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THE DIAGNOSTIC YIELD OF IMPLANTABLE LOOP RECORDERS IN UNEXPLAINED SYNCOPE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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	the proportions of patients with the specific etiologic diagnoses on the total of subjects and the proportion of an analyzable ECG recording after symptoms. We used a random effects model for the meta-analyses. Results Forty-nine studies, for a total of 4381 subjects, were included. The overall diagnostic yield was 43.9% (95% CI 40.2%, 47.6%; I2=79.8%). The proportions of subjects finally diagnosed with arrhythmic syncope, ventricular arrhythmias, supraventricular arrhythmias and bradyarrhythmias were 26.5%, 2.7%, 4.9% and 18.2%, respectively. The proportion of an analysable ECG recording after symptoms was 89.5% (95% IC 86.1%, 92.1%; 1236 subjects; 36 studies; I2=44.9%). Median time to diagnosis was 134 days. Heterogeneity is an important limitation to be acknowledged and none of the subgroup or sensitivity analyses and meta-regressions performed enabled us to account for it. Conclusions About a half of unexplained syncope subjects implanted with an ILR were diagnosed, and around 50% of them had an arrhythmia. Life-threatening arrhythmias as well as ILR complications and death due to arrhythmic events were very rare.

THE DIAGNOSTIC YIELD OF IMPLANTABLE LOOP RECORDERS IN UNEXPLAINED SYNCOPE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objective

The aim of this systematic review was to analyze the diagnostic yield of Implantable Loop Recorders (ILRs) in unexplained syncope.

Methods

We performed a systematic search in order to retrieve studies enrolling adults undergoing ILR implantation for undetermined syncope. The primary outcome was the overall diagnostic yield, defined as the proportion of patients with syncope recurrence and an available ILR recording or an automatic detection of a significant arrhythmia. Secondary outcomes were the proportions of patients with the specific etiologic diagnoses on the total of subjects and the proportion of an analyzable ECG recording after symptoms. We used a random effects model for the meta-analyses.

Results

Forty-nine studies, for a total of 4381 subjects, were included. The overall diagnostic yield was 43.9% (95% CI 40.2%, 47.6%; I2=79.8%). The proportions of subjects finally diagnosed with arrhythmic syncope, ventricular arrhythmias, supraventricular arrhythmias and bradyarrhythmias were 26.5%, 2.7%, 4.9% and 18.2%, respectively. The proportion of an analysable ECG recording after symptoms was 89.5% (95% IC 86.1%, 92.1%; 1236 subjects; 36 studies; I2=44.9%). Median time to diagnosis was 134 days. Heterogeneity is an important limitation to be acknowledged and none of the subgroup or sensitivity analyses and meta-regressions performed enabled us to account for it.

Conclusions

About a half of unexplained syncope subjects implanted with an ILR were diagnosed, and around 50% of them had an arrhythmia. Life-threatening arrhythmias as well as ILR complications and death due to arrhythmic events were very rare.

SUMMARY

What is already known about this subject?

A significant proportion of syncope subjects remain without a diagnosis despite an extensive evaluation. The capability of implantable loop recorders to capture arrhythmias during spontaneous syncope has increased their use as an earlier tool in the diagnostic pathway of undetermined syncope.

What does this study add?

Our study is the first systematic review on the diagnostic yield of ILRs in unexplained syncope. We enrolled 49 studies considering 4381 subjects overall. Our results show that the ILR diagnostic yield was 43.9%. Adverse events following ILR implantation were rare. Moreover, information on the prevalence of arrhythmias in subject with unexplained syncope was gathered. The proportions of subjects finally diagnosed with arrhythmic syncope, ventricular arrhythmias, supraventricular arrhythmias and bradyarrhythmias were 26.5%, 2.7%, 4.9% and 18.2%, respectively. Median time to diagnosis was 134 days.

How might this impact on clinical practice?

Knowing the diagnostic yield of implantable loop recorders, as well as the proportions of the different etiologies is of great interest in the management of patients with unexplained syncope.

INTRODUCTION

Syncope is a common condition involving about 30% of people during their lifetime. Most of the causes of syncope can be easily recognized by history, physical examination and first level diagnostic tests. However, a significant proportion of subjects remain without a diagnosis despite an extensive evaluation[1,2]. These patients could have an increased risk of syncope recurrence thus leading to either a significant trauma or a reduction in quality of life[3]. Moreover, in a significant proportion of patients, an arrhythmia might be the cause of the loss of consciousness[4,5], leading to possible fatalities[6,7]. For these reasons, implantable loop recorders (ILRs) have gained popularity and are suggested as an earlier tool in the diagnostic pathway of undetermined syncope[8]. ILRs are small devices implanted subcutaneously under local anesthesia in the left side of the chest and have a battery life of up to 36 months. They have no intravascular leads, recording a bipolar ECG signal from small electrodes on either end of the devices. ILRs have a retrospective (loop) memory that continuously records and deletes the patient's ECG. They include a patient-activation function that allows the patient or a bystander to activate ECG storage in case of syncope and an auto-activation feature capturing pre-defined arrhythmias[9]. Obtaining an ECG recording during spontaneous syncope is very appealing and is considered by some physicians the reference standard for the diagnosis of arrhythmic syncope[1,10]. The ILR diagnostic yield depends on both the recurrence of syncope and the device ability of recording the ECG. Its cost-effectiveness relies on the proportion of arrhythmias diagnosed, side effects and costs.

The aim of this systematic review was to analyze the diagnostic yield of ILRs in syncope of unknown cause.

METHODS

According to a pre-defined protocol, we included both prospective and retrospective studies enrolling adults who underwent ILR implantation for undetermined syncope. Data on syncope or pre-syncope recurrence and ECG analysis during symptoms had to be available. We excluded articles published in languages different from English, Italian, French, German and Spanish.

To retrieve all the possible relevant articles, we performed a systematic search in PubMed, Embase and the Cochrane Library with the following search terms: (((Electrocardiography, Ambulatory) OR (Loop recorder) OR (ILR) OR (Implantable recorder) OR (Implantable loop recorder) OR (Internal recorder) OR (Event recorder) OR (Confirm) OR (Reveal) OR (Sleuth)) AND ((syncope) OR (lipothymia) OR (dizziness) OR (drop attack) OR (faint*) OR (unconscious*) OR (loss of consciousness))). Search was performed on November 17th, 2015.

Two independent reviewers screened the titles and abstracts of the retrieved publications. In case of discordance the article was initially included. The full texts of the selected studies were retrieved and assessed by two independent reviewers for inclusion. Discordances were resolved by discussion or by the opinion of a third reviewer. Finally, relevant data were independently extracted and an Excel database was created.

The primary outcome was the diagnostic yield of ILR in undetermined syncope. Diagnostic yield was defined as the proportion of patients with either an available ILR recording during syncope recurrence (even in absence of an arrhythmia finding) or an automatic detection of a significant arrhythmia, even if asymptomatic.

Secondary outcomes were 1) the proportions of patients with a final diagnosis of a) arrhythmic syncope (including ventricular arrhythmia, supraventricular tachycardia and bradyarrhythmia), b) ventricular arrhythmia, c) supraventricular tachycardia or d) need for a pacemaker implantation on the total of subjects; 2) the proportion of an analyzable ECG recording after symptoms.

We investigated potential sources of heterogeneity among the primary studies through subgroup analyses and simple meta-regression analyses. The pre-defined subgroup analyses performed included: i) studies in which arrhythmias were detected during symptoms or during both symptoms and asymptomatic

events; ii) prospective vs. retrospective studies; iii) studies in which less than 5% of patients were lost at follow-up; iv) studies in which consecutive patients were enrolled. The meta-regressions performed explored the influence of i) year of the beginning of the study; ii) number of enrolled patients; iii) percentage of patients affected by cardiovascular disease; iv) mean duration of follow up and v) mean time to diagnosis on the primary outcome. Due to expected clinical and methodological differences between the primary studies, following the DerSimonian-Laird approach, all meta-analyses were performed using a random-effects model on the logit transformed rates. Statistical heterogeneity was formally assessed by a chi-square test, and was quantified using the inconsistency index (I2) statistic, which ranges from 0% to 100% and is defined as the percentage of the observed between-trial variability that is due to heterogeneity rather than chance. In case of an I2 index between 0% and 40%, heterogeneity is considered negligible; an I2 index between 30% and 60% represents moderate heterogeneity; an I2 index between 50% and 90% represents substantial heterogeneity; an I2 index from 75% to 100% means considerable heterogeneity[11]. All analyses were performed using the SAS (release 9.4) statistical software.

To assess the methodological quality of the included studies we used the applicable items of QUADAS[12] and QUADAS-2[13]: 1) Was a consecutive or random sample of patients enrolled? 2) Was the spectrum of patients representative of the patients who will receive the test in practice? 3) Were selection criteria clearly described? 4) Were uninterpretable/intermediate test results reported? 5) Were withdrawals from the study explained? Each item was scored as “yes”, “no”, “unclear” to identify the possible risk of bias for each item.

The possible publication bias (i.e. the fact that studies with a higher diagnostic yield would be more prone to publication) was visually assessed by a funnel plot of the diagnostic yield estimates from individual studies against the number of patients enrolled in each study.

RESULTS

Supplementary Figure 1 shows the process of study selection. We identified 2781 articles (1090 from Embase, 1116 from Medline and 575 from the Cochrane Library); 477 of these studies were duplicates and were therefore eliminated, leaving 2304 articles for consideration. After the exclusion of irrelevant studies, which were identified by reviewing the titles and abstracts of all retrieved articles, 145 publications remained for analysis. Ninety-six of them were subsequently excluded after reading the full-length paper. The review of the references of original studies and guidelines identified no additional study.

Forty-nine studies were included in the meta-analysis[14–62]. Four studies considered 2 different groups each; therefore 53 populations, for a total of 4381 subjects, were analyzed. The studies were published from 1998 to 2015. Most of them were conducted in Europe, eight in the USA, two in Oceania, three in various countries and one in Asia. Most of them were single-center studies. The percentage of males in each study varied between 27 and 72 and the mean age of the population recruited varied between 40 and 83 years. The number of patients enrolled in each study varied between 12 and 650 (median 50) and the mean follow-up between 168 and 660 days (median 365 days). Recurrent unexplained syncope was the inclusion criterion for most of the studies, while three studies enrolled subjects with suspected cardiac syncope and three studies included subjects with syncope and bundle branch block. Data on the number of syncope episodes before enrolment were available for 22 studies and varied between 2.4 and 11 episodes (median 4 episodes). The proportion of subjects with any cardiovascular disease in each study varied between 13 and 100% and the proportion of subjects with abnormal ECG between 0 and 100%. Medtronic Reveal was the ILR of choice in most of the studies and mean time to diagnosis ranged from 30 to 600 days (median 134 days). Supplementary Table 1 describes the main characteristics of the included studies.

The diagnostic yield of ILR, defined as the proportion of patients in which ILR was useful in determining a syncope diagnosis, was 43.9% (95%CI 40.2%, 47.6%; 4381 subjects; 53 studies; I2=79.8%), ranging from 12% to 91% (Figure 1). A considerable heterogeneity across the studies was found.

Data on the diagnostic yield of ILR for the diagnosis of arrhythmic syncope were available in 41 studies. The proportion of subjects finally diagnosed with arrhythmic syncope on the total number of patients

was 26.5% (95% CI 23.5%, 29.7%; 3425 subjects; 41 studies; I2=69.6%), ranging from 5.4% to 55.6% (Figure 2). A substantial heterogeneity across the studies was found.

Ventricular arrhythmias (ventricular tachycardia or ventricular fibrillation) were diagnosed in 2.7% (95% CI 2.0%, 3.6%; 2876 subjects; 43 studies; I2 = 11.7%) of subjects, ranging from 0% to 12.7% (Figure 3). Heterogeneity was found to be negligible in this case.

The proportion of subjects with a diagnosis of supraventricular arrhythmia was available in 45 studies and ranged from 0% to 23.3%, being overall 4.9% (95% CI 3.6%, 6.5%; 3001 subjects; 45 studies; I2=58.3%) (Figure 4). A substantial heterogeneity was found.

Finally, a significant bradyarrhythmia (requiring a permanent pacemaker implantation) was diagnosed in 18.2% (95% CI 16.0%, 20.6%; 3020 subjects; 36 studies; I2=51.3%) of patients, ranging from 5.0% to 38.9% (Figure 5). A moderate heterogeneity was found.

The proportion of an analysable ECG recording after symptoms was 89.5% overall (95% IC 86.1%, 92.1%; 1236 subjects; 36 studies; I2=44.9%), ranging from 62.5% to 100% (Figure 6). A moderate heterogeneity was found. The proportion did not change when studies published before and after 2000 were analysed separately, as an ILR with the ability to automatically detect arrhythmias was first made available in 2000.

Data on the incidence of ILR-related complications, such as device infection or death due to arrhythmias, were scanty and did not allow a formal meta-analysis. However, the studies which have specifically reported on this outcome showed a very infrequent incidence of such complications (Supplementary Table 1).

Predefined sensitivity and subgroup analyses have been performed in order to investigate heterogeneity. None of these led to significantly different results. Moreover, only the analysis of the subgroup of studies in which the diagnosis was reached during both symptoms and asymptomatic arrhythmias showed a reduction in heterogeneity. This might be due to the low number of studies in this group (Supplementary Table 2).

Meta-regressions found no influence of year of the beginning of the study, number of enrolled patients, percentage of patients affected by cardiovascular disease, mean duration of follow up and mean time to diagnosis on the primary outcome (Supplementary Figure 2).

Figure 7 depicts the funnel plot of the diagnostic yield estimates from individual studies against the number of patients enrolled in each study. The absence of a marked asymmetry suggests that publication bias might not be a concern[63].

Figure 8 shows the risk of bias of the included studies. A proportion between 32% and 66% of the included studies were deemed at a low risk of bias.

DISCUSSION

ILRs are often use to investigate indeterminate syncope and the ECG recording during spontaneous syncope is widely considered the reference standard for the diagnosis of arrhythmic syncope[64]. The aim of the present systematic review was to evaluate its diagnostic yield in determining the cause of syncope and to describe the relative prevalence of the different aetiologies. In 2010 Parry and Matthews published a "state of the art" review in order to describe the use of ILRs in syncope[65]. They reported data from observational and case-control studies showing that loop recorders lead to earlier diagnosis and reduce the rate of unexplained syncope. However, even if a systematic literature search was performed, no attempt to combine the available data was made. One of the strengths of the present study is that data of 44 studies enrolling more than 4000 subjects were combined. Moreover, clinically relevant outcomes, such as the proportion of subjects needing a PM implant or being diagnosed with ventricular tachyarrhythmia, besides the overall diagnostic yield, were analyzed.

Our data show that the overall diagnostic yield of ILR in subjects with unexplained syncope is 44%. About 25% of the enrolled patients was diagnosed with an arrhythmia, while for the others the cause was considered non arrhythmic. Most of the arrhythmias detected were bradyarrhythmia (18.2% of the total subjects), followed by supraventricular tachyarrhythmia (4.9%) and ventricular tachycardia (2.7%).

The diagnostic yield of ILRs relies on both the syncope recurrence probability and the capability of the ILR to record the ECG during syncope. However, from a clinical perspective, syncope recurrence itself might not be so important, as the influence of ILR guided therapy depends upon the diagnosis that is made and the availability of appropriate therapy for that diagnosis itself. Indeed, if ILRs were implanted in young subjects with reflex syncope their diagnostic yield could be high, as reflex syncope is very likely to recur. However, even if sometimes excluding arrhythmic syncope is necessary, their capability of changing patients' outcomes is far less evident in this case. Ideally, ILRs should be used in situations where life-threatening arrhythmias (such as ventricular fibrillation or tachycardia) have been reasonably excluded and the capture of a relevant arrhythmia during spontaneous syncope might change the patient's management.

Besides their ability in recognizing treatable arrhythmias, in order to judge the clinical benefit of ILRs, both ILR-related adverse events and quality of life should be considered[66]. While the present work

shows that ILR infections or complications and death due to arrhythmic events are rare, data on the quality of life of patients who received an ILR-guided diagnosis as compared to a conventional diagnostic strategy are lacking. Also, we tried to assess the ability of an ILR-guided therapy to reduce syncope recurrence. Unfortunately, only a few studies reported in this outcome, and none of them was specifically designed for this purpose. Therefore, a formal meta-analysis was not possible in this case.

Heterogeneity is an important limitation to be acknowledged: the proportion of subjects diagnosed with either bradyarrhytmia or ventricular arrhythmia ranged from 5% to 39% and from 0% to 12.7%, respectively. None of the subgroup and sensitivity analyses have explained such heterogeneity and meta-regressions did not find any significant association between the diagnostic yield and the studies' characteristics. Heterogeneity could be due to different causes including the different enrolled populations, follow up, reference standard for diagnosis and healthcare systems of the studies. Since the new-generation ILRs perform very well in recording ECG during syncope, their diagnostic yield relies mainly on patients' selection. Albeit the studies' selection criteria were similar, their results seem to suggest that the patients who were included were remarkably different. The absence of standardised methods to assess unexplained syncope makes physicians with different expertise or working in different settings use different criteria to deem a patient eligible for ILR implant. Indeed, the pre-implant syncope assessment included ECG and ECG monitoring with either Holter ECG or telemetry in all patients, while the proportion of subjects undergoing an echocardiogram, a tilt table test or an electrophysiology study was very different among the studies. Moreover, even if classification criteria for ILR finding have been suggested[10], they have not been validated and were not widely adopted in the included studies. Therefore, no reference standard exists and the same ECG finding at ILR recording might have been interpreted differently in the various studies. Furthermore, the inclusion of both symptomatic and asymptomatic (even though significant) arrhythmias could be a source of heterogeneity. The separate analysis of symptomatic and asymptomatic events was impossible, as it would have required individual patients' data. However, the pre-defined subgroup analysis of studies in which arrhythmias were detected during symptoms or during both symptoms and asymptomatic events did not show a difference in the diagnostic yield.

Finally, although this is unlikely, as we have checked for and tried to exclude them, the inclusion of both big registry studies and local data reports might have led to the duplicate reporting of the same patient. Unfortunately, not even the analysis of individual patients data could have avoided this.

In conclusion, the overall diagnostic yield of ILR in subjects with unexplained syncope was 44%. About 25% of the enrolled patients were diagnosed with an arrhythmia and most of the arrhythmias detected were bradyarrhythmias, followed by supraventricular tachyarrhythmias and ventricular tachycardias. A ILRs-based diagnostic strategy seems to be safe, as life-threatening arrhythmias were infrequent and ILR infections or complications and death due to arrhythmic events were rare. Future studies should adopt homogeneous inclusion criteria and consistent reference standards for the diagnosis of the different syncope aetiologies. Moreover, further data on the capability of ILRs to change clinically relevant outcomes, besides increasing the diagnostic rate, are warranted.

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FIGURE LEGENDS

Figure 1 – Pooled estimate of the diagnostic yield of ILRs.

Figure 2 – Pooled estimate of the diagnostic yield of ILR for the diagnosis of arrhythmic syncope.

Figure 3 – Pooled estimate of the diagnostic yield of ILR for the diagnosis of ventricular arrhythmias.

Figure 4 – Pooled estimate of the diagnostic yield of ILR for the diagnosis of supraventricular arrhythmias.

Figure 5 – Pooled estimate of the diagnostic yield of ILR for the diagnosis of bradycardia requiring a permanent pacemaker implantation.

Figure 6 – Pooled estimate of the proportion of an analysable ECG recording after symptoms.

Figure 7 – Funnel plot of the diagnostic yield on the number of enrolled patients.

Figure 8 – Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

APPENDICES

Supplementary Figure 1 – Study selection progression.

Supplementary Figure 2 – Meta-regressions of i) year of the beginning of the study; ii) number of enrolled patients; iii) percentage of patients affected by cardiovascular disease; iv) mean duration of follow up and v) mean time to diagnosis on the primary outcome.

Supplementary Table 1 – Characteristics of the included studies.

Supplementary Table 2 – Subgroup and sensitivity analyses.

PRISMA 2009 Checklist

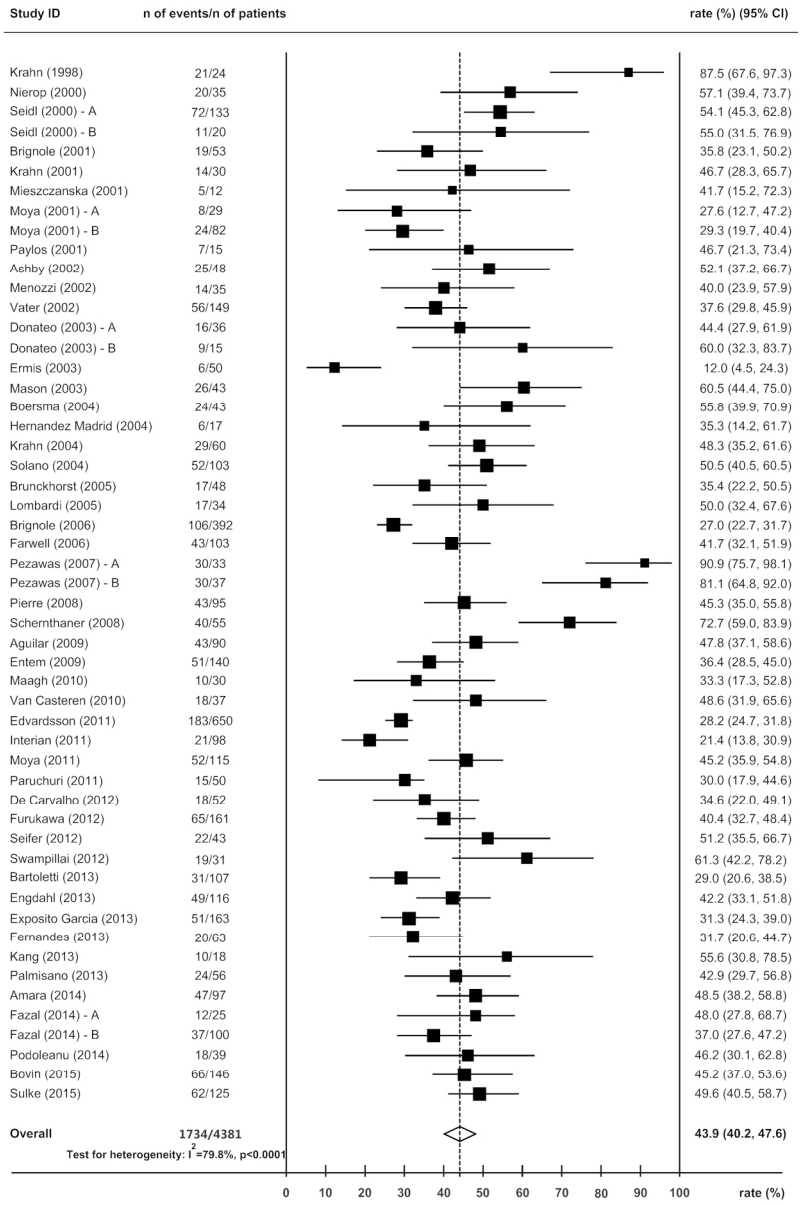
Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

PRISMA 2009 Checklist

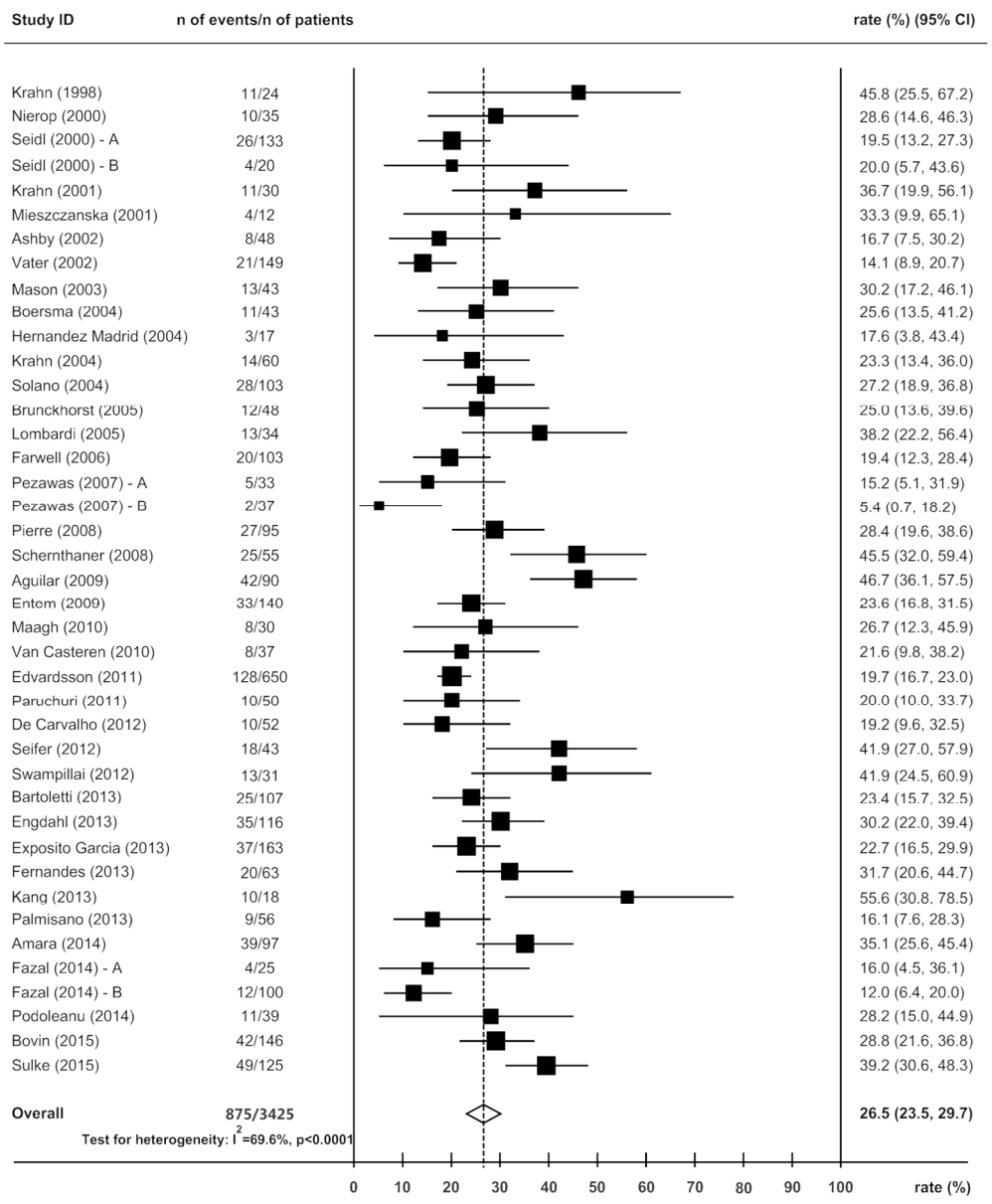
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6-7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Figure 8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 1-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.



Pooled estimate of the diagnostic yield of ILRs.
135x203mm (300 x 300 DPI)



Pooled estimate of the diagnostic yield of ILR for the diagnosis of arrhythmic syncope.
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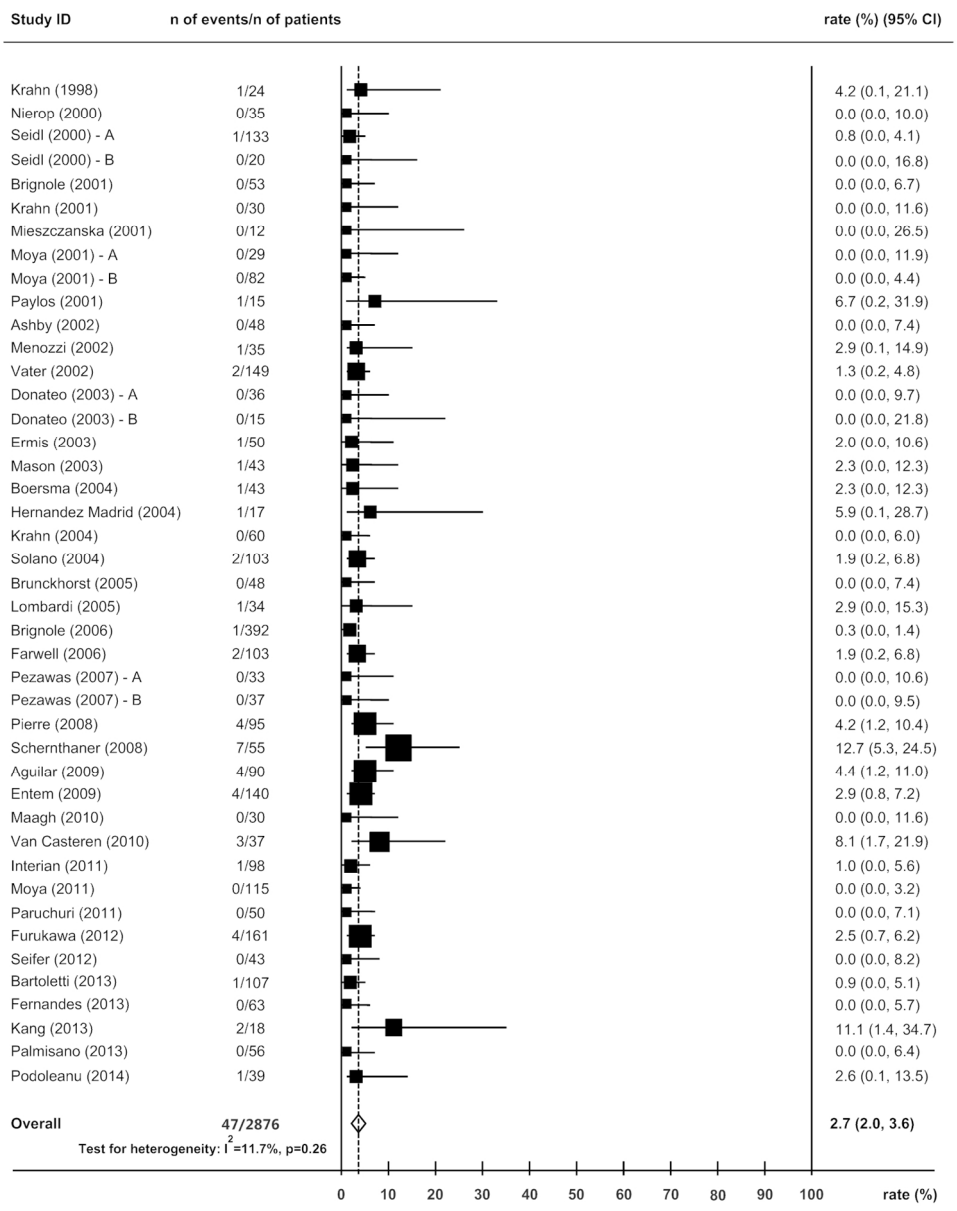

Pooled estimate of the diagnostic yield of ILR for the diagnosis of ventricular arrhythmias.
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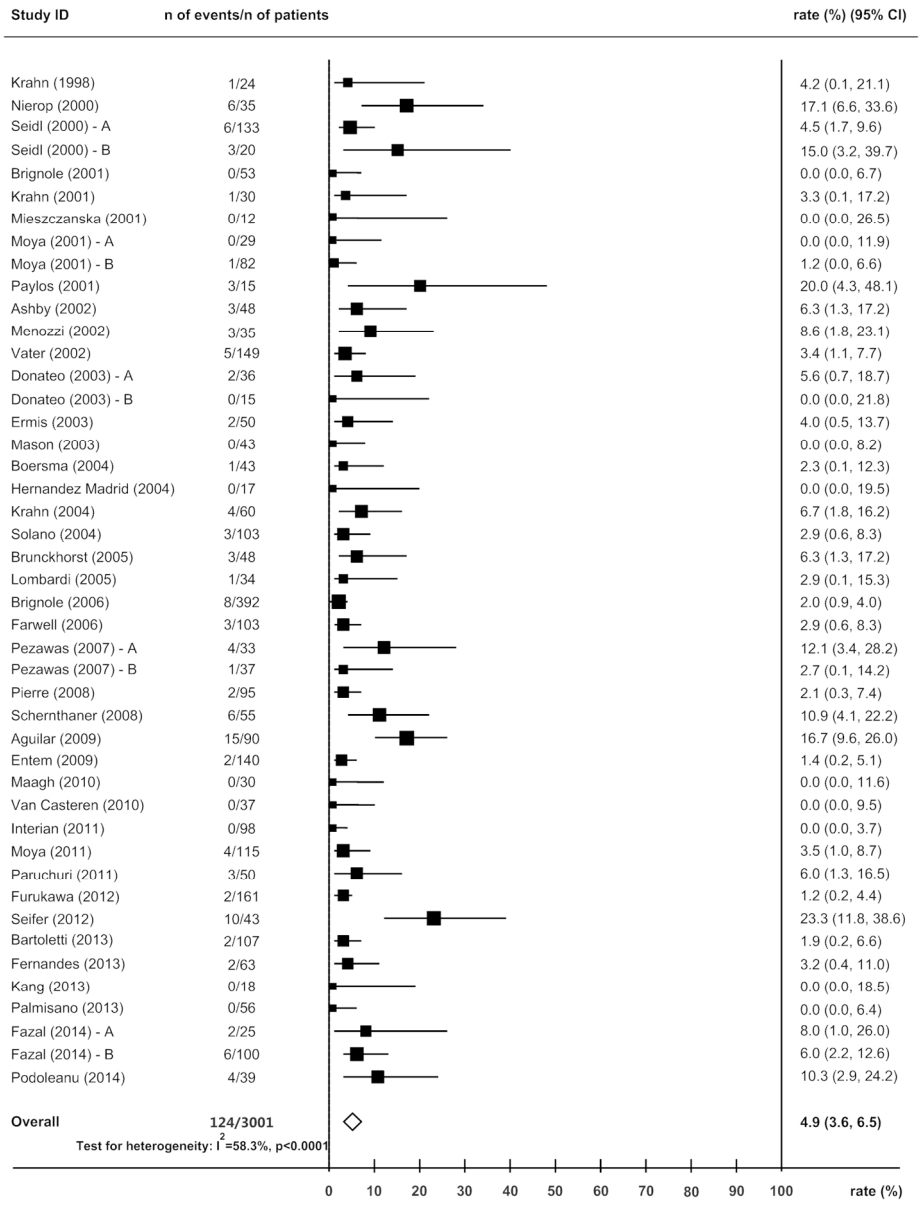

Pooled estimate of the diagnostic yield of ILR for the diagnosis of supraventricular arrhythmias.
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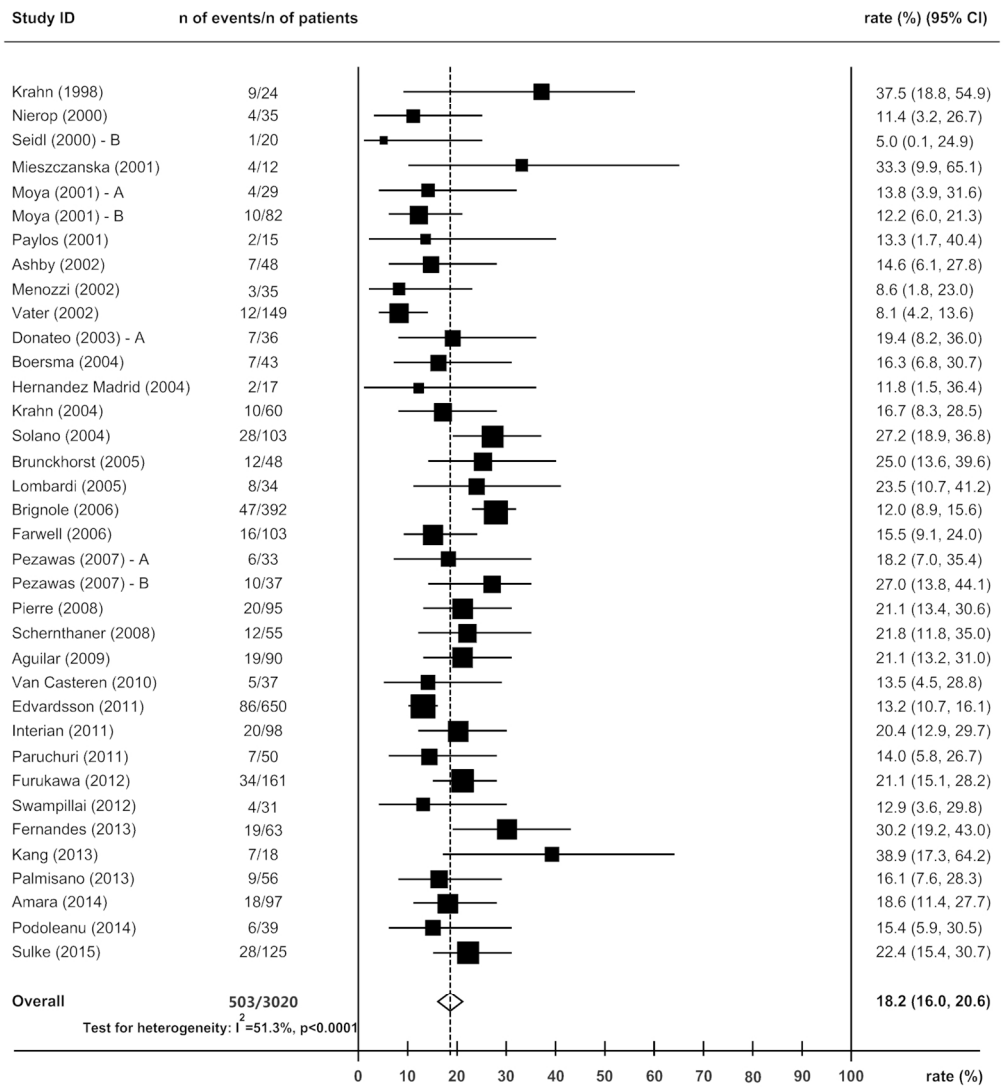
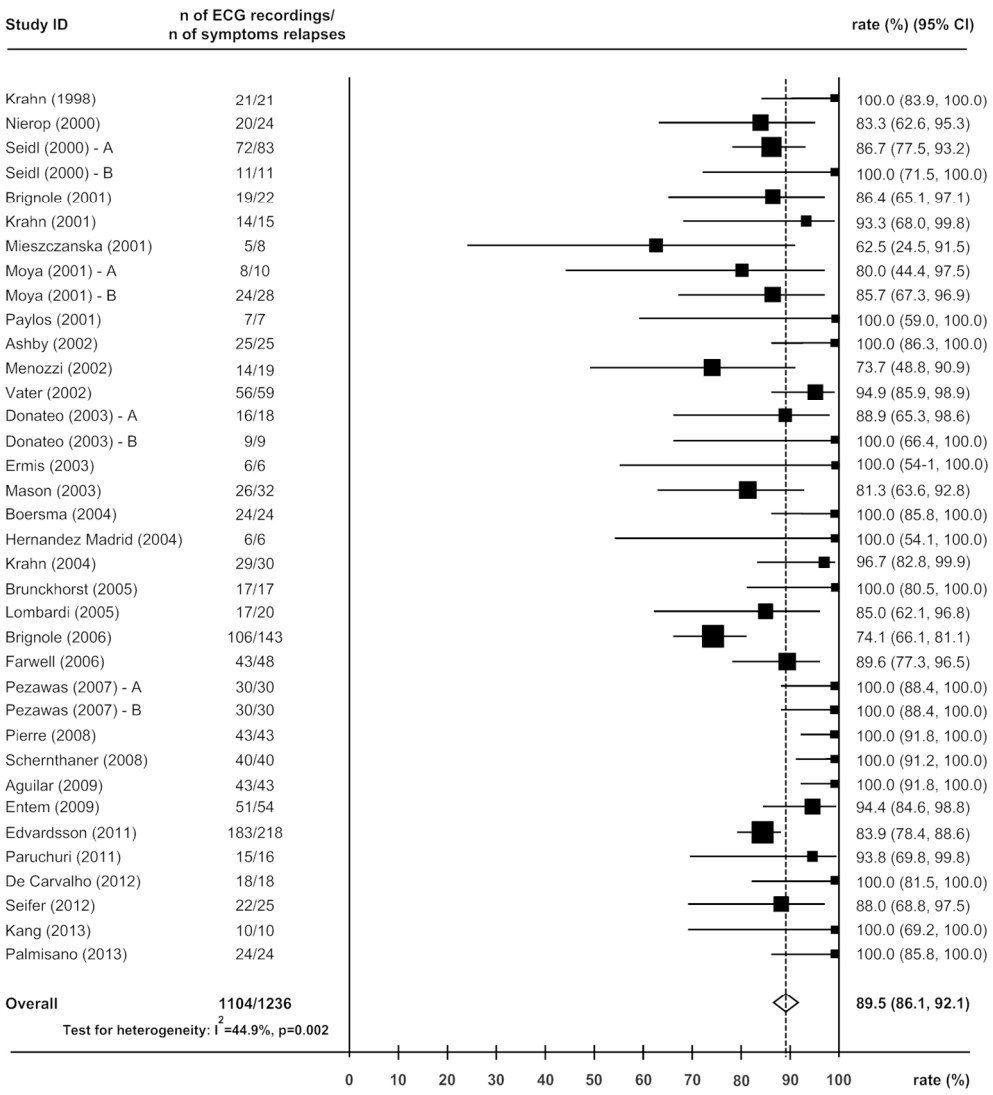
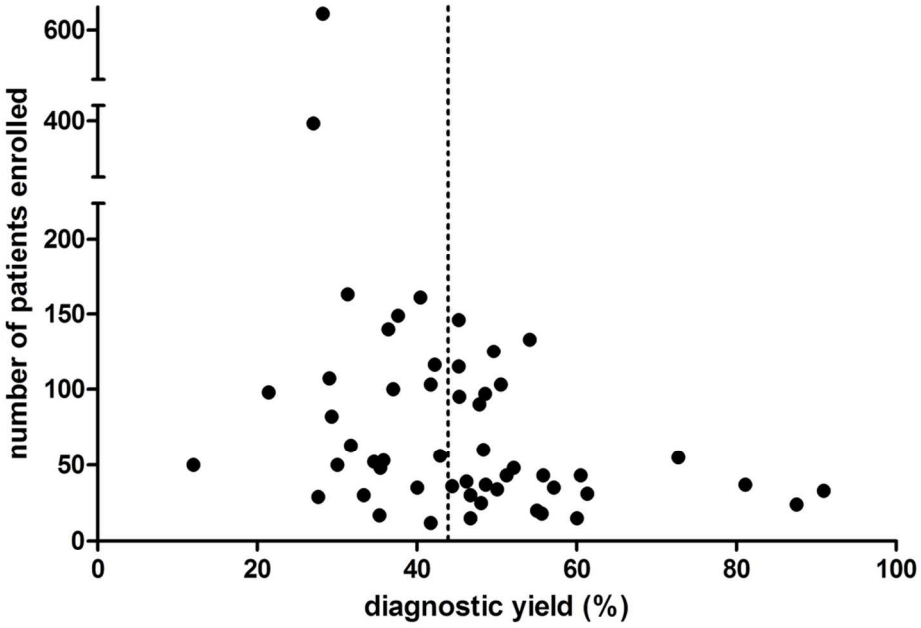


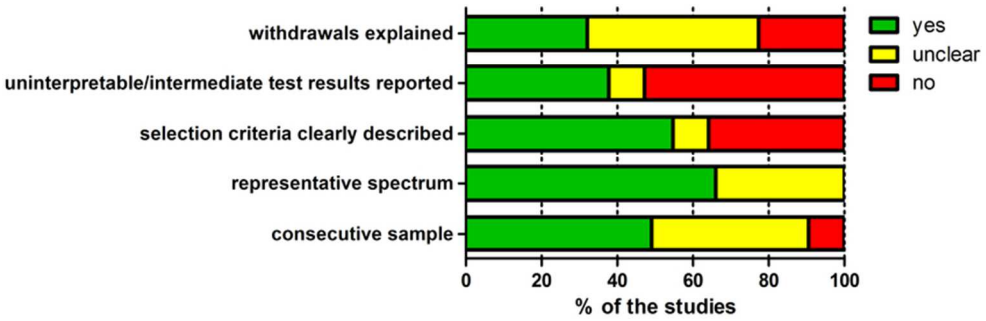
Pooled estimate of the diagnostic yield of ILR for the diagnosis of bradycardia requiring a permanent pacemaker implantation.
135x146mm (300 x 300 DPI)



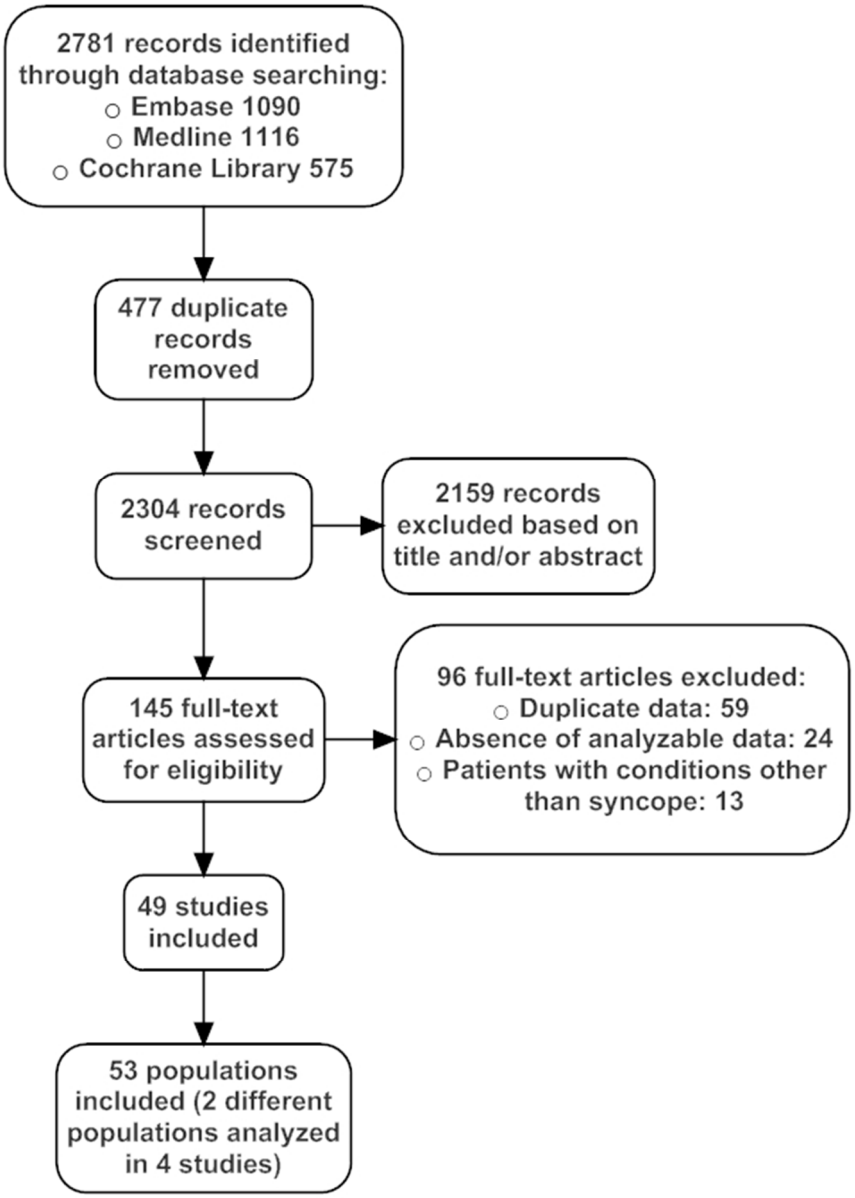
Pooled estimate of the proportion of an analysable ECG recording after symptoms.
136x148mm (300 x 300 DPI)



Funnel plot of the diagnostic yield on the number of enrolled patients.
101x69mm (300 x 300 DPI)



Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.
72x26mm (300 x 300 DPI)



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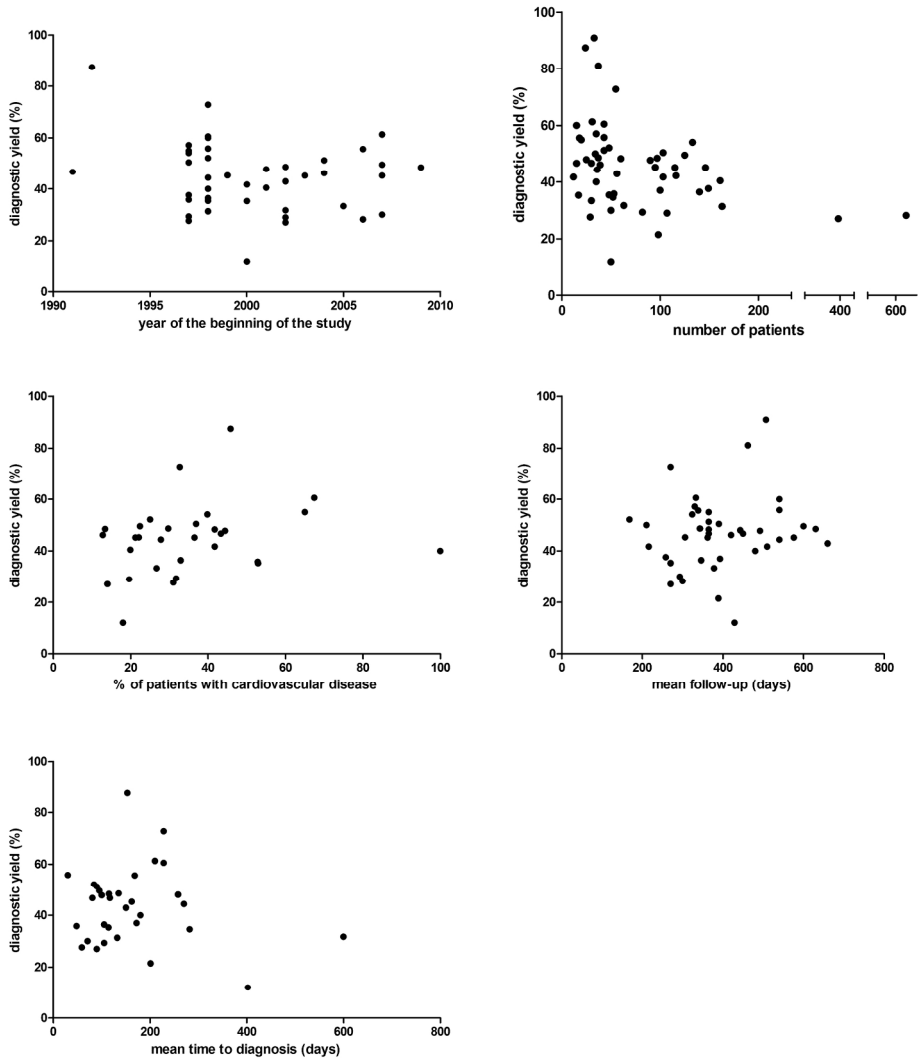

206x230mm (300 x 300 DPI)

Supplementary Table 1 – Characteristics of the included studies

Author and citaction	Publication year	Region of origin	Year of study begin	Multicenter study	Prospective study	Type of ILR	Population enrolled	Mean follow-up (days)	Number of patients	% of males	Mean age (years)	Number of syncope spells before enrollment	% of patients with cardiovascular diseases	% of patients with ECG abnormalities	% of patients with bifascicular block	Measured outcome	Mean time to diagnosis (days)	Number of deaths	Number of cardiovascular deaths	Number of patients with ILR-related complications
Krahn	1998	North America	1992	no	yes	Reveal	Recurrent syncope	n.r.	24	70	59	7.2	46			syncope	153	0		
Nierop	2000	Europe	1997	no	yes	Reveal 9525	Recurrent syncope	330	35	43	65			46	29	syncope or pre-syncope		3		
Seidl	2000	Various	1997	yes	no	Reveal 9525	Recurrent syncope	324	133	50	56		40			syncope or pre-syncope		3	0	5
Seidl	2000	Europe	1997	no	yes	Reveal	Recurrent syncope	365	20	55	63		65			syncope or pre-syncope				
Brignole	2001	Europe	1997	yes	yes	Reveal	Syncope and BBB	n.r.	53	83	71		53	100	79	syncope	48	1	1	
Krahn	2001	North America	n.r.	no	yes	Reveal	Recurrent syncope	365	30	63	68	4.1	43	33		syncope or pre-syncope	117	1	0	0
Mieszczanska	2001	n.r.	n.r.	no	no	Reveal, Reveal plus	Recurrent syncope	216	12	50	61	6	42			syncope				0
Moya	2001	Europe	1997	yes	yes	Reveal	Recurrent syncope	300 270	29 82	38 55	64 63		31 32	24 26		syncope	59 105	0 0		
Paylos	2001	Europe	1991	no	yes	Reveal 9525	Recurrent syncope	450	15	27	40					syncope or pre-syncope	81	0		0
Ashby	2002	Oceania	1998	yes	no	Reveal	Recurrent syncope	168	48	44	71		25			syncope or pre-syncope	84			
Menozzi	2002	Europe	1998	yes	yes	Reveal	Suspected	480	35	89	66		100	0	0	syncope or	180	0	0	0

							cardiac syncope									pre-syncope				
Vater	2002	Europe	1997	yes	no	Reveal	Recurrent syncope	258	149	51	55					syncope or pre-syncope				1
Donateo	2003	Europe	1998	yes	yes	Reveal	Recurrent syncope	540 480	36 15	39 67	69 61	6	28			syncope	270	0	0	0
Ermis	2003	North America	2000	yes	n.r.	Reveal plus	Recurrent syncope	429	50	54	64		18			syncope or pre-syncope	402	3		0
Mason	2003	North America	1998	yes	no	Reveal, Reveal plus	Recurrent syncope	333	43	39	63		67			syncope	228	0	0	2
Boersma	2004	Europe	1998	yes	yes	Reveal, Reveal 9526	Recurrent syncope	540	43	49	57	4		19	12	syncope or pre-syncope	30			
Hernandez Madrid	2004	Europe	2000	no	yes	Reveal	Syncope and BBB	270	17	65	70	2.4	53			syncope or pre-syncope	114	0		
Krahn	2004	North America	n.r.	no	yes	Reveal plus	Recurrent syncope	365	60	45	67	4	42			syncope	115			
Solano	2004	Europe	1997	yes	yes	Reveal, Reveal plus	Recurrent syncope	390	103	55	69	11	37	25		diagnosis		4	1	
Brunckhorst	2005	Europe	1998	no	yes	Reveal, Reveal plus	Recurrent syncope	270	48	48	42			21	10	syncope				
Lombardi	2005	Europe	n.r.	yes	yes	Reveal plus	Recurrent syncope	210	34	62	60					syncope or pre-syncope				0
Brignole	2006	Various	2002	yes	yes	Reveal plus	Recurrent syncope	270	392	45	66	6	14	14		syncope	90	7	2	4
Farwell	2006	Europe	2000	no	yes	Reveal plus	Recurrent syncope	510	103	45	74	3				syncope		8		0
Pezawas	2007	Europe	n.r.	no	yes	Reveal plus	Recurrent syncope	507 462	33 37	58 41	58 51	2.4 5.2			8	syncope or pre-syncope		0 0		
Pierre	2008	Europe	1999	no	yes	Reveal plus	Recurrent syncope	306	95	60	64	4.9	22	31	13	syncope	162	1	1	
Schernthaner	2008	Europe	1998	no	no	Reveal,	Recurrent	270	55	62	60		33	7		syncope or	228			

						Reveal plus	syncope								pre-syncope				
Aguilar	2009	Europe	2001	no	yes	Reveal plus	Recurrent syncope	492	90	47	60		44			syncope or pre-syncope	100	0		0
Entem	2009	Europe	1998	no	yes	Reveal, Reveal plus	Recurrent syncope	346	140	62	64		33			syncope	105	7		1
Maagh	2010	Europe	2005	no	no	n.r.	Recurrent syncope	378	30	43	58		27			syncope			0	
Van Casteren	2010	Europe	2002	no	no	Reveal plus, Reveal XT	Recurrent syncope	343	37	43	49		30	11		diagnosis				
Edvardsson	2011	Various	2006	yes	yes	Reveal plus, DX, XT	Recurrent syncope	300	650	46	61	4				syncope				
Interian	2011	North America	n.r.	no	n.r.	n.r.	Recurrent syncope	389	98	37	75					syncope or pre-syncope	201			
Moya	2011	Europe	2003	yes	yes	Reveal plus	Syncope and BBB	576	115	59	73	3	37	100	79	diagnosis		3	3	
Paruchuri	2011	North America	2007	no	yes	Sleuth	Suspected cardiac syncope	293	50	36	70			30	18	syncope or pre-syncope	71	3		
De Carvalho	2012	Europe	n.r.	no	n.r.	n.r.	Recurrent syncope	n.r.	52	42	61					syncope	282			0
Furukawa	2012	Europe	2001	n.r.	no	Reveal plus, DX	Recurrent syncope	n.r.	161	55	69	3	20	27		diagnosis		3	3	2
Seifer	2012	North America	2004	no	yes	Reveal plus, Dx	Recurrent syncope	365	43	33	83	4				syncope	90			
Swampillai	2012	Oceania	2007	no	no	n.r.	Recurrent syncope	480	31	55	46					diagnosis	210	2	2	
Bartoletti	2013	Europe	2002	yes	no	Reveal plus, DX, XT	Recurrent syncope	n.r.	107	60	67	3	20		14	diagnosis				
Engdahl	2013	Europe	n.r.	yes	no	n.r.	Recurrent syncope	n.r.	116	70	59	7.2				syncope	153	0		
Exposito Garcia	2013	Europe	1998	no	no	Reveal,	Recurrent	n.r.	163	63	65					syncope	132			

						Reveal plus, DX	syncope												
Fernandes	2013	Europe	2002	no	n.r.	n.r.	Recurrent syncope	n.r.	63	n.r.	63				8	syncope	600			
Kang	2013	Asia	2006	no	no	Reveal plus, DX, Confirm	Recurrent syncope	339	18	72	61	5				syncope	168			
Palmisano	2013	Europe	2002	yes	no	Reveal plus, DX, XT	Suspected cardiac syncope	660	56	61	68	3		55	11	syncope	150	0		0
Amara	2014	Europe	2009	no	no	Reveal XT, DX	Recurrent syncope	630	97	57	71	1.7	13		12	diagnosis	135	2	0	2
Fazal	2014	Europe	n.r.	no	no	Reveal XT	Recurrent syncope	404	125	38	53					diagnosis	189			
Podoleanu	2014	Europe	2004	yes	yes	Reveal, Reveal plus	Recurrent syncope	420	39	46	68	4.6	13			diagnosis				
Bovin	2015	Europe	2007	no	no	n.r.	Recurrent syncope	362	146	31	n.r.		21			diagnosis				
Sulke	2015	Europe	2007	no	yes	Sleuth	Recurrent syncope	600	125	38	72		22			diagnosis	95			1

n.r.: not reported or unclear; ILR: Implantable Loop Recorder; BBB: bundle branch block.

Supplementary Table 2 – Subgroup and sensitivity analyses

Subgroup	n of events	N of patients	N of studies	Diagnostic yield	95% IC	I^2
Diagnosis during symptoms	1255	3295	41	43.7%	39.1, 48.4	82.1
Diagnosis during both symptoms and asymptomatic arrhythmias	479	1086	12	44.6%	40.4, 48.9	46.9
Prospective studies only	1006	2591	30	45.8%	40.6, 51.1	81.8
Studies with less than 5% of patients lost to follow-up	614	1401	17	51.7%	43.5, 59.9	86.4
Studies with consecutive patients only	791	1877	26	47.0%	41.3, 52.7	80.5