Real-World Use of Prophylactic Antibiotics in Insertable Cardiac Monitor Procedures

SEAN C. BEINART, M.D., M.S.C.R., F.A.C.C., F.H.R.S.,* ANDREA NATALE, M.D., F.A.C.C., F.H.R.S., F.E.S.C., † ATUL VERMA, M.D., F.R.C.P.,‡ ALPESH AMIN, M.D., M.B.A., M.A.C.P., S.F.H.M.,§ SCOTT KASNER, M.D., M.S.C.E., F.A.H.A., F.A.A.N.,¶ HANS-CHRISTOPH DIENER, M.D., Ph.D., ** ERIKA POULIOT, M.S., †† NORELI FRANCO, Ph.D., ‡‡ and SUNEET MITTAL, M.D., F.A.C.C.¶¶

From the *Center for Cardiac and Vascular Research, Washington Adventist Hospital, Rockville, Maryland; †Texas Cardiac Arrhythmia Institute, St. David’s Medical Center, Austin, Texas; ‡Southlake Regional Health Centre, Newmarket, Ontario, Canada; §Department of Medicine, University of California, Irvine, California; ¶Department of Neurology Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; **Department of Neurology and Stroke Center, University Hospital Essen, Essen, Germany; ††Medtronic plc, Mounds View, Minnesota; and ‡‡Electrophysiology Laboratory, The Valley Hospital Health System, Ridgewood, New Jersey

Background: The use of prophylactic antibiotics during insertable cardiac monitor (ICM) procedures is a carryover of the common practice used with therapeutic cardiac implantable electronic devices. We sought to characterize the current practice of ICM insertion procedures to evaluate the influence of prophylactic antibiotic administration on the occurrence of infections.

Methods: We characterized insertion procedures and procedure-related infections from an ongoing multicenter registry (Reveal LINQ™ Registry). In order to accurately capture infections, only patients enrolled before or the day of insertion who also had a record of whether or not preoperative antibiotics were used were included in this analysis. Infections were defined based on the physician’s assessment and reported upon occurrence. Patients were categorized into two analysis cohorts based on prophylactic antibiotic use.

Results: We analyzed 375 patients from 14 U.S. centers (age 63.1 ± 15.6 years; male 54.1%). Approximately two-thirds of patients (66.4%) did not receive any preprocedural antibiotics. The overall infection rate was 1.1% (0.3–2.7% confidence interval [CI]) and corresponded to four events. In the group that did not receive preprocedural antibiotics, there were two minor infections (0.8%, [0.1–2.9% CI]), whereas in the group receiving preprocedural antibiotics a serious and a minor infection occurred (1.6%, [0.2–5.6% CI]); this serious infection resulted in an explant.

Conclusions: Current real-world practice shows that ICM insertions are increasingly performed without the use of prophylactic antibiotics, which is associated with a very low infection rate. (PACE 2016; 39:837–842)

insertable cardiac monitor, insertion procedure, antibiotics, infections, safety

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Address for reprints: Sean C. Beinart, M.D., M.S.C.R., F.A.C.C., F.H.R.S., Washington Adventist Hospital, 15225 Shady Grove Rd., Ste 201, Rockville, MD 20850-3278. Fax: 866-274-3089; e-mail: sbeinart@gmail.com

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Introduction
Detecting and monitoring cardiac arrhythmias can be challenging, especially in patients who are asymptomatic, have infrequent symptoms, or suffer from cryptogenic stroke. It is important to identify the etiology of symptoms or conditions, such as unexplained syncope, palpitations, chest pain, or cryptogenic stroke in order to provide appropriate treatment and maintain quality of life. The insertable cardiac monitor (ICM) that continuously assesses a patient’s cardiac rhythm for up to 3 years without burdensome leads or wires has played a significant role in addressing these needs.

The miniaturized Reveal LINQ™ ICM (Medtronic plc, Dublin, Ireland) is 87% smaller than its predecessor and is the smallest insertable cardiac monitoring device available ($7 \times 45 \times 4 \text{ mm}^3$). It has been widely adopted in the United States due to its size and the simplicity of the insertion procedure. An insertion tool preloaded with the ICM is used to deliver the device subcutaneously through an incision <1 cm in length. In contrast to previous iterations, no conscious sedation is required given the minimally invasive nature of the procedure and active fixation of the device is unnecessary given that the subcutaneous pocket created is smaller and tighter. The wound can be closed using sutures, staples, surgical glue, or adhesive strips.\[1–3\] Furthermore, a recent analysis combining safety results from this ongoing registry and the Reveal LINQ Usability study showed that the insertion procedure was associated with a low rate of infections (1.3–1.6%) and serious adverse events leading to device explant (0.7–1.6%).\[1\] In the aforementioned studies, administration of prophylactic antibiotics was observed in 48% and 42% of patients, respectively.

The use of prophylactic antibiotics during ICM insertions is a carryover of the common practice used with therapeutic cardiac implantable electronic devices (e.g., pacemakers, implantable cardioverter defibrillators). However, since ICMs are leadless devices placed subcutaneously and do not require transvenous access, antibiotics may not be required. In this analysis of a real-world registry, we sought to characterize the current practice of ICM insertion procedures in the United States and to evaluate the association of prophylactic antibiotic administration with rates of infection.

Methods

Study Overview
The Reveal LINQ™ Registry is an ongoing, global, nonrandomized, prospective, post-market surveillance registry (ClinicalTrials.gov, NCT01524276) with planned enrollment of approximately 2,300 patients with Reveal LINQ™ ICM devices. The study was designed and conducted in accordance with the declaration of Helsinki. The local Institutional Review Boards approved the study protocol at each participating center and all patients provided written informed consent. Eligibility was based on currently approved indications for use of the device: 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. The present report is an interim analysis of the data collected thus far.

Procedures
The site of service for the procedure, patient sedation, use of local anesthetics, wound closure method, use of antibiotics, and ICM fixation (use of sutures to hold the device in place) were at the discretion of the implanting physician. Procedure-related acute infection events were reported upon occurrence and defined by the investigators based on their clinical acumen; no external adjudication process was implemented. Infection events were considered serious if they led to device explant; resulted in death or in a serious deterioration in health as indicated by a life-threatening illness or injury, permanent impairment of body function, or damage; or led to inpatient prolonged hospitalization, medical or surgical intervention to prevent life-threatening illness, or an injury or permanent impairment to a body structure or body function.

Data Analysis
Patients were categorized into two analysis cohorts based on prophylactic antibiotic use. Infection rates were calculated by dividing the number of patients with infections by the number of patients undergoing a device insertion procedure in the corresponding analysis cohort. Two-sided 95% confidence intervals (CIs) were calculated using the Exact Binomial method. Subject baseline characteristics were obtained and summarized using descriptive statistics (SAS software, version 9.4, SAS Institute, Cary, NC, USA).

Results

Study Population
The registry enrolled patients who were eligible to receive an ICM. In order to accurately capture all infection events, we limited the analysis to the 375 patients from 14 U.S. centers who were enrolled before or on the day of the
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### Table I.
Baseline Characteristics and Primary Indication for ICM

| Patient Characteristics | Total (375) | No Preprocedural Antibiotics (249) | Preprocedural Antibiotics (126) | P-Value |
|-------------------------|-------------|----------------------------------|---------------------------------|---------|
| Age (years)             | 63.1 ± 15.6 | 63.6 ± 15.3                      | 62.1 ± 16.1                    | 0.3903  |
| Male (n, %)             | 203 (54.1%) | 140 (56.2%)                      | 63 (50.0%)                     | 0.2735  |
| BMI                     | 29.9 ± 6.9  | 30.0 ± 7.1                       | 29.8 ± 6.6                     | 0.7905  |
| Primary indication for ICM (n, %) |            |                                  |                                |         |
| Syncope                 | 120 (32.0%) | 71 (28.5%)                       | 49 (38.9%)                     | 0.0467  |
| AF management           | 61 (16.3%)  | 52 (20.9%)                       | 9 (7.1%)                       | 0.0006  |
| Palpitations            | 42 (11.2%)  | 24 (9.6%)                        | 18 (14.3%)                     | 0.2243  |
| Cryptogenic stroke      | 38 (10.1%)  | 29 (11.6%)                       | 9 (7.1%)                       | 0.2065  |
| Suspected AF            | 36 (9.6%)   | 18 (7.2%)                        | 18 (14.3%)                     | 0.0399  |
| Post-AF ablation monitor | 24 (6.4%)  | 19 (7.6%)                        | 5 (4.0%)                       | 0.1892  |
| Pre-AF ablation monitoring | 20 (5.3%) | 13 (5.2%)                       | 7 (5.6%)                       | 1.0000  |
| Ventricular tachycardia | 8 (2.1%)    | 6 (2.4%)                         | 2 (1.6%)                       | 0.7228  |
| Other                   | 26 (6.9%)   | 17 (6.8%)                        | 9 (7.1%)                       | 1.0000  |
| History of COPD, n (%)  | 34 (9.1%)   | 16 (6.4%)                        | 18 (14.3%)                     | 0.0209  |
| History of cancer, n (%)| 42 (11.2%)  | 24 (9.6%)                        | 18 (14.3%)                     | 0.2243  |
| Diabetes, n (%)         | 74 (19.7%)  | 49 (19.7%)                       | 25 (19.8%)                     | 1.0000  |
| Heart failure, n (%)    | 27 (7.2%)   | 13 (5.2%)                        | 14 (11.1%)                     | 0.0549  |
| Peripheral vascular disease, n (%) | 18 (4.8%) | 9 (3.6%)                       | 9 (7.1%)                       | 0.1988  |
| Medications: OAC, n (%) | 135 (36.0%) | 105 (42.2%)                      | 30 (23.8%)                     | 0.0004  |

AF = atrial fibrillation; BMI = body mass index; COPD = chronic obstructive pulmonary disease; ICM = insertable cardiac monitor; OAC = oral anticoagulation.

The baseline characteristics of all patients are summarized in Table I. The mean age of patients was 63.1 ± 15.6 years and 54.1% were male. The primary indications for an ICM were syncope (32.0%), atrial fibrillation (AF) management (16.3%), palpitations (11.2%), and cryptogenic stroke (10.1%). In Table I, patients who received preprocedural antibiotics (n = 126) were compared with those untreated (n = 249). There were no significant differences in age, gender, body mass index (BMI), prevalence of peripheral vascular disease, cancer, diabetes, or heart failure between both groups. Primary indication of an ICM for syncope, AF management, and suspected AF, as well as history of chronic obstructive pulmonary disease (COPD) and preoperative oral anticoagulation medication were all statistically significantly different between both groups (Table I). Patients treated with preprocedural antibiotics were more often monitored for syncope (38.9% vs 28.5%, P = 0.0467) or suspected AF (14.3% vs 7.2%, P = 0.0399) but less often for AF management (7.1% vs 29.9%, P = 0.0006); they were less often on oral anticoagulation therapy (23.8% vs 42.2%, P = 0.0004) and had a lower prevalence of COPD (6.4% vs 14.3%, P = 0.0209).

**Insertion Procedure**

Procedural characteristics are shown in Table II. More than half (60.5%) of the procedures took place in a catheterization or electrophysiology laboratory. The majority of patients did not receive any preprocedural antibiotics (n = 249, 66.4%; Table III). Among the 126 patients treated with antibiotics, the route of administration was intravenous in 116 and oral in 20 (10 had both). Postprocedural antibiotics were administered to 49 patients (13.1%): 25 intravenously and 24 orally. Of these 49 patients, 45 also received preprocedural antibiotics. Patients having device insertions in the cardiac catheterization or electrophysiology laboratory were more likely to receive preprocedural antibiotics (118 out of 227) than those having procedures in less resource-intensive environments, such as a clean room or an electrophysiology laboratory holding area (eight out of 148; 52.0% vs 5.4%; P < 0.0001; Table III).

The use of antibiotics was different among centers: five centers never prescribed prophylactic antibiotics before the insertion procedure (n = 149); two centers always prescribed antibiotics.
Table II.

| Procedure Characteristics, n (%) | Total (375) |
|----------------------------------|-------------|
| Location of procedure            |             |
| Cath or EP lab                   | 227 (60.5%) |
| Clean room                       | 135 (36.0%) |
| EP lab holding area              | 13 (3.5%)  |
| Anesthesia                       |             |
| Local anesthetic                 | 325 (86.7%) |
| General anesthesia               | 3 (0.8%)    |
| Conscious sedation               | 62 (16.5%)  |
| Use of provided incision tool    | 187 (49.9%) |
| Use of provided insertion tool   | 299 (79.7%) |
| Device fixation with sutures     |             |
| Yes                              | 17 (4.5%)   |
| No                               | 341 (90.9%) |
| Unknown                          | 17 (4.5%)   |
| Wound closure method             |             |
| Suture                           | 93 (24.8%)  |
| Staples                          | 113 (30.1%) |
| Surgical glue                    | 48 (12.8%)  |
| Adhesive strips                  | 286 (76.3%) |

Cath = catheterization; EP = electrophysiology.

Infections

The overall infection rate was 1.1% (0.3–2.7% CI). There were two infections in the group not receiving preprocedural antibiotics (0.8%, [0.1–2.9% CI]; #1 and #2) and two infections in the group receiving preprocedural antibiotics (1.6%, [0.2–5.6% CI]; #3 and #4). Table IV summarizes the characteristics for each infection event.

Infections in the group not receiving antibiotics were both classified as not serious mild erythemas and were resolved with oral antibiotics (cephalexin). The corresponding procedures were performed in clean rooms, the incisions were closed using adhesive strips and staples, and were dressed with sterile semipermeable film and nonadherent dressing. One patient was diabetic.

In the group receiving preprocedural antibiotics, there was a minor infection (#3) and a serious infection (#4). Infection #3 showed a scab tender to the touch and was resolved with cephalaxin. Infection #4 presented with drainage and pain, required hospitalization (≤24 hours) leading to device explant, and the infection was resolved with cephalaxin. Both corresponding insertion procedures were performed in a catheterization or electrophysiology lab and used the provided incision and insertion tools.

Discussion

In this interim report of the real-world Reveal LINQ™ Registry, we evaluated current medical practice of ICM insertions in US centers, as well as the incidence of procedure-related infections. Our findings showed that two-thirds of ICM insertions (66.4%) were performed without administration of preprocedural antibiotics, and that the infection rate was low (0.8%) for this group. Of note, the infection rate in patients not receiving antibiotics was 50% less than in patients receiving antibiotics. It is unknown whether the

Table III.

| Antibiotic Use, n (%) | Total (375) | No Preprocedural Antibiotics (249) | Preprocedural Antibiotics (126) | P-Value |
|----------------------|-------------|-----------------------------------|---------------------------------|---------|
| Preprocedural antibiotics |             |                                   |                                 |         |
| Oral                 | 20 (5.3%)   | 0 (0.0%)                          | 20 (15.9%)                      | <0.0001 |
| Intravenous          | 116 (30.9%) | 0 (0.0%)                          | 116 (92.1%)                     | <0.0001 |
| Postprocedural antibiotics |         |                                   |                                 |         |
| Intravenous          | 25 (6.7%)   | 2 (0.8%)                          | 23 (18.3%)                      | <0.0001 |
| Postdischarge oral   | 24 (6.4%)   | 2 (0.8%)                          | 22 (17.5%)                      | <0.0001 |
| Location of the procedure |         |                                   |                                 | <0.0001 |
| Cath or EP lab       | 227 (60.5%) | 109 (43.8%)                       | 118 (93.7%)                     |         |
| Clean room or EP lab holding area | 148 (39.5%) | 140 (56.2%)                       | 8 (6.3%)                        |         |

*P-value indicates a statistically significant association between whether or not preoperative antibiotics were administered and the site of service (we cannot say which influenced the other).
Cath = catheterization; EP = electrophysiology.
infections seen in the antibiotic group (1.6%) were due to lapses in sterile technique or due to patient-specific risk factors rendering them susceptible to infection. Per the information collected, no patient in this group had a history of risk factors most associated with infection (e.g., diabetes, immunosuppression, etc.). Although statistically significant differences in patient characteristics (indication for implant, history of COPD, and preoperative oral anticoagulation) were observed based on prophylactic antibiotic use between the two groups, no intensive statistical modeling was carried out given the low number of events. There were no significant differences in the other known risk factors for infection (age, BMI, peripheral vascular disease, cancer, diabetes, or heart failure). The overall rate of infection in our cohort was low (1.1%), which limits the ability to confirm that preprocedural antibiotic administration affected the risk of infection.

Our data indicate that the real-world infection rate is decreasing despite the fact that antibiotic use is also decreasing. Indeed, we previously reported an infection rate of 1.6% and use of preprocedural antibiotics in 42% of procedures in a smaller patient cohort from the Reveal LINQ Registry (n = 122). The Reveal LINQ Usability study (performed in Europe and Australia) also showed a low infection rate (1.3%), although a higher percentage of patients received preprocedural antibiotics (48.3%). The two events reported in that study occurred in patients who had received preprocedural antibiotics. The study was conducted soon after the ICM was market released and thus the higher use of preprocedural antibiotics may be reflective of previous practice. It is important to note that while these events were classified as superficial infections, removing the excessive amount of surgical glue resolved the erythema in both cases and no subsequent antibiotics were required for treatment. Risk factors that may predispose patients to surgical site infections include advanced age, high BMI, smoking status, and comorbidities such as diabetes, COPD, congestive heart failure, acute myocardial infarction, renal insufficiency, hypertension, osteoporosis, or immunosuppressive therapy. While the registry does not capture all of these, for those that are collected, the relative percentage of risk factors is relatively low which may explain the low infection rate. Whether our low infection rate with ICM insertions translates to populations with a higher prevalence of these risk factors requires further investigation.

The differences observed in antibiotic use may have been influenced by center practice.
in this analysis. In particular, there were five centers (accounting for 40% of patients) where antibiotics were never used before insertion of the device. This report and other studies\(^5\) show that many U.S. clinicians are moving away from administering prophylactic antibiotics for “clean procedures” (which corresponds to an uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered), including ICM insertion.\(^6\) One potential reason for the decrease in antibiotic use is awareness that overuse of antibiotics, in both inpatient and outpatient settings, has increased in parallel with the spread and maintenance of resistant organisms.\(^7,8\) Moreover, the use of prophylactic antibiotics is associated with their reduced global efficacy, allergic reactions, gastrointestinal adverse events, \textit{Clostridium difficile} risk,\(^9\) and with a significant cost for health institutions.

To our knowledge, there are no data suggesting that administering antibiotics is either helpful or needed in procedures such as ICM insertions. A recent consensus statement from the American Association of Plastic Surgeons reported that, with the exception of cosmetic breast surgery, patients undergoing clean procedures have not been shown to benefit from routine antibiotic prophylaxis, thereby recommending against routine administration of prophylactic antibiotics in these patients.\(^9\) This is consistent with studies and recommendations from areas other than plastic surgery.\(^10\) We recognize that our analysis of 375 patients does not definitively prove that antibiotics are not required prior to ICM insertion. Indeed, trials with larger sample sizes would be better positioned to answer this question and shed light on whether specific subpopulations warrant antibiotics versus others. Rather, our report is meant to increase awareness of current real-world practice and the overall low infection rate.

The main strength of our report is that it reflects current real-world practice of ICM insertions in the United States. On the other hand, one of the limitations is that it is a postmarket observational registry and patients were enrolled in the real-world settings with no randomization. The analysis was carried out to provide information on infection rates in association with prophylactic use of antibiotics but was not powered to detect any differences in infection rates. Further analyses will be undertaken as more patients are enrolled in this ongoing registry.

**Conclusions**

This report characterizing current real-world practice of ICM insertions in the United States showed that most procedures were performed without the use of prophylactic antibiotics and that the infection rate was very low.

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