama S, Rajeswaran A, Metzger JT, Lovis C, Unger P-F & Junod A-F, 2001. 'Prospective evaluation of patients with syncope: A population-based study'. *American Journal of Medicine,* 111 (3), 177-84.

Zimetbaum, P.J., Kim, K.Y., Ho, K.K.L., Zebede, J., Josephson, M.E. & Goldberger, A.L. 1997. 'Utility of patient-activated cardiac event recorders in general clinical practice', *American Journal of Cardiology*, 79 (3), 371–372.

**Study protocol only**

Kenny, R.A. 1999. 'SAFE PACE 2: Syncope and Falls in the Elderly--Pacing and Carotid Sinus Evaluation: a randomized controlled trial of cardiac pacing in older patients with falls and carotid sinus hypersensitivity', *Europace*, 1 (1), 69–72.

# Appendix H Applicant information

**Table H1 Estimated number of eligible patients for ILR early diagnosis: Prevalence estimates**

| Estimated number of eligible patients | % | Number |
|---|---|---|
| Approximate Australian population | 100 | 19,200,000 |
| Percentage of population who are evaluated and treated for syncope per year | 0.36 | 68,327[a] |
| Percentage of syncope patients who have recurrent syncope | 33.7[b] | 23,026 |
| Patients with recurrent undiagnosed syncope post medical history, physical examination and surface ECG | 41[c] | 9,441 |
| Patients with recurrent undiagnosed syncope- arrhythmia suspected or unexplained | 35[d] | 3,304 |

[a]National Disease and Therapeutic Index on Syncope and Collapse, ISC #780.2:1997 (USA: 1 million per year evaluated and treated for syncope; ie 1 million/281 million = 0.36%), could not verify estimate as publication not supplied
[b]37.7% in Kapoor (1987) Am J. Med 83:700-708
[c]Could not verify this estimate, could not locate citation in application or independent search
[d]Could not verify estimate; publication not supplied and cited only as Fox (2002), this could not be located in independent search

**Table H2 Estimated number of eligible patients for ILR later diagnosis: Prevalence estimates**

| Estimated number of eligible patients | % | Number |
|---|---|---|
| Approximate Australian population | 100 | 19,200,000 |
| Percentage of population who are evaluated and treated for syncope per year | 0.36[a] | 68,327 |
| Percentage of syncope patients who have recurrent syncope | 33.7[b] | 23,026 |
| Patients with recurrent undiagnosed syncope post medical history, physical examination and surface ECG | 41[c] | 9,441 |
| Patients with recurrent undiagnosed syncope – arrhythmia suspected or unexplained | 100[d] | 9,441 |
| Patients with recurrent undiagnosed syncope – arrhythmia or neurocardiogenic cause suspected who remain undiagnosed post HM/ELR/TT testing | 61.3 | 5,789[e] |
| Patients with recurrent undiagnosed syncope- arrhythmia or neurocardiogenic cause suspected who remain undiagnosed post HM/ELR/TT testing and do not have cardiac structural damage | 60[f] | 3,473 |

[a]National Disease & Therapeutic Index on Syncope and Collapse, ISC #780.2: 1997 (USA- 1 million per year evaluated and treated for syncope; ie 1 million/281 million= 0.36%); could not verify estimate in the publication
[b]37.7% in Kapoor (1987) Am J Med 83, 700–708
[c]Could not verify this estimate; could not locate citation in application or independent search
[d]Could not verify estimate; publication not supplied and cited only as Fox (2002), this could not be located in independent search
[e]From application, the derivation of assumption of 5,789 patients is as follows:
Arrhythmia (35% of 9,441 = 3,304) application of early diagnostic testing
3,304 having average diagnostic yield of 19.5% (early conventional diagnostic test yield), therefore 2,660 patients (80.5% of 3,304) will remain undiagnosed post early conventional testing
Neurocardiogenic (65% of 9,441 = 6,137)
6,137 TT having average diagnostic yield of 49%- nb, range = 11–87%, therefore 3,129 patients (51% of 6,137) will remain undiagnosed post tilt table testing
Total = 2,660+3,129 = 5,789
(could not verify all original references)
[f]This estimate refers to 60% of syncopal patients and not specifically to patients with recurrent undiagnosed syncope- arrhythmia or neurocardiogenic case suspected who remain undiagnosed post HM/ELR/TT testing

# Abbreviations

| | |
|---|---|
| AHMAC | Australian Health Ministers' Advisory Council |
| AV block | Atrioventricular block |
| CI | Confidence interval |
| ECG | Electrocardiogram |
| ELR | External loop recorder |
| ILR | Implantable loop recorder |
| mmHg | millimetres of mercury |
| MRI | Magnetic resonance imaging |
| MSAC | Medical Services Advisory Committee |
| NHMRC | National Health and Medical Research Council |
| QALY | Quality adjusted life years |
| RCT | Randomised controlled trial |
| SCD | Sudden cardiac death |
| SD | Standard deviation |
| TGA | Therapeutic Goods Administration |

# References


Ammirati F, Colivicchi F, Velardi A & Santini M, 2001. 'Prevalence and correlates of syncope-related traumatic injuries in tilt-induced vasovagal syncope'. *Ital Heart J,* 2 (1), 38-41.

Armstrong, V.L., Lawson, J., Kamper, A.M., Newton, J. & Kenny, R.A. 2003. 'The use of an implantable loop recorder in the investigation of unexplained syncope in older people', *Age and Ageing*, 32 (2), 185–188.

Ashby, D.T., Cehic, D.A., Disney, P.J., Mahar, L.J. & Young, G.D. 2002. 'A retrospective case study to assess the value of the implantable loop recorder for the investigation of undiagnosed syncope', *Pacing & Clinical Electrophysiology*, 25 (8), 1200–1205.

Australian Bureau of Statistics 2003, [Internet]. Australian Bureau of Statistics, Available from: www.abs.gov.au/ [Accessed 7th July 2003].

Bloemers, B.L. & Sreeram, N. 2002. 'Implantable loop recorders in pediatric practice', *Journal of Electrocardiology*, 35 (Suppl) 131–135.

Brignole M, Alboni P, Benditt D, Bergfeldt L, Blanc JJ, Bloch Thomsen PE, van Dijk JG, Fitzpatrick A, Hohnloser S, Janousek J, Kapoor W, Kenny RA, Kulakowski P, Moya A, Raviele A, Sutton R, Theodorakis G & Wieling W, 2001. 'Guidelines on management (diagnosis and treatment) of syncope'. *Eur Heart J,* 22 (15), 1256-306.

Brignole M, Menozzi C, Moya A, Garcia-Civera R, Donateo P, Puggioni E, Migliorini R, Navarro X & International Study on Syncope of Uncertain Etiology I, 2002. 'Nonarrhythmic syncope documented by an implantable loop recorder (an ISSUE substudy)'. *American Journal of Cardiology.,* 90 (6), 654-7.

Chrysostomakis, S.I., Simantirakis, E.N., Marketou, M.E. & Vardas, P.E. 2002. 'Implantable loop recorder undersensing mimicking complete heart block', *Europace*, 4 (2) 211–213.

Chrysostomakis, S.I., Klapsinos, N.C., Simantirakis, E.N., Marketou, M.E., Kambouraki, D.C. & Vardas, P.E. 2003. 'Sensing issues related to the clinical use of implantable loop recorders', *Europace*, 5 (2), 143–148.

Cochrane Methods Working Group on Systematic Review of Screening and Diagnostic Tests. 1996, *Cochrane methods working group on systematic review of screening and diagnostic tests: Recommended methods* [Internet]. Available from: http//www.cochrane.org.au

De Cock, C.G., Spruijt, J.H., Van Campen, L.M.C., Plu, A.W. & Visser, C.A. 2000. 'Electromagnetic interference of an implantable loop recorder by commonly encountered electronic devices', *Pacing & Clinical Electrophysiology*, 23 (10 part 1), 1516–1518.

Donateo P, Brignole M, Menozzi C, Bottoni N, Alboni P, Dinelli M, Del Rosso A, Croci F, Oddone D, Solano A & Puggioni E, 2003. 'Mechanism of syncope in patients with positive adenosine triphosphate tests'. *Journal of the American College of Cardiology.,* 41 (1), 93-8.

Garcia-Civera R, Ruiz-Granell R, Morell-Cabedo S, Sanjuan-Manez R, Perez-Alcala F,

Plancha E, Navarro A, Botella S & Llacer A, 2003. 'Selective use of diagnostic tests in patients with syncope of unknown cause'. *Journal of the American College of Cardiology,* 41 787-90.

Gimbel, J.R. & Wilkoff, B.L. 2003. 'Artefact mimicking tachycardia during magnetic resonance imaging in a patient with an implantable loop recorder', *Heart*, 89 (3), e10.

Grubb, B.P. 1998, 'Neurocardiogenic syncope-Chapter 3', In: Grubb BP & Olshansky B. *Syncope: Mechanisms and Management*, Futura Publishing Company, Armonk, NY, USA.

Hartog, J., Hugl, B., Klein, G. & Schiltgen, M. 2000. 'Evaluation of asymptomatic arrhythmia detected during the initial phase of the Reveal Plus clinical study', In: European Society of Cardiology (ESC) poster presentation,

Huikuri, H.V., Mahaux, V. & Bloch-Thomsen, P.E. 2003. 'Cardiac arrhythmias and risk stratification after myocardial infarction: results of the CARISMA pilot study', *Pacing and Clinical Electrophysiology*, 26 (2), 416–419.

Jaeschke, R., Guyatt, G. & Sackett, D.L. 1994. 'Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group', *Journal of the American Medical Association*, 271 (5), 389–391.

Kapoor, W.N. 1992. 'Evaluation and managment of patients with syncope', *Journal of the American Medical Association*, 268 (18), 2553–2560.

Kapoor, W.N. 1998, 'An Overview of the evaluation and management of syncope-Chapter 1', In: Grubb BP & Olshansky B. *Syncope: Mechanisms and Management*, Futura Publishing Company, Armonk, NY, USA.

Kapoor, W.N. 2000. 'Syncope'. *New England Journal of Medicine*, 343 (25), 1856–1862.

Kenny, R.A. & Krahn, A.D. 1999. 'Implantable loop recorder: evaluation of unexplained syncope', *Heart*, 81 (4), 431–433.

Krahn, A.D., Klein, G.J., Norris, C. & Yee, R. 1995. 'The etiology of syncope in patients with negative tilt table and electrophysiological testing', *Circulation*, 92 (7), 1819–1824.

Krahn, A.D., Klein, G.J., Yee, R. & Norris, C. 1998. 'Final results from a pilot study with an implantable loop recorder to determine the etiology of syncope in patients with negative noninvasive and invasive testing', *American Journal of Cardiology*, 82 (1), 117–119.

Krahn, A.D., Klein, G.J., Yee, R., Takle-Newhouse, T. & Norris, C. 1999. 'Use of an extended monitoring strategy in patients with problematic syncope. Reveal Investigators', *Circulation*, 99 (3,) 406–410.

Krahn, A.D., Klein, G.J., Yee, R. & Skanes, A.C. 2001a. 'Randomized assessment of syncope trial: Conventional diagnostic testing versus a prolonged monitoring strategy', *Circulation*, 104 (1), 46–51.

Krahn AD, Klein GJ, Yee R, Skanes AC & The RI, 2001b. 'Predictive value of presyncope in patients monitored for assessment of syncope'. *American Heart Journal.,* 141 (5), 817-21.

Krahn AD, Klein GJ, Fitzpatrick A, Seidl K, Zaidi A, Skanes A & Yee R, 2002. 'Predicting the outcome of patients with unexplained syncope undergoing prolonged monitoring'. *Pacing & Clinical Electrophysiology.,* 25 (1), 37-41.

Krahn, A.D., Klein, G.J., Yee, R., Hoch, J.S. & Skanes, A.C. 2003a. 'Cost Implications of Testing Strategy in Patients with Syncope', *Journal of the American College of Cardiology*, 42 (3), 495–501.

Krahn, A.D., Klein, G.J., Yee, R. & Skanes, A.C. 2003b. 'Use of the implantable loop recorder in patients with unexplained syncope', *Minerva Cardioangiologica*, 51 (1), 21–27.

Linzer, M., Yang, E.H., Estes, III N.A.M., Wang, P., Vorperian, V.R. & Kapoor, W.N. 1997. 'Diagnosing syncope: Part 1: Value of history, physical examination, and electrocardiography', *Annals of Internal Medicine*, 126 (12), 989–996.

Luria, D.M. & Shen, W.K. 2001. 'Syncope in the elderly: new trends in diagnostic approach and nonpharmacologic management', *American Journal of Geriatric Cardiology*, 10 (2) 91–96.

Menozzi C, Brignole M, Garcia-Civera R, Moya A, Botto G, Tercedor L, Migliorini R, Navarro X & International Study on Syncope of Uncertain Etiology I, 2002. 'Mechanism of syncope in patients with heart disease and negative electrophysiologic test'. *Circulation.,* 105 (23), 2741-5.

Mieszczanska, H., Ibrahim, B. & Cohen, T.J. 2001. 'Initial clinical experience with implantable loop recorders', *Journal of Invasive Cardiology*, 13 (12), 802–804.

Moya A, Brignole M, Menozzi C, Garcia-Civera R, Tognarini S, Mont L, Botto G, Giada F, Cornacchia D & International Study on Syncope of Uncertain Etiology I, 2001. 'Mechanism of syncope in patients with isolated syncope and in patients with tilt-positive syncope'. *Circulation.,* 104 (11), 1261-7..

NHMRC. 1999. *A guide to the development, implementation and evaluation of clinical practice guidelines*, National Health and Medical Research Council, Canberra.

NHMRC. 2000. *How to use the evidence: assessment and application of scientific evidence*, National Health and Medical Research Council, Canberra.

NHS Centre for Reviews and Dissemination. 2001, *Undertaking systematic review of research on effectiveness. CRD's guidance for those carrying out or commissioning reviews* [Internet]. Available from: http://www.york.ac.uk/inst/crd/report4.htm

Nierop, P.R., van Mechelen, R., van Elsacker, A., Luijten, R.H. & Elhendy, A. 2000. 'Heart rhythm during syncope and presyncope: results of implantable loop recorders', *Pacing & Clinical Electrophysiology*, 23 (10 Pt 1), 1532–1538.

Olshansky, B. 1998, 'Syncope: Overview and approach to management-Chapter 2', In: Grubb BP & Olshansky B. *Syncope: Mechanisms and Management*, Futura Publishing Company, Armonk, NY, USA.

Recchia, D. & Barzilai, B. 1995. 'Echocardiography in the evaluation of patients with syncope', *Journal of General Internal Medicine*, 10 (12), 649–655.

Rose, M.S., Koshman, M.L., Spreng, S. & Sheldon, R. 2000. 'The relationship between health-related quality of life and frequency of spells in patients with syncope', *Journal of Clinical Epidemiology*, 53 (12), 1209–1216.

Sackett, D., Strauss, S., Richardson, W., Rosenberg, W. & Haynes, R. 2000, *Evidence-Based Medicine: How to Practice and Teach EBM*, Churchill Livingstone, Edinburgh.

Seidl K, Rameken M, Breunung S, Senges J, Jung W, Andresen D, van Toor A, Krahn AD, Klein GJ & Reveal I, 2000. 'Diagnostic assessment of recurrent unexplained syncope with a new subcutaneously implantable loop recorder. Reveal-Investigators'. *Europace.,* 2 (3), 256-62.

Simpson CS, Krahn AD, Klein GJ, Yee R, Skanes AC, Manda V & Norris C, 1999. 'A cost effective approach to the investigation of syncope: relative merit of different diagnostic strategies'. *Can J Cardiol,* 15 (5), 579-84.

Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ & Levy D, 2002. 'Incidence and prognosis of syncope'. *New England Journal of Medicine,* 347 878-85.

.