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Pacing and Clinical Electrophysiology, 2015; 38(12):1464-1469

Originally published at:
http://doi.org/10.1111/pace.12752

Safety Profile of a Miniaturized Insertable Cardiac Monitor: Results from Two Prospective Trials

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Background: *Insertable cardiac monitors (ICMs) are used to continuously monitor the patient's electrocardiogram. In response to patient activation or based on automated device algorithms, arrhythmia episodes are stored and automatically transmitted daily to the clinician. Thus, ICMs can be used to diagnose arrhythmias in at-risk patients and in those with symptoms potentially attributable to arrhythmias. The ICM described in this report has undergone a dramatic change in size and method of insertion.*

Methods: *To evaluate the safety profile of the ICM procedure, we analyzed procedure-related adverse events (AEs) from two separate trials: A controlled, nonrandomized multicenter study (Reveal LINQ™ Usability study) and a multicenter registry (Reveal LINQ™ Registry) evaluating real-world experience. For the Registry we reported all procedure-related AEs upon occurrence, whereas for the Usability study, we reported events occurring during the first month of follow-up.*

Results: *The Usability study enrolled 151 patients (age 56.6 ± 12.1 years; male 67%) at 16 centers; during follow-up, an infection was observed in 1.3% patients and a procedure-related serious AE (SAE) in 0.7% patients. The Registry enrolled 122 patients (age 61.0 ± 17.8 years; male 47%) at seven centers; during follow-up, an infection was observed in 1.6% patients and a procedure-related SAE in 1.6% patients.*

Conclusions: *The cumulative experience from a controlled clinical trial and a "real-world" registry demonstrate that the new ICM can be inserted with very low incidence of AEs. (PACE 2015; 38:1464–1469)*

insertable cardiac monitor, arrhythmia monitoring, safety, adverse events

Introduction

Insertable cardiac monitors (ICMs) are leadless devices that are inserted subcutaneously.

Disclosures: S. Mittal reports consultancy fees from Medtronic. P. Sanders reports having served on the advisory board of Biosense Webster, Medtronic, and St. Jude Medical; having received lecture fees from Biosense Webster, Medtronic, St. Jude Medical, and Boston Scientific; and having received research funding from Medtronic, St. Jude Medical, Boston Scientific, Biotronik, and Sorin. E. Pokushalov reports having received honoraria from Medtronic, Biosense Webster, and Boston Scientific. L. Dekker reports having received consultancy fees from Medtronic and St. Jude Medical, and research support from Medtronic, St. Jude Medical, and Philips. D. Kereiakes reports having received consultancy fees from HCRI, Sanofi, Boston Scientific, and Abbott Vascular; and holding stock options from Ablative Solutions. E. Schloss reports having received consultancy and speaker fees for Boston Scientific and Medtronic, and holding stock at AliveCor. E. Pouliot, N. Franco, Y. Zhong, and M. Di Bacco are Medtronic employees and shareholders. H. Pürerfellner reports having received consultancy fees from Medtronic and honoraria from St. Jude Medical, Biosense Webster, Sanofi, Daiichi-Sankyo, Böhringer-Ingelheim, and Bristol-Myers Squib.

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Received June 30, 2015; revised August 17, 2015; accepted September 20, 2015.

doi: 10.1111/pace.12752

They are used to continuously monitor the heart rhythm over a period of several years. This allows for automatic detection and storage of cardiac arrhythmias, such as atrial fibrillation (AF), atrial tachycardia, ventricular tachycardia, as well as episodes of bradycardia. Prior studies in patients with unexplained syncope have demonstrated that ICMs can be implanted safely, have a diagnostic yield as high as 80%, and are cost-effective.[1–3] The addition of automated device-based algorithms designed to detect AF has expanded the use of ICMs to include AF monitoring in patients with cryptogenic stroke,[4] before and after rhythm control interventions,[5–7] and help guide decisions regarding the optimal duration of anticoagulation.[8,9]

ICM technology has evolved dramatically since the original devices were released in the late 1990s. One of the most obvious advances has been the marked reduction in size of the ICM. The first ICM (Medtronic Reveal, Medtronic Plc., Minneapolis, MN, USA) was 19 × 61 × 8 mm^3 in size and was implanted subcutaneously by performing a small incision with a scalpel, and then suturing the device to underlying tissue in order to minimize migration. The implantation procedure was usually done in-hospital, in a catheterization or an electrophysiology laboratory. The latest iteration of the device (Reveal LINQ™, Medtronic Inc.) that was used in this analysis is only 7 × 45 × 4 mm^3 in size, making it 87% smaller than its predecessor. The LINQ™ has a 3-year battery life, records cardiac information automatically in response to detected arrhythmias (or on demand based on patient activation), and uses remote cardiac telemetry to transmit data to the physician. The insertion technique has been greatly simplified. The ICM is provided preloaded in an insertion tool that is used to deliver the device subcutaneously through a small incision (<1 cm) that is then closed using surgical glue, surgical tape, stitches, or staples.[10]

The first generation of ICM devices was associated with an incidence of infection that was reported to be as high as 2.3–4.3%.[3,4,11–13] Given the significant change in device size and insertion procedure, we sought to evaluate whether these modifications have favorably influenced the safety profile of the current ICM. The safety results presented were obtained from two separate ongoing trials: A controlled, nonrandomized multicenter study (referred to here as Usability study), and a real-world multicenter registry (called the Registry).

Materials and Methods

Study Overview

Both studies were designed and conducted in accordance with the Declaration of Helsinki. The local Institutional Review Boards (IRBs) or Ethics committees approved the study protocols at each participating site. All patients provided written informed consent. No patient was coenrolled in both studies.

Table I.

Patient Characteristics and Primary Indication for ICM

Patient Characteristics	Usability (n = 151)	Registry (n = 122)
Age (years)	56.6 ± 12.1	61.0 ± 17.8
Male (n, %)	101 (66.9%)	57 (46.7%)
Primary indication for ICM (n, %)		
Syncope	19 (12.6%)	63 (51.6%)
Palpitations	3 (2.0%)	5 (4.1%)
Ventricular tachycardia	0 (0.0%)	3 (2.5%)
Suspected AF	5 (3.3%)	17 (13.9%)
Cryptogenic stroke	1 (0.7%)	6 (4.9%)
AF ablation monitoring	104 (68.9%)	17 (13.9%)
AF management	19 (12.6%)	9 (7.4%)
Other	1 (0.7%)	8 (6.6%)

AF = atrial fibrillation; ICM = Insertable cardiac monitors.

The Reveal LINQ™ Usability study is an ongoing, global, prospective, nonrandomized, multicenter trial (ClinicalTrials.gov, NCT01965899) being conducted in Europe and Australia. It enrolled 151 patients at 16 centers between September 2013 and June 2014. The study has two phases: During the first phase, 30 patients with any indication for a LINQ™ ICM were enrolled; for the second phase, patients with a documented history of AF who were candidates for ablation were included.[10]

The Reveal LINQ™ Registry is an ongoing, global, nonrandomized, prospective postmarket surveillance registry (ClinicalTrials.gov, NCT01524276) with planned enrollment of at least 1,200 patients with ICM devices. The first enrollment was in March 2014 and as of March 2015, a total of 161 patients had been enrolled. Patients eligible to receive an ICM were enrolled either at preinsertion or within 48 hours postinsertion. In order to accurately capture all adverse events (AEs), we limited the analysis to 122 patients from seven centers who were enrolled for predevice insertion (Online Appendix). Enrollment to date has occurred predominantly (88%) in the United States and eligibility was based on currently approved indications for use: Clinical syndromes or situations at increased risk of cardiac arrhythmias, and transient symptoms suggesting a cardiac arrhythmia, such as dizziness, palpitations, syncope, or chest pain.

Study Procedures

For the Usability study, centers were instructed to execute the insertion under guidance from the study protocol using the provided incision and insertion tools. Two thoracic anatomical locations were recommended for ICM insertion over the fourth intercostal space on the left hemithorax: (Best) 45° with the superior end of the device positioned approximately 2 cm left lateral from the sternal border, and (Good) approximately 2 cm parallel to the sternal border.[14] Insertions in the Usability study could take place either in a catheterization or electrophysiology laboratory, an operating room, or a clean room (an enclosed environment within a hospital meeting a recognized cleanliness standard). In contrast, the Registry did not specify either insertion procedure or site of service. Patient sedation, use of local anesthetics, wound closure method, the use of perioperative prophylactic antibiotics, and ICM fixation (the use of sutures to hold the device in place) were at the physician's discretion in both studies.

The Usability study required an in-office follow-up visit at 30 days postinsertion. AEs were classified by an AE advisory committee (AEAC) and all procedure-related AEs reported within the first month were included in this report. For the Registry, procedure-related AEs were reported upon occurrence and classified by the investigators.

Data Analysis

A procedure-related AE was defined as a clinical sign, symptom, or health condition that was causally related to the device insertion procedure. A procedure-related serious AE (SAE) was an AE that led to death or a serious deterioration in health as indicated by a life-threatening illness or injury, permanent impairment of body function or damage; in-patient or prolonged hospitalization, medical or surgical intervention to prevent life-threatening illness or an injury, or permanent impairment to a body structure or body function. In both studies, infections were defined based on the physician's assessment.

AE and infection rates were calculated by dividing the number of patients with infections or AEs by the number of patients in the corresponding analysis cohort. Two-sided 95% confidence intervals were calculated using the Exact Binomial method. Subject baseline characteristics were obtained and summarized using descriptive statistics.

Results

Study Population

The baseline characteristics of all patients are summarized in Table I. The Usability study enrolled 151 patients; one patient was explanted and exited the study 13 days postdevice insertion. The remaining 150 patients completed 1-month follow-up. In the Registry, five of 122 patients included in this analysis exited the study (Online Appendix).

The mean age of patients in the Usability study was 56.6 ± 12.1 years; 67% were men. The primary indications for an ICM were AF ablation monitoring (69%) and syncope (13%). The mean age in the Registry was 61 ± 17.8 years; 46.7% were men. Approximately half (52%) of Registry patients were prescribed the ICM due to syncope; an additional 35% were implanted for AF management, monitoring of suspected AF (e.g., cryptogenic stroke), or AF ablation.

Table II shows the procedure characteristics for the Usability study and the Registry.

Adverse Procedure-Related Events

Table III shows all procedure-related AEs for both studies. In the Usability study, the AEAC reported AEs in eight patients, of whom only one (0.7%) was classified as serious. The solitary SAE began as pain at the insertion site and progressed to a perforation and spontaneous device explant through the insertion site 13 days postdevice insertion. The AEAC classified two additional patients as having significant insertion site pain. In one patient, the pain could be relieved with an analgesic (paracetamol/acetaminophen); in the other patient, the device had to be explanted 5.4 months postinsertion. Two patients were classified as having superficial wound infections. Both insertions were performed by the same operator, and in both instances, removing the surgical glue that had been applied at the time of device insertion treated the infection. In neither instance was the patient administered an antibiotic for treatment or the device explanted. These infections were reported at 4 days and 15 days postdevice insertion; both patients had received preprocedural intravenous antibiotics, and wound closure had been achieved with either surgical glue or surgical glue and adhesive strips. Both ICM insertions were performed in a catheterization laboratory, within the first month of study enrollment; they corresponded to the second and third procedures, from a total of eight, performed at that center. Two patients experienced minor bleeding from the insertion site; in both instances, application of pressure resolved the bleeding. Finally, in one patient clear fluid was reported to emanate from the wound 26 days postdevice insertion; the physician adjudication committee did not deem this event to represent an infection. The infection rate in the Usability study was 1.3%.

Table II.

Procedure Characteristics

Procedure Characteristics	Usability (n = 151)	Registry (n = 122)
Location of procedure		
Catheterization or electrophysiology lab	130 (86.1%)	94 (77.0%)
Clean room	15 (9.9%)	28 (23.0%)
Operating room	2 (1.3%)	0 (0.0%)
Practice office	1 (0.7%)	0 (0.0%)
Other†	3 (2.0%)	0 (0.0%)
Anesthesia		
Local anesthetic	150 (99.3%)	98 (80.3%)
General anesthesia	4 (2.6%)	1 (0.8%)
Moderate intravenous sedation	None	24 (19.7%)
None	1 (0.7%)	4 (3.3%)
Preprocedural antibiotics	73 (48.3%)	51 (41.8%)
Oral	12 (7.9%)	NR
Intravenous	60 (39.7%)	NR
Unknown	1 (0.6%)	NR
None	78 (51.7%)	NR
Incision site preparation prior to insertion		
No	1 (0.7%)	NR
Yes	150 (99.3%)	NR
Betadine	48 (31.8%)	NR
Chlorhexidine	73 (48.3%)	NR
Isoniazid (antibacterial)	17 (11.3%)	NR
Benzyl alcohol	11 (7.3%)	NR
Unknown	1 (0.7%)	NR
Use of provided incision tool	151 (100%)	76 (62.3%)
Use of provided insertion tool	145 (96.7%)	111 (91.0%)
Thoracic anatomical location		
Best	139 (92.1%)	88 (77.2%)
Good	9 (6.0%)	6 (5.3%)
Other	3 (2.0%)	20 (17.5%)
Device fixation with sutures		
Yes	22 (14.6%)	7 (5.7%)
No	129 (85.4%)	112 (91.8%)
Not specified	0 (0.0%)	3 (2.5%)
Wound closure method		
Suture	64 (42.4%)	20 (16.4%)
Staples	None	31 (25.4%)
Surgical glue	14 (9.3%)	29 (23.8%)
Adhesive strips	60 (39.7%)	85 (69.7%)
Other	13 (8.6%)	0 (0.0%)
Suture and adhesive strips *or* glue	11 (7.3%)	0 (0.0%)
Antibiotics postinsertion	13 (8.6%)	5 (4.1%)

†Other locations were patient room within the hospital, practice office, and outpatient clinic.
NR = not reported for some or all patients.

In the Registry, three procedure-related AEs were reported; two of these three events were classified as serious (1.6%; Table III). One SAE was insertion site pain, which necessitated device removal at the patient's request 27 days postinsertion. The other serious event was an insertion site infection that resulted in pain and drainage from the incision site and was treated with device explantation 45 days postdevice insertion. This particular patient had received

Table III.

Comparison of Procedure-Related Adverse Events between the Two Studies

Study	Key Term	AE	AE Rate (Two-sided 95% CI)	SAE	SAE Rate (Two-sided 95% CI)
Usability (n = 151)	Insertion site pain	3	2.0% (0.4%, 5.7%)	1	0.7% (0.0%, 3.6%)
	Incision site complication	1	0.7% (0.0%, 3.6%)	0	0.0% (0.0%, 2.4%)
	Minor bleeding	2	1.3% (0.2%, 4.7%)	0	0.0% (0.0%, 2.4%)
	Wound infection	2	1.3% (0.2%, 4.7%)	0	0.0% (0.0%, 2.4%)
Registry (n = 122)	Insertion site pain	1	0.8% (0.0%, 4.5%)	1	0.8% (0.0%, 4.5%)
	Insertion site infection	2	1.6% (0.2%, 5.8%)	1	0.8% (0.0%, 4.5%)

The Exact method was used to calculate the confidence intervals.
AE = procedure-related adverse event; CI = confidence interval; SAE = procedure-related serious adverse event.

preprocedural antibiotics intravenously, the procedure had been performed in an electrophysiology laboratory, and the incision had been closed using adhesive strips. Finally, a second insertion site infection was not classified as an SAE. Mild erythema was noted around the incision site 10 days postdevice insertion; the issue resolved completely following administration of oral antibiotics. This particular patient received preprocedural intravenous, oral, and topical antibiotics. The incision was closed using adhesive strips and staples, and the insertion was performed in a clean room. The two infections occurred at different centers within the first 6 months of the Registry. The infection rate in the Registry was 1.6%.

Overall, the combined cohort of 273 patients had an infection rate of 1.5% (n = 4), an AE rate of 4.0% (n = 11), and an SAE rate of 1.1% (n = 3). These statistical summaries do not adjust for the differences between the two studies.

Discussion

Following device iteration and miniaturization accompanied by a change in insertion technique, it is important to objectively assess the safety of the ICM. This report, which includes the largest group of patients (n = 273) inserted with the miniaturized ICM to date, showed that its insertion is associated with a low rate of procedure-related SAEs and infections. Of 151 patients inserted with the ICM during the Usability study, 99.3% had no SAEs during 1-month follow-up, and 98.7% were free of infections. Furthermore, the results obtained so far from the Registry indicate that real-world complication rates agree with the rates observed in the controlled clinical trial (98.4% without SAEs and 98.4% without infections).

Infection rates have been consistently low as follows: 1.3% and 1.6% for the Usability study and the Registry, respectively. Moreover, out of 23 centers where ICM insertions were performed, only three centers reported infections, one of which accounted for two infection events. The fact that three of four patients with infections were among the first procedures performed in those centers suggests that these events may be related to physician inexperience with the insertion procedure. Indeed, some procedure-related AEs may occur when a new technology is adopted, but their number is expected to decrease as users become more experienced.

Some of the differences observed in procedure characteristics may be explained by the fact that these two studies were done in different geographies (the Registry has mainly taken place in the United States, whereas the Usability study is European and Australian). However, our report shows that despite the variation in methods for closing the skin after the procedure, the administration of perioperative antibiotics, and whether participants were selected or not in a controlled manner, the insertion procedure of this miniaturized ICM has a very favorable safety profile. Indeed, the infection rates are comparable, and slightly lower, than those previously reported with larger ICM models (of range 2.3–4.3%).[3,4,11–13]

The main strength of our report is the comparison of the ICM insertion as performed in a controlled study and following protocol directions with a real-world study, where procedures were done at the physician's discretion. Despite this, infection and SAE rates were comparably low. Additionally, the global nature of the data also reinforces the favorable safety profile of the device. On the other hand, one of the limitations was that AE adjudication for the Registry was based on the physician's judgment. A second limitation is that, unlike the Usability study, the Registry did not have a scheduled follow-up visit within the first

month after ICM insertion. This may be causing an underestimation of AEs for which patients might choose not to consult their physicians. However, we think this may have a minimal impact since patients were given the usual postsurgery discharge instructions informing them to look for signs/symptoms of infection. Finally, the study design being different for both studies, elements such as incision site preparation prior to insertion and type of preprocedural antibiotics used were not directly comparable.

Conclusions

This report assessed AEs related to the insertion procedure of a miniaturized ICM in a controlled clinical trial and a real-world product surveillance registry, and demonstrated that the device can be inserted with minimal associated AEs. The changes made to the size and insertion procedure of the ICM do not alter the safety profile compared with earlier devices. On the contrary, these changes are improvements that have simplified the procedure and will allow more patients to benefit from long-term cardiac monitoring.

Acknowledgments: We would like to thank Baerbel Maus, Shelby Li, Tracy Bergemann, and Brien Neudeck for their contributions to the analysis and critical review of the manuscript, as well as all the LINQ Usability and LINQ Registry investigators for their hard work and participation in the study.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix: Patient flow charts. (A) LINQ™ Usability Study. (B) LINQ™ Registry Wiley: Please check "Supporting Information (Online appendix)" and its citations as typeset for correctness.Author: Please check "Supporting Information (Online appendix)" for correctness.