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CLINICAL REVIEW

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Implantable loop recorder in clinical practice

Antonio Bisignani MD[1] | Silvana De Bonis MD[2] | Luigi Mancuso MSc[3] | Gianluca Ceravolo MSc[3] | Giovanni Bisignani MD[2]

[1]Institute of Cardiology, Catholic University of the Sacred Heart, Rome, Italy

[2]Department of Cardiology, Ospedale "Ferrari", Castrovillari (CS), Italy

[3]Biotronik Italia S.p.A., Milan, Italy

Correspondence
Giovanni Bisignani, Department of Cardiology, Ospedale "Ferrari", Castrovillari (CS), Italy.
Email: giovanni.bisignani@virgilio.it

Abstract

The implantable loop recorder (ILR), also known as insertable cardiac monitor (ICM) is a subcutaneous device used for diagnosing heart rhythm disorders. These devices have been strongly improved and miniaturized during the last years showing several reliable features along with the availability of remote monitoring which improves the diagnostic timing and the follow-up strategy with a potential reduction of costs for health care. The recent advent of injectable ILRs makes the procedure even easier and more tolerated by patients. ILR allows the investigation of unexplained recurrent syncope with uncertain diagnosis, revealing a possible relationship with cardiac arrhythmias. In addition, it has recently been equipped with sophisticated algorithms able to detect atrial fibrillation episodes. This new opportunity may provide to the physicians systematic heart rhythm screening with possible effects on patient antiarrhythmic and anticoagulant therapy management. The use of such devices will surely increase, since they may be helpful to diagnose a wide range of disorders and pathologies. Indeed, further studies should be performed in order to identify all the potentialities of these tools.

KEYWORDS

anticoagulant therapy, atrial fibrillation, implantable cardiac monitor, implantable loop recorder, unexplained syncope

1 | INTRODUCTION

The implantable loop recorder (ILR), also known as insertable cardiac monitor (ICM) is a subcutaneous device used for diagnosing heart rhythm disorders.[1]

The first ILR, introduced in 1990,[2] was built on a pacemaker platform with poles for electrocardiographic (ECG) signal detection placed on the generator case.[3] During the following years, many technological improvements, including miniaturization, more accurate algorithms, and remote monitoring, were implemented in the new devices (Figure 1).

This device should allow to establish a correlation between symptoms and arrhythmias in order to define the best therapy for the patient.[1] Recently, ILRs have been also equipped with algorithms for atrial fibrillation (AF) detection. It is well established that there is a poor correlation between symptoms and AF.[1] Also, silent AF frequently occurs and these devices may detect a high incidence of episodes without any symptoms.

As reported in the EHRA Position Paper,[1] continuous heart rhythm monitoring with ILR will increase in clinical practice. The use of ILR may be useful for different patients, even in the absence of an established indication provided by international guidelines. In this review, we have summarized the main indications to ILR and the relative available literature.

1.1 | ILR available on the market

The ILR is a subcutaneous device that can continuously monitor heart rhythm. It can record and store ECG snapshots in case of brady or tachyarrhythmias. As for all implantable devices, the reduction in

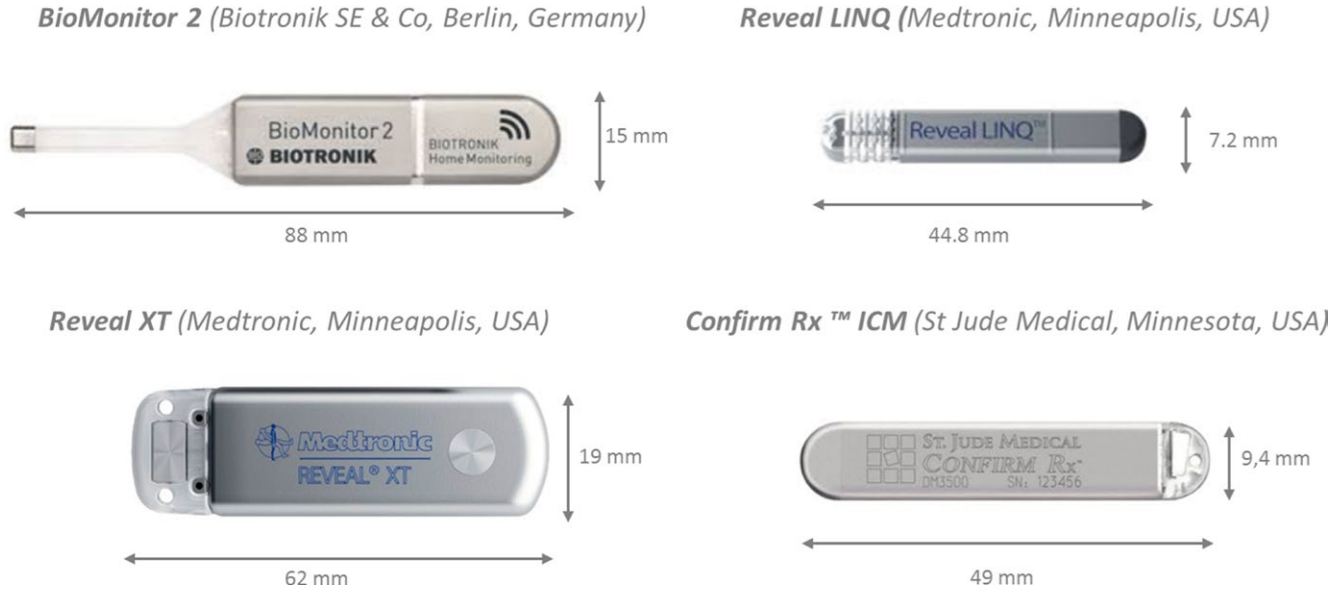

FIGURE 1 Overview of the ILR currently on the market

terms of size and weight has simplified the implant procedure making it less invasive for the patient. The last models proposed are therefore so miniaturized that they can be defined as "injectable" and, thanks to the almost negligible volume, "disappear" in the patient's subcutaneous tissue, leaving the esthetics unaltered. Equally important is the longevity of the device which is usually around 3 years. Even with several automatic algorithms, the diagnostic performances of these devices can be hampered by false-positive recordings or underdetection of true arrhythmias. The main cause is the ILR subcutaneous signal, since the electrodes are not in direct contact with the heart chambers and, therefore, the signal is more affected by interference and electrical noise. Therefore, it is crucial to avoid both "under-sensing" phenomenon that can lead to an incorrect detection of the R waves caused by the reduction of the signal amplitude, and "over-sensing" caused by myopotential signals. ILRs have limited memory; therefore, the management of their archive is crucial to avoid overwriting of significant episodes. Beyond the automatically recorded episodes, these devices can be manually activated by the patients with a remote control in case of symptoms. All devices are equipped with remote monitoring.

Table 1 summarizes the main features of the loop recorders currently available on the market.

The **BioMonitor2** (Biotronik SE & Co, Berlin, Germany) has the longest dipole (88 mm) and a battery duration of 4 years. The memory management is based on SMART algorithm which allows for storing the first, the longest, and the last episode of every automatic arrhythmia detection (atrial fibrillation, asystole, bradycardia, and high ventricular rate), in case the memory is full. The device is equipped with *Home Monitoring*^{TM} system for remote monitoring.

The **Reveal LINQ** (Medtronic, Minneapolis, USA) is the last ILR launched on the market with 2.5 g weight dipole. It is the smallest ILR, with a battery duration of 3 years and a memory management based on first in, first out (per episode) algorithm. The device is equipped with CARELINK remote monitoring.

The **Reveal XT** is the first ILR launched on the market, and the first that was equipped with separate memory between automatic recordings and activated by patient. This device is no more on the Japanese market.

The **Confirm Rx™** (St Jude Medical, Minnesota, USA) is a 3 g weight dipole with the lowest longevity, since the battery duration is 2 years. It does not have separate memory between automatic recordings and activated by patient and it is equipped with Merlyn remote monitoring provided with app for Smartphone.

2 | CLINICAL APPLICATION

2.1 | Transient loss of consciousness (T-LOC) and recurrent falls

"Transient loss of consciousness (T-LOC) is defined as a state of real or apparent LOC with loss of awareness, characterized by amnesia for the period of unconsciousness, abnormal motor control, loss of responsiveness, and a short duration."[4] Unexplained falls have recently been considered related to syncope, especially in elderly patients. Actually, it is reported that 30 percent of patients with witnessed syncope have amnesia due to loss of consciousness, and most of older patients with orthostatic hypotension presenting with falls deny loss of consciousness. For all these reasons, it often results difficult to distinguish falls and syncope.

In these cases, the early ILR implant may be taken in consideration as it has been showed to have high diagnostic performances and to reduce the number and timing of further diagnostic investigations.[5–9] A careful clinical evaluation of patient characteristics is always crucial; however, ILR can provide additional diagnostic value in patients with a first diagnosis of real or apparent T-LOC. In addition, prescreening is needed to exclude high-risk patients who would otherwise require immediate further evaluation and

TABLE 1 Implantable loop recorder available on the market

Feature	BioMonitor 2	REVEAL LINQ	REVEAL XT[a]	CONFIRM RX
Dimensions	88 × 15 × 6	44.8 × 7.2 × 4	62 × 19 × 8	49 × 9.4 × 3.1
Volume (cc)	5	1.2	9	1.4
Weight (g)	10	2.5	15	3
Length of sensing dipole (mm)	88	38	40	39
Battery duration	4 y	3 y	3 y	2 y
Total time recording	>60 min	60 min	<60 min	60 min
Time per recording	55 × 40 s episodes 4 × 7.5 min activated by patient	27 min episodes 30 min activated by patient 2 min long AF episodes	27 min episodes 22.5 min activated by patient	Non separate memory between automatic recordings and activated by patient
Memory management	SMART memory management[b]	First in, first out (per episode)	First in, first out	Priority (High, Low)
Daily transmissions	6	1	NO	NO
MRI compatibility	Yes	Yes	Yes	Yes 1.5T No 3T

MRI, magnetic resonance imaging.
[a]The device is no more on the Japanese market.
[b]SMART memory management which allows for storing the first, the longest and the last episode of every automatic detected arrhythmia (atrial fibrillation, asystole, bradycardia, and high ventricular rate), in case the memory is full.

treatment, that is, those with implantable Cardioverter defibrillator (ICD), pacemaker or other therapy indication irrespective of a definitive syncope diagnosis. In case of recurrent episodes, ILR is beneficial both for the patient who does not need exhausting and numerous diagnostic investigations and for the physician for whom diagnosis may be made easier with consequent gratification, as well as for health care costs.[9–13] A study from Maggi et al.[9] enrolled 58 patients with ILR implanted and real or apparent T-LOC in order to distinguish epilepsy and unexplained fall from syncope. The ILR allowed for finding a diagnosis of syncope in 15 patients due to a documented arrhythmic event: 12 patients presented an asystole of 6 s during the recurrence of T-LOC, two patients showed atrial tachyarrhythmias and one ventricular tachyarrhythmias. In 18 patients, ILR did not document any arrhythmic event at the time of T-LOC thus excluding arrhythmic origin, while in the last 25 patients ILR was unable to document any syncopal episodes. These results may introduce the diagnostic value of the ILR in patients with initial diagnosis of real or apparent T-LOC.

In the PACE SAFE study, a strong correlation between nonaccidental falls and cardioinhibitory hypersensitivity of the carotid sinus was found.[14] Bradycardia induces hypotension and facilitates the instability of elderly patients that can lead to falls without loss of consciousness. The ILR can document bradycardia preceding falls and provide evidence for permanent cardiac pacing indication. Solbiati et al[15] demonstrated that ILR can detect cardiac arrhythmias in 70% of patients, and that 20% of the falls were caused by heart rhythm disorders which may be treated with the appropriate therapy.

The study Safepace 2 enrolled 141 patients with cardioinhibitory carotid sinus hypersensitivity and unexplained falls, randomizing them between rate responsive pacemaker and ILR trying to assess the efficacy of dual-chamber pacing in this group of patients.[16] No significant reduction in falls was observed in the pacemaker arm compared with ILR, assuming that the fall was not caused by bradycardic events. However, ILR was able to record in three patients, events that could be related to T-LOC. In order to make this tool more and more efficient, further studies are requested to test its efficacy in patients with unexplained falls.

2.2 | Unexplained syncope

Among T-LOC, the most established clinical application of ILR was in patients with recurrent syncope for whom the initial evaluation (clinical history, physical examination, holter ECG, echocardiogram) did not lead to a diagnosis. Syncope is a clinical syndrome characterized by transient loss of consciousness and postural tone, which is often caused by temporary cerebral hypoperfusion characterized by rapid onset, short duration, spontaneous, and complete resolution.

Although in most cases the prognosis is benign, in a subgroup of patients with secondary syncope and heart disease, mortality can reach up to 30% per year.[5,17–20]

The evaluation of patients with recurrent syncope requires an early and multi-disciplinary approach in order to identify the exact cause and establish the best treatment. The conventional clinical follow up for patients with unexplained syncope includes the monitoring with external loop recorder, tilt testing, and electrophysiological study (EPS).

The guidelines for evaluation and management of patients with syncope[1,3,5] report some key points when dealing with such patients:

- Clinical evaluation and careful medical history are sufficient to establish a likely mechanism of syncope in most patients
- Excluding high-risk patients, that is, those with ICD or pacemaker indication, to avoid delaying the appropriate therapy.
- Including patients with a high chance of arrhythmic events.
- Including patients with a high chance of syncope recurrence.
- The final aim of ILR use is to detect the correlation between ECG disorders and syncope recurrence.

Few data are available in literature on the reproducibility of ILR results. The ISSUE-1 and 2 trials included 26 patients with at least two syncopal episodes documented by ILR, nine of which due to arrhythmia[6,21]; in 25 of them the second syncope episode was caused by the same arrhythmia detected during the first event. Despite the small sample size, it could suggest that the correlation found between the first syncope and arrhythmia may be representative of a diagnostic finding and therefore a therapeutic decision may be taken. Recent data from five randomized trials,[10,22–25] where the conventional strategy has been compared with the prolonged monitoring strategy with ILR, showed the superiority of ILR approach in defining the cause of unexplained syncope. Actually, the early implantation of ILR after the first event of unexplained syncope provides a 3.7 (2.7-5.0)-fold increased probability of defining the cause with respect to conventional strategy. Another study[26] tried to evaluate the presence of gender- and age-related differences in patients with unexplained syncope and ILR implanted. Enrolling 570 patients (54% women) it showed that gender and age are relevant both in clinical evaluation and in the rate of episode recurrence and in the subsequent treatment, but they are not relevant for diagnostic yield of the device. Actually the more is the time from the implantation, the more are the possibilities to discover the arrhythmia which causes the syncope. Generally, the ILR implant is not advisable when the probability of syncope recurrence in the ILR observation period is low and when the identification of the correlation between symptoms and ECG arrhythmia is not required for therapeutic decision.

Further studies may contribute to make the ILR the standard approach in case of unexplained syncope when an arrhythmic cause of syncope is suspected but not sufficiently proved to allow an etiological treatment.

The Table 2 summarizes all the indications of ILR for unexplained syncope.[4]

2.3 | ILR in patients with palpitations

Palpitations are very common and they are one of the most frequent symptoms reported to the attending physician.[27] An initial clinical evaluation provides a definitive or probable diagnosis of the cause of palpitations in about half of the patients and excludes with reasonable certainty the presence of causes with a severe prognosis. However, in many cases, the management of these patients is difficult, inefficient, and extremely arduous. High-risk patients may need aggressive intervention, including hospitalization and invasive tests to rule out potentially fatal arrhythmias. In these cases, the ILR cannot be indicated.

On the other hand, low-risk patients with frequent symptoms are the best ILR candidates. When the nature of palpitations remains unexplained, a correlation between symptoms and ECG findings can be found using continuous heart rhythm monitoring.

The current management of patients with palpitations is mainly based on the clinical experience of the cardiologist. However, ILRs play a minor role in patients with unexplained recurrent palpitation as compared to those with syncope. Few studies are available on this topic.[28,29]

According to the guidelines[1], ILRs in undocumented palpitations are currently recommended for patients whose symptoms are likely due to heart rhythm disorders as all other evaluations were not conclusive. Regarding the interpretation of the results, palpitations have to be considered as a cardiac-related issue only if the arrhythmia is documented during the symptoms. Indeed, the presence of normal sinus rhythm during palpitations excludes an arrhythmic cause.

TABLE 2 Guidelines for ILR implant

Indication for ILR implant in patients with unexplained syncope occurrence or undocumented palpitations	
Class I	1. In an early phase of evaluation of patients with recurrent syncope of uncertain origin who have: • absence of high-risk criteria that require immediate hospitalization or intensive evaluation; ***(Level of evidence A)*** • a likely recurrence within battery longevity of the device ***(Level of evidence A)*** 2. In high-risk patients in whom a complete evaluation did not demonstrate a cause of syncope or lead to specific treatment **(Level of evidence A)**
Class II A	1. To assess the contribution of bradycardia in patients with suspected or certain neurally mediated syncope presenting with frequent or traumatic syncopal episodes, before starting with cardiac pacing ***(Level of evidence B)*** 2. ILRs may be indicated in selected cases with severe infrequent symptoms when other ECG monitoring systems fail to document the underlying cause ***(Level of evidence B)***
Class II B	In patients with Transient loss of consciousness of uncertain syncopal origin in order to definitely exclude an arrhythmic mechanism ***(Level of evidence C)***

3 | ATRIAL FIBRILLATION AND THERAPY MANAGEMENT

The correlation between symptoms and AF is often difficult, but there are different reasons why it is so important to have a definite quantification of the arrhythmic burden. The main are the evaluation of the effectiveness of the antiarrhythmic therapy and the management of the anticoagulant therapy. Traditional intermittent monitoring systems often do not document AF recurrences, as they can be silent and unpredictable. The continuous monitoring provided by implantable devices increases the likelihood of detecting AF, but sometimes it may be affected by false episode detection due to artifacts. New devices have sophisticated algorithms that have improved AF detection performance. In addition, remote monitoring provides daily alarms to the physician in case of AF. Physicians can also set 1 day periodic subcutaneous ECG in order to receive a daily snapshot of the patient's rhythm for visual inspection. A recent study[30] has shown that ILR has an AF detection sensitivity of 95.4% and a positive predictive value of 76.3%. Therefore, ILR is able to provide long-term ECG monitoring in patients at risk from or with documented AF.

The implantable loop recorder may also play an important role in patients with cryptogenic stroke which is the only established indication in order to detect the presence of eventual AF.[31] The CRYSTAL-AF study[32] conducted on 441 patients showed that ECG monitoring with ILR was superior to conventional follow-up for detecting AF after cryptogenic stroke. The last ESC guidelines on AF management[33] introduced for the first time, with class indication IIB, the use of ILR to investigate AF in patients with cryptogenic stroke. Since the detection of AF is frequent in unselected patients with stroke,[34] ILR with continuous ECG monitoring allows for AF detection and classification in this population.[35–38] The implantation of ILR can assume an important role in patients with history of AF who need to be evaluated for antiarrhythmic therapy or, more importantly, for anticoagulant therapy, especially in case of high risk of stroke or bleeding. In addition, this tool may be important after AF ablation for the management of anticoagulant therapy.[39–42] Guidelines for the management of AF[33] recommend anticoagulant therapy for patients with paroxysmal AF at "high risk" of stroke. If anticoagulation reduces the risk of stroke, on the other side, it exposes the patient to the risk of bleeding. In order to reduce the risk of bleeding, stop and go anticoagulation therapy has been proposed. This therapeutic option for patients with paroxysmal AF was based on the ILR monitoring capacity and the new anticoagulants (NOACs), which provide rapid anticoagulation with a single dose. This approach, known as "pill in the pocket" has been thought after paroxysmal AF, to potentially limit the risk of bleeding associated with the continuous use of anticoagulants, providing at the same time protection from eventual embolic events.

Despite promising results from The REACT.COM study[43] which, enrolling 59 patients, tried to demonstrate the feasibility of this approach, the recent IMPACT study[44] (Combined Use of BIOTRONIK Home Monitoring and Predefined Anticoagulation to Reduce Stroke Risk), which randomized 2718 patients with dual-chamber and biventricular defibrillators to start and stop anticoagulation based on Remote Monitoring (RM) or conventional in-hospital follow-up (FU), failed to show the superiority of RM. This data supported the hypothesis of the absence of temporal relationship between atrial high rate episodes (AHREs) and thromboembolic events. AHREs should so be considered only as risk factor and not the direct cause of the stroke events, ruling out the efficacy of the stop and go anticoagulation. The administration of anticoagulant therapy may be more appropriately based on both the duration of AHRE events and the risk profile of the patient. As suggested by Botto et al.,[45] patients with low CHA2DS2-VASC score, may benefit from anticoagulation if a single AHRE episode exceeds 24 hours; while for patients with a score >2 the anticoagulation could be appropriately started for AHRE lasting >6 minutes. The RM associated with ILR implant still remains the less invasive and most rapid option to monitor and quantify AF events. Despite some recommendations, it is still under discussion which is the amount of AF that requires anticoagulation. Interestingly, recent analysis has shown that the prediction of patients who will experience AF episodes is difficult even when considering their clinical characteristics. This finding highlights the importance of continuous heart monitoring for AF detection.[46] Further studies will try to understand who deserves anticoagulant therapy. Certainly, studies conducted with ILR and associated with the use of NOAC could give answers to these open questions.

3.1 | ILR in epileptic patients: "Convulsive syncope"

The misdiagnosis of epilepsy, estimated in about 20% of patients,[1] has a serious impact on health costs and significant emotional commitment for the patient. The most common alternative diagnosis is a convulsive syncope.[47]

In the REVISE study[48] it was shown, thanks to ILR implantation, that one of the eight patients (12.5%) with a previous undeniable diagnosis of epilepsy, had instead a cardiac syncope. In this study, ILR was also able to confirm the diagnosis of epilepsy in four (50%) of the patients.

Epileptic population is associated with frequent episodes of syncope which may remain unexplained despite adequate doses of anticonvulsant drugs.[49] Among the various hypotheses, a cardiovascular cause has also been suggested. Two types of clinical events were reported in this population.

The first is a cardiac event related to convulsions, the second is a primary cardiac event.[50] ILR may be useful for diagnosing a cardiac event in these classes of patients.

A study enrolled 20 patients with refractory epilepsy and ILR implantation to record rhythm during convulsions.[51] Overall, 377 episodes were analyzed, showing sinus bradycardia and sinus arrest in eight events (2.1%) and four patients (21%), respectively. This bradycardia is temporally related to convulsions (ictal bradycardia) and can correspond to parasympathetic activation. It was also reported that bradycardia may be the first manifestation of epilepsy.

TABLE 3 Summary of the ILR indications

Established	T-LOC suspected of arrhythmic cause Recurrent unexplained syncope Undocumented palpitations AF detection after cryptogenic stroke
Not-Established	AF management Convulsive syncope Risk stratification

T-LOC, transient loss of consciousness; AF, atrial fibrillation.

The implantation of a pacemaker was proposed to prevent death and disability in this case.

The second mechanism is a neuro-cardiogenic syncope that is difficult to distinguish from epilepsy. In this situation, the ILR can be useful to monitor the heart rhythm during the convulsive episodes.[52] A prolonged asystole or paroxysmal atrioventricular block was often reported. In these patients, a neuro-mediated mechanism is suspected due to a slowing of the heart rhythm recorded before asystole.[53] The disappearance of convulsions after implantation of a bicameral pacemaker was also reported in patients with ineffective antiepileptic drugs. It is therefore important to diagnose the cardiac origin of a convulsive syncope to avoid an inappropriate anticonvulsant treatment or to assess the presence of hypokinetic arrhythmia in patients with persistence of syncope after specific anticonvulsant therapy.

3.2 | ILR for risk stratification

The ILRs use has been thought not only in symptomatic situations, but also in for prespecified group of patients who can be candidate for ICD or PM implant due to previous cardiac related episodes.

The CARISMA study[54] was designed to document the incidence and prognostic significance of arrhythmias in patients with a previous myocardial infarction (MI) and FE <40%, showing significant brady and/or tachyarrhythmia in 137 patients (46%) during 2-year follow-up, where 86% of these had no symptoms.

The CARISMA study showed that ILRs may be useful for finding arrhythmias in different clinical situations:

- asymptomatic arrhythmias, especially a high-grade AV block which is relatively frequent among post-MI patients with depressed ventricular function;
- non sustained ventricular tachycardia
- sinus bradycardia or sinus arrest.

The implantable loop recorders are useful tools for clinical research and epidemiology of cardiac arrhythmias, but the clinical usefulness of ILRs is yet to be demonstrated to guide medical therapy and eventual implantation of an ICD in patients after myocardial infarction.

Another group of patients studied with ILR is the population hospitalized for acute heart failure, but without ICD indication. A recent pilot study[41] concludes that after hospitalization for acute heart failure, patients with FEVS <40% and who still have no indication for an ICD implant have a high incidence of cardiovascular events. In these patients, ILR allows early detection of threatening cardiac arrhythmias and suggests the most appropriate and timely treatment.

ILR has also potential diagnostic indication in some inherited cardiopathies (Brugada syndrome, long or short QT syndrome, hypertrophic cardiomyopathy, or arrhythmogenic right ventricular dysplasia) even if there is no established evidence. In these conditions, syncope is generally considered a serious symptom leading to the indication of an ICD implant. However, the mechanism of syncope can be heterogeneous and sometimes unclear. Actually, it is not always easy to differentiate between benign and malignant forms of syncope. The ILR implantation has been proposed by some authors,[55] especially when the characteristics of syncope are not convincing or the patient refuses the ICD implantation. HERA recommendations indicate that ILR may have a potential role to identify the correlation between symptoms and suspected ventricular tachyarrhythmia in these selected, high-risk patients with inherited pathologies. This hypothesis must be validated by clinical studies and needs more evidence. In Table 3 a summary of all the ILR indication, already established and not established yet.

4 | CONCLUSION

The ILR is still underutilized in clinical practice, despite potential clinical advantages and the recent technological improvements, including miniaturizing and automatic algorithms for AF detection. A reliable acquisition of the subcutaneous ECG signal allows to significantly reduce the incidence of artifacts and false positives.[56] The availability of remote monitoring improves the diagnostic timing and the follow-up strategy for ILR subjects with a potential reduction of costs for health care. The recent advent of injectable ILRs makes the procedure even easier. The continuous development of new algorithms, especially for a more reliable detection of AF,[57] provides new opportunities for physicians. Clearly, the ILR cannot replace a first detailed evaluation, an accurate history, and a diagnostic procedure tailored to patient characteristics. However, it may be useful in several situations and it can acquire more and more importance in the next years.

CONFLICT OF INTEREST

Luigi Mancuso and Gianluca Ceravolo are employees of Biotronik Italia. Antonio Bisignani, Silvana De Bonis, Giovanni Bisignani: Nothing to disclose.

ORCID

Gianluca Ceravolo http://orcid.org/0000-0002-7817-1999

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