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Discrepancy between clinical practice and standardized indications for an implantable loop recorder in patients with unexplained syncope†

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Aim An implantable loop recorder (ILR) is indicated in patients with unexplained syncope after complete conventional work-up. Data from the literature imply that, in clinical practice, the ILR is underused. The aim of the study was to verify if there is any discrepancy between the use of ILRs in clinical practice and the potential indications based on the most potentially appropriate guideline indications.

Method and results We compared the prevalence of ILRs actually implanted in patients with unexplained syncope in the Syncope Unit Project (SUP) study and the potential one using the standard given by the guidelines. In the SUP study, 28 (18%) out of 159 patients with unexplained syncope received an ILR. Appropriate criteria for implantation of ILRs according to guidelines were present in 110 (69%) patients. Moreover, 7 (25%) of ILRs actually implanted did not satisfy the guideline standards. During the follow-up, 32% of patients who had received an ILR had a diagnosis compared with 5% of those who did not ($P = 0.001$).

Conclusions The estimated indications were four times higher than those observed. Moreover, in about one quarter of the cases, the use of ILRs proved to be potentially inappropriate according to guideline indications. Two-thirds of patients with unexplained syncope had indications potentially appropriate for ILRs.

Keywords Syncope • Electrocardiographic monitoring • Implantable loop recorders, guidelines

Introduction

Despite recent advances in diagnostic procedures, syncope remains unexplained in 17–37% of patients.[1] Even in specialized syncope facilities, the rate of unexplained syncope is, with a few exceptions, around 18–20%.[1] Thus, the present strategy of management cannot be considered satisfactory. Implantable loop recorders (ILRs) are indicated in patients with unexplained syncope after a complete conventional work-up.[1] Currently, the prevalence of using ILRs in the real-world is unknown for patients with unexplained syncope. Solano *et al.*[2] have estimated that 5% of all patients referred to two tertiary centres for the evaluation of syncope and 28% of those with unexplained syncope had received an ILR after complete work-up. In the Evaluation of Guidelines in Syncope Study 2,[3] of 269 patients referred to Emergency Department, only 1% received an ILR.

We assumed that ILRs are still underused in everyday clinical practice. As a consequence, we have studied patients in the Syncope Unit Project (SUP)[4] who still remained with a diagnosis

†The Syncope Unit Project (SUP) investigators are listed in the Appendix.

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of unexplained syncope after the complete conventional work-up. The aim of our study was to confirm if there is a discrepancy between the use of ILRs in everyday clinical practice and their potential for greater use. The indications were based on the application of restricted criteria from the recently published position paper of the European Heart Rhythm Association (EHRA)[5] and the guidelines on syncope of the European society of Cardiology (ESC).[1]

Method

In the multicentre, prospective, and observational SUP study,[4] the real-world practice of nine Italian hospitals equipped with Syncope Units was documented. In brief, physicians of the nine Syncope Units applied the diagnostic-therapeutic pathway protocol for diagnosis and treatment of syncope from ESC guidelines and were supported by software called 'Syncope web'.[4] Consecutive patients, referred from 15 March to 15 September 2008 were included. Of the 700 patients who underwent investigations to identify the nature of loss of consciousness, a diagnosis was established in 541 patients at the end of full conventional work-up and remained unexplained in 159 patients. These patients with unexplained syncope constitute the population of the present study and, at this point, started clinical follow-up. Follow-up data were collected in autumn 2009.

We compared the prevalence of ILRs actually implanted (indicated by the physician investigator) and that estimated using restricted criteria based on Class I recommendations of the recently published EHRA[5] and ESC guidelines.[1] The implant of an ILR was considered appropriate when the patient had one of these characteristics:

(i) unexplained syncope and structural heart disease or coronary artery disease,
(ii) unexplained syncope in patients with bundle branch block, and
(iii) unexplained syncope in patients with absence of significant structural heart disease, age $\geq$40, and three or more episodes of syncope during the last 2 years.

These criteria are more restrictive than those of Class I of EHRA[5] and ESC guidelines[1] because, in contrast, patients without cardiac disease were included only if they had had three or more episodes of syncope in the previous 2 years and age $\geq$40 years.

Moreover, we calculated the number of ILRs which did not meet the previously mentioned requirements, and were thus considered inappropriate indications.

For all other inclusion and exclusion criteria, reference to the SUP[4] study should be made. Data were reported as mean $\pm$ 1 standard deviation or as median with inter-quartile range as appropriate. Comparison between actual observed and estimated indications for ILRs was performed by means of cross-tabulation and Kappa statistics for measurements of agreement between indications according to physician practice and guidelines. Comparison between two continuous variables, which had a non-Gaussian distribution, was performed by applying the Mann–Whitney non-parametric test. Comparison between proportions was made by means of the Fisher's exact test.

Results

The clinical data of the 159 patients with unexplained syncope are shown in *Table 1*; 28 received an ILR and 131 did not. There were no significant differences between those who received an ILR and those who did not.

Appropriate criteria for implantation of an ILR (as established by our method) were present in 110 (69%) patients. In contrast, ILRs had been actually implanted in 28 (18%) patients, $P < 0.0001$ vs. estimated criteria (*Table 2* and *Figure 1*). Consequently, there was a high discrepancy between observed and estimated indications [kappa test = 0.03 (CI −0.06 to 0.10)]. Thus, the estimated indications were four times higher than those observed: 110 (16%) vs. 28 (4%) of all 700 patients who had undergone a full conventional diagnostic work-up, which corresponds to 69 vs. 18% of the 159 patients with unexplained syncope. Among the 110 patients with potential indications for an ILR, 56 belonged to the subgroup with structural or coronary heart

Table 1 Characteristics of the 131 patients with unexplained syncope who did not receive an ILR and of those 28 who did

	No ILR (n = 131)	ILR (n = 28)	P -value
Median age (inter-quartile range)	73 (65–80)	70 (61–75)	0.90
Male gender (%)	81 (62)	17 (61)	0.90
History of T-LOCs:			
First episode (%)	33 (25)	3 (11)	0.17
Recurrent T-LOCs, n (%)	98 (75)	25 (89)	0.17
median number (inter-quartile range)	3 (2–6)	4 (3–6)	0.11
duration (years; inter-quartile range)	2 (1–5)	4 (1–5)	0.58
No warning at the onset of the attack (%)	55 (42)	14 (50)	0.57
Structural heart disease (%)	68 (52)	8 (28)	0.36
coronary artery disease (%)	33 (25)	6 (21)	0.84
hypertensive cardiopathy (%)	13 (10)	1 (4)	0.52
valvular (%)	7 (5)	1 (4)	0.79
others (%)	15 (11)	0 (0)	0.14
Electrocardiographic abnormalities (%)	66 (50)	9 (32)	0.13
sinus bradycardia <50 b.p.m. (%)	14 (11)	0 (0)	0.14
bundle branch block (%)	34 (27)	7 (25)	0.13
ST-T abnormalities and/or ischaemia (%)	9 (7)	1 (4)	0.14
atrial fibrillation/flutter (%)	9 (7)	1 (4)	0.98
OESIL risk score, median (inter-quartile range)[6]	3 (1–3)	2 (1–3)	0.87
EGSYS risk score, median (inter-quartile range)[7]	2 (0–3)	1 (0–3)	0.14

T-LOC, transient loss of consciousness; OESIL, Osservatorio Epidemiologico sulla Sincope nel Lazio; EGSYS, Evaluation of Guidelines in Syncope Study.

Table 2 Relationship between observed and estimated implantable loop recorder indications

Total patients with unexplained syncope ($n = 159$)	ILR implanted (observed) ($n = 28$)	ILR not implanted (observed) ($n = 131$)
ILR potentially indicated (estimated) ($n = 110$)	21	89
ILR not indicated ($n = 49$)	7	42

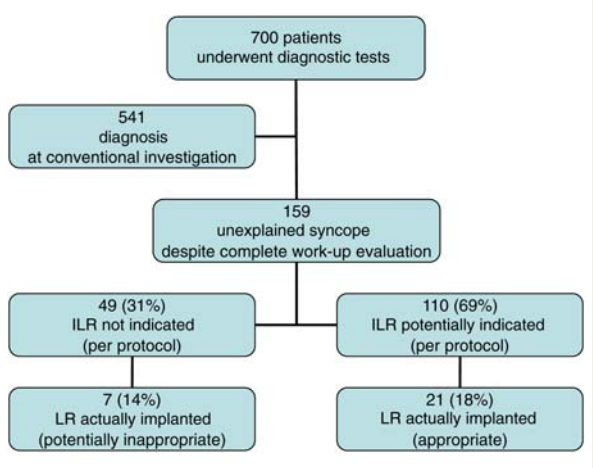

Figure 1 Flow diagram of the patients evaluated for syncope. ILR, implantable loop recorder; LR, loop recorder.

disease, 11 to that of bundle branch block in the absence of overt structural heart disease, and 43 to that of recurrent syncope without structural heart disease. The prevalence of ILRs actually implanted in these three subgroups was 8 (14%), 4 (36%), and 9 (21%), respectively. Finally, the remaining seven (25%) implanted patients had potentially inappropriate ILR indication. They belonged to the group with recurrent syncope without structural heart disease: five of these had no structural heart disease and less than three syncopal episodes during the last 2 years and two had no structural heart disease and age <40 years.

During the subsequent follow-up period, 32% of patients who had received an ILR had a diagnosis compared with 5% of those who did not: odds ratio 8.7 (CI 2.9–26.5), $P = 0.001$ (*Table 3*). As a consequence, more ILR patients finally received a therapy. Specifically, a cardiac pacemaker was implanted in 25% of ILR patients vs. 8% of those who did not receive an ILR ($P = 0.02$).

Discussion

The most important conclusion of this study is that there is a discrepancy between clinical practice and standardized indications for ILRs in patients with unexplained syncope. Apparently, there were no major clinical differences between those who received an ILR and those who did not. The estimated indications were four times more than those observed. In addition, in about one quarter of cases, the use of ILRs proved likely to be inappropriate. Inappropriate indications were observed in patients with recurrent syncope without structural cardiac disease or coronary artery disease.

Table 3 Follow-up results

	No ILR ($n = 131$)	ILR ($n = 28$)	*P* -value
Follow-up length (days)	385 ± 175	360 ± 221	0.5
Death (%)	6 (5)	1 (4)	0.6
Syncopal recurrence			
patients (%)	18 (15)	6 (21)	0.2
ECG documentation (%)	1 (1)	6 (21)	0.001
Other symptomatic ECG-documented events (%)	0 (0)	3 (11)	0.005
Total diagnoses, *n* (%)	6 (5)	9 (32)	0.001
long asystolic pauses		6	
Severe bradycardia	1[a]	2	
Carotid sinus syndrome	2		
Ventricular tachycardia	1[a]		
Rapid atrial fibrillation	1[a]		
Cadioinhibitory vasovagal syncope (tilt testing)	1		
Psychogenic pseudosyncope		1	
Time to diagnosis (days)	157 ± 122	110 ± 129	0.07
Cardiac pacing, *n* (%)	11 (8)	7 (25)	0.02
ECG-guided cardiac pacing (diagnosis)	3	6	
Empirical cardiac pacing (no diagnosis)	8		
Implantable defibrillator (%)	1 (1)	0 (0)	0.8
ILR after syncopal recurrence (%)	3 (2)	–	

[a]Diagnosed by Holter monitoring.

The follow-up data of the present study confirm the diagnostic usefulness of an ILR strategy (*Table 3*). Indeed, without ILRs, the electrocardiogram (ECG) documentation of a spontaneous syncope was very unlikely during the subsequent year of follow-up, and a presumed diagnosis based on new positive findings of tests that were initially negative could be made in only 5% of cases. Conversely, the ILR strategy allowed 8.7 higher likelihood of ECG diagnosis, which was bradyarrhythmic in most of the cases. As a consequence, specific therapy could be prescribed in a higher percentage of patients.

According to the criteria used in this study, made in accordance with Class I indications of the recent EHRA and ESC guidelines,[1,5] two-thirds of patients with unexplained syncope had indications potentially appropriate for ILRs. These indications are justified, on one hand, by the high risk of life-threatening arrhythmias in patients with structural or coronary heart diseases or bundle branch block and, on the other hand, by the need to prevent cases of potentially traumatic syncopal relapses. Although it is well known that structural cardiac disease is itself the most

important negative predictor of unfavourable outcomes,[1,8] paradoxically the most important discrepancy with clinical practice was observed in the patients with unexplained syncope and concomitant heart disease who received an ILR only in 14% of cases.

Our follow-up data are in line with those reported in the literature. Several previous studies have shown the usefulness of ILRs in discovering the arrhythmic cause of unexplained syncope, so leading to a specific therapy. Indeed, several studies[9–16] have thoroughly documented that the ILR is able to provide a correlation between syncope and ECG findings in 34% of cases (265 of 787 patients). In particular, in patients with unexplained syncope and presence of moderate structural heart disease (defined as ejection fraction >35% and negative electrophysiological study), Krahn *et al.*[17] and Menozzi *et al.*[10] have shown that the mechanism of syncope is heterogeneous, thus justifying the need for a precise diagnosis. In patients with syncope, bundle branch block, and negative electrophysiological study, ILRs were reliable in correlating the syncopal relapse and abnormal ECG in 37% of cases, two-thirds of these being caused by prolonged asystole due to paroxysmal atrioventricular block.[11] In the patients with recurrent syncope, some studies[9,12,14] showed that ILRs had a diagnostic yield ranging between 29 and 69% with a high percentage of cases having a rather homogeneous mechanism, i.e. a cardioinhibitory vasovagal reflex (bradycardia and or sinus arrest). Finally, about a quarter of the ILR patients benefited from ILR-guided specific therapy, the most frequent being cardiac pacing.[2,9–11,18,19]

In our study, we analysed only the indication for the patients with unexplained syncope because there is more scientific evidence for this. However, there are other indications for implantation of an ILR even if less well established. The International Study on Syncope of Uncertain Etiology 2[12] showed the usefulness of ILRs in patients aged >40 years with suspected neurally mediated syncope and three or more episodes of syncope. In fact, of 392 patients enrolled in this study, 106 (33%) had documentation of syncopal relapse within a median of 3 months from ILR implantation. Of these latter patients, 106 (51%) benefited by ILR-guided specific therapy, especially cardiac pacing. During the subsequent 9 months of follow-up, syncope recurred in 11% of patients who had received ILR-guided specific therapy and in 35% of patients who did not. Based on this study, the recent EHRA position paper ranks asystolic recurrent neurally mediated syncope as Class IIA indication for an ILR.[5] If this recommendation is applied to patients in the present database,[4] of 433 patients with diagnosis of reflex syncope or probably reflex syncope, a further 28 (5%) patients will have appropriate criteria for implantation of ILRs.

Finally, this study was not in a position to calculate the other indications for ILRs, for example, those for differential diagnosis between syncope and epilepsy[20,21] or syncope and non-accidental falls in older patients.[22]

Incidence

Assuming a population of the referral districts of the nine Syncope Units of 1 870 000 inhabitants[4] the observed incidence of implanted ILRs is 30 per million inhabitants per year (CI 23–39), a figure which is very similar to that of 34 per million inhabitants per year calculated by Solano *et al.*[2] in patients with unexplained syncope. These figures seem, therefore, to be representative of real-world practice in Italy. On the contrary, the estimated incidence according to our predefined criteria (based on Class I indications of the EHRA and ESC guidelines[1,5]) is 118 ILRs per million inhabitants per year (CI 103–134). How much of the dissemination of the guidelines will be able to close the gap between the observed and estimated incidence is a matter of future studies.

In addition, we have calculated the estimated incidence according to Class IIA indications of the above guidelines, i.e. in patients with suspected or certain neurally mediated syncope, assuming as appropriate the ILR implantation in patients with three or more recurrent syncopal episodes during the last 2 years with an absence of a prodrome. The resulting figure is further 23 ILRs per million inhabitants per year (CI 17–31). Thus, the total estimated incidence for Class I and IIA indications is 143 per million inhabitants per year (CI 126–161).

Study limitation

The main and obvious limitation of this study is that its results were a theoretical estimate of appropriate tests done by means of cross-sectional analysis of a database. For this reason, they are probably inaccurate. Only the systematic application of appropriate criteria in a future prospective study will be able to evaluate the real impact of ILRs in clinical practice. The incidence values should be considered purely indicative as several uncontrolled factors may affect its calculation, such as the small sample size and the potential selection bias of the patients referred to the Syncope Units. The high confidence interval of our estimation has important implications. Although supported by several studies in the literature and by the recent recommendations of EHRA and ESC guidelines,[1,5] the criteria for ILRs examined in this study remain arbitrary and might not be universally accepted. Nevertheless, this study, to our knowledge, is probably the first to attempt to estimate how ILRs should be used in patients referred to Syncope Units.

Perspectives

Syncope Unit Project study[4] showed that syncope remained unexplained despite complete work-up in 18% of patients evaluated for syncope in specialized Syncope Units. The patients referred to the Syncope Unit are *per se* the most difficult cases because they have been selected from many others. The finding that patients potentially at high risk remain without a diagnosis cannot be considered satisfactory for a specialized facility and indicates the need for a new management strategy. The present study shows that the ILR is potentially indicated in two-thirds of these patients and that it was greatly underutilized. The favourable observed diagnostic yield of an ILR strategy suggests more extensive usage of this diagnostic tool.

Conflict of interest: S.G. and L.B. are employees of Medtronic Inc.

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Appendix

The following persons participated in the SUP study:

Steering Committee: M. Brignole, Lavagna (chairman); F. Ammirati, Ostia (co-chairman); A. Castro, Roma; A. Del Rosso, Empoli; G. Demarchi, Alessandria; F. Giada, Mestre; M. Gulizia, Catania; M. Lunati M, Milano; M. Santini, Roma; A. Ungar, Firenze.

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Definition Committee: M. Brignole, R. Maggi, A. Del Rosso, F. Giada F.

Analysis of data: M. Brignole, R. Maggi, S. Giuli.

Cost analysis: N. Grovale, F. Tronconi, I. Casagranda, E. Vitale, M.R. Vecchi, A. Ungar, M. Brignole.

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Empoli, Ospedale S Giuseppe: *Attilio Del Rosso*; *Nunzia Rosa Petix; Vincenzo Guarnaccia.*

Firenze, Ospedale Careggi: *Andrea Ungar; Alessandro Morrione; Martina Rafanelli; Emilia Ruffolo.*

Lavagna, Ospedali del Tigullio: *Roberto Maggi, Francesco Croci, Alberto Solano, Daniele Oddone.*

Milano, Ospedale Niguarda: *Maria Rita Vecchi; Stefania Meregalli; Marco Strozzi.*

Ostia, Ospedale Grassi: *Fabrizio Ammirati; Roberto Colaceci; Maria Grazia Romano.*

Roma, Ospedale S. Filippo Neri: *Maurizio Piermattei; Vito Altamura; Renato Ricci*

Roma, Ospedale Pertini: Massimo Sasdelli; Antonello Castro

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