Health and Economic Outcomes Associated with Use of an Antimicrobial Envelope as a Standard of Care for Cardiac Implantable Electronic Device Implantation

Running Title: Outcomes with Routine Use of Antimicrobial Envelope

Nasir Shariff, MD[1]
Elizabeth Eby, MPH[2]
Evan Adelstein, MD[1]
Sandeep Jain, MD[1]
Alaa Shalaby, MD[3]
Samir Saba, MD[1]
Norman C. Wang, MD[1]
David Schwartzman, MD[1]

[1]Heart, Lung and Vascular Medicine Institute, University of Pittsburgh, Pittsburgh, PA
[2]Medtronic Incorporated, Minneapolis, MN
[3]Pittsburgh Veterans Administration Healthcare System, Pittsburgh, PA

Correspondence to:
David Schwartzman, MD
UPMC Presbyterian, B535
Pittsburgh, Pennsylvania, USA 15213-2582
Email: schwartzmand@upmc.edu

E. Adelstein reports research grant support from St. Jude Medical & Medtronic. E. Eby is an employee of Medtronic. S. Jain reports research grant support from Medtronic, Boston Scientific & St. Jude Medical. S. Saba reports research grant support from Boston Scientific, Medtronic and St. Jude Medical, and serving as a consultant for Boston Scientific. D. Schwartzman reports research grant support from Biosense Webster, Boston Scientific & Medtronic; he has served as a consultant to Atricure, Avery-Dennison, Biosense Webster, QuantMD, & Epicardial Frontiers. N.C.Wang reports research support from Boston Scientific. Other authors: No disclosures.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jce.12684.

ABSTRACT

Introduction: Infection of cardiac implanted electrical devices (CIED) is a problem. In selected patients, use of an "antibacterial envelope" (AIGISRx®) is associated with low CIED infection rates. The value of this device when used as a standard of care is unclear.

Methods and Results: Retrospective analysis of all patients (N=1476) who underwent CIED implantation at a single hospital. During the study period, some implanters used the AIGISRx as a standard of care (Yes-AIGISRx Group, N=365), whereas others did not use it at all (No-AIGISRx Group, N=1111). A risk score based on preoperative factors was calculated for each patient. Rates of CIED infection within 6 months were measured, and associated costs were estimated. The Yes-AIGISRx and No-AIGISRx groups had similar preoperative infection risk. In the No-AIGISRx group, 19 infections were observed (1.7%), versus 0 in the Yes-AIGISRx group (p=0.006). The 6 month mortality rate among patients with infection was significantly greater than among those without infection (15.7% vs. 4.5%, p=0.021). The average hospital duration for infection care was 13 days. By extrapolating the infection rate and costs observed in the No-AIGISRx group to the Yes-AIGISRx group, we estimated that there would have been 6.2 additional infections costing approximately $340,000. This cost was similar to the actual cost of the devices in the Yes-AIGISRx group, estimated at $320,000.

Conclusions: Standard of care use of an antibacterial envelope as a standard of care was associated with a significantly lower rate of CIED infection, and appeared to be economically reasonable. Prospective trials to address these findings may be worthwhile.

Keywords: infection, antibiotic, cardiac implantable electronic device, pacemaker, defibrillator, cardiac resynchronization therapy

INTRODUCTION

Bacterial infection of cardiac implanted electrical devices (CIED) is a pressing issue.[1] It is believed that most infections are due to contamination of the subcutaneous "pocket" which houses the system pulse generator.[2] Despite best practices, infection rates as high as 4% are reported.[3] The repercussions of infection are severe, including mortality and high cost. In 2008, TYRX Inc. (Monmouth Junction, NJ, now a subsidiary of Medtronic, Inc., Minneapolis, MN) received Food and Drug Administration clearance to market AIGISRx® (now called the TYRX™ Antibacterial Envelope), a device into which the pulse generator is placed, which is then implanted into the subcutaneous pocket.[4,5] Polypropylene strands comprising the device are coated with a polymer which elutes the antibiotics minocycline and rifampin over a 1-2 week period. This broad spectrum combination likely produces a bactericidal pocket environment.[6] Data addressing device efficacy have thus far been derived from studies in which patients receiving the device were selected for perceived infection risk.[3,5,7] During a period comprising approximately 28 consecutive months during calendar years 2011-2013, at a single tertiary care hospital some CIED implanters used the AIGISRx device in all patients as a standard of care, whereas other implanters did not use it at all. These disparate practices provided an opportunity to gain further insight into the health and economic outcomes associated with device use.

METHODS

This retrospective, observational analysis was approved by the Institutional Review Board of the University of Pittsburgh Medical Center. Demographic, clinical and follow-up data were obtained from hospital and clinic charts. Operative data including procedure duration and staff were garnered from laboratory records.

Patients and Practice

Every patient undergoing a CIED procedure in the electrophysiology laboratory was included in this study. In each of the 2 years prior to the study period, the infection rate in this laboratory was between 1 and 2%, similar among implanters. During the study period, some implanters used the AIGISRx device in every patient as a standard of care (hereinafter termed "Yes-AIGISRx" Group), whereas other implanters did not use it at all (hereinafter termed "No-AIGISRx" Group). Among users, incorporation of the device was driven by a desire to eliminate infection as a complication, which outweighed the increased technical complexity (e.g., greater pocket dissection), implications of non-resorbability, and cost associated with its routine use.

Key Procedural Elements

A. Preoperative: patients in whom use of the AIGISRx device was being considered were specifically queried for a history of allergy to tetracyclines or rifampin. Preparation for surgery included clipper preparation. Most patients received intravenous cefazolin (1 gram) unless penicillin allergic, in which case intravenous vancomycin (1 gram) was given. Antibiotics were delivered at least 30 minutes prior to the initial skin incision.

B. Intraoperative: The laboratory met all operating room standards for structure and practice, including room ventilation, staff training, table setup, room traffic, and patient preparation. Anesthesia was provided by a team comprised of nurse anesthetist and attending physician. Laboratory staff included nurses, fellows, vendors and attending physician faculty. The skin surface was prepared using ChloraPrep® (chlorhexidine gluconate 2% and isopropyl alcohol 70%, Carefusion Inc., San Diego, CA) prior to draping. Commercial surgical drapes (Medline Industries, Mundelein, Ill.) were used. Pocket irrigation was routinely performed using normal saline containing an antibiotic (cefazolin 1g/L or vancomycin 500 mg/L). In our practice, use of the AIGISRx device involved creation of substantially more pocket space than in its absence. Wounds were closed using absorbable synthetic suture (Polysorb™, Covidien USA Inc., Mansfield, MA).

C. Postoperative: prescriptions were at the discretion of the individual faculty member, but intravenous antibiotics (cefazolin or vancomycin) were used in the vast majority of patients remaining in the hospital for 24 hours after the procedure. For patients leaving the hospital on the day of procedure, an oral antibiotic (cephalexin or clindamycin for 3-5 days) was typically prescribed among No-AIGISRx patients but not Yes-AIGISRx patients.

Categories and Definitions

A. Procedure types: 1. new CIED system implantation; 2. CIED system pulse generator replacement; 3. CIED system "upgrade," including single to dual lead pacemaker (PM) or defibrillator (ICD), PM to ICD, or PM/ICD to cardiac resynchronization system (CRT).
B. CIED system types: the following categories were used: 1. pacemaker (PM, single or dual); 2. implantable cardioverter-defibrillator (ICD, single or dual); 3. cardiac resynchronization therapy system (CRT, defibrillator or pacemaker)
C. CIED system infection: typical pocket stigmata and/or bacteremia without another cause, detected within 6 months of CIED procedure. In each case of infection diagnosed in the present study, CIED system extraction was performed.
D. Early reintervention: any pocket reentry within 1 month of the index CIED procedure.
E. Pocket hematoma: specifically reported during post-implantation hospital stay or subsequent clinic visits.
F. Procedure duration: interval between entry and exit from the laboratory.

Analytical Methods

The following factors were assessed for their potential association with CIED infection: age, gender, co-existing medical conditions (heart failure, diabetes mellitus, hypertension), prior cardiac surgery, prior CIED infection, renal failure (dialysis dependence), renal insufficiency (serum creatinine >1.5 mg/dl), chronic corticosteroid use, oral anticoagulation (warfarin, dabigatran, rivaroxaban), procedure type, CIED system type, total number of leads, presence of temporary pacemaker at the time of the CIED procedure, procedure duration, presence of epicardial lead(s), hematoma, and early reintervention. A preoperative infection risk "score" was calculated, incorporating factors that have been repeatedly associated with CIED infection.[1, 3-5, 7-13] Each factor was assigned a value of one point: 1. diabetes mellitus, 2. heart failure, 3. oral anticoagulation, 4. chronic corticosteroid use, 5. renal insufficiency or failure, 6. prior CIED infection, 7. more than two leads, 8. presence of epicardial lead(s), 9. temporary pacemaker at implantation, and 10. CIED system pulse generator replacement or upgrade. Although early reintervention has also been repeatedly associated with CIED infection, it was not included in the preoperative score as it is not a factor that can be identified prior to the procedure. [1,4,5,7,8,11,13] Therefore, in the present analysis it was considered separately.

Among the 58 patients who died within 6 months of the index CIED procedure, those without evidence of infection prior to death, based on direct patient contact and/or review of medical records, were classified in the analysis as having been infection-free.

Among patients with infection, attributable hospital costs were estimated using observed lengths of stay and previously published financial data. Additional costs that could be reasonably estimated included observed durations of home intravenous antibiotics[14] and LifeVest® (Zoll Medical, Pittsburgh, PA).[15] All costs were adjusted to 2013 values using the Consumer Price Index Medical Care Services Inflation Index. To examine the economics of routine AIGISRx use, infection rates and averaged costs of infection care observed in the No-AIGISRx group were extrapolated to the Yes-AIGISRx group. The manufacturer's suggested selling price of the AIGISRx device ($795 for pacemakers, $895 for defibrillators) was used.

Categorical data are expressed as proportions, and continuous data as mean ± standard deviation, unless otherwise stated. Statistical comparisons were performed using chi-square, Fisher's exact test, t-test, ANOVA and non-parametric Kruskal-Wallace tests, as appropriate. Multivariable Cox regression analysis was used to compare mortality outcomes between groups. The mortality outcomes were adjusted for the following baseline variables: age, gender, heart failure, diabetes mellitus, hypertension, renal insufficiency, steroid use, oral

anticoagulation use, cardiac surgery, use of temporary pacemaker, prior CIED infection, more than 2 leads, epicardial leads, device type, and procedure type. A propensity-score matching method was utilized to determine the influence of the AIGISRx on the incidence of subsequent infection following adjustment for potential confounding.[16] Propensity scores were developed using logistic regression to determine the probability for a patient in the study cohort to receive AIGISRx. The logistic regression model included 17 baseline and procedural covariates: diabetes mellitus, heart failure, steroid use, oral anticoagulant use, renal insufficiency, epicardial lead, temporary pacemaker, prior CIED infection, more than 2 leads, de novo implant, risk score, hypertension, prior cardiac surgery, device type (pacemaker, ICD, or CRT), age, and gender. The nearest neighbor-matching algorithm using a caliper size of 0.002 standard deviations as implemented in the R package Matchit [17] was used to match each patient receiving AIGISRx to a patient not receiving the device. Matching performance was assessed using the standardized difference in the 17 baseline variables used to construct the propensity score. McNemar's test was used to assess the effect of the AIGISRx device in the matched dataset.

RESULTS

A total of 1476 patients underwent a CIED procedure during the study period. All except 73 patients were followed in clinic for the 6 months after the operative procedure. For each of the 73 patients who were not followed in clinic, outcomes were obtained from caring physician(s) and patient/family. There were 1111 patients in the No-AIGISRx group, and 365 patients in the Yes-AIGIS group. Clinical and CIED system data are shown in Table 1. There were no significant differences between groups in proportions of CIED component manufacturer nor individual support personnel (nurses, vendors, fellows, anesthesia staff). The preoperative infection risk scores were not significantly different between groups (Table 1). Early reintervention after the index procedure was required for hematoma evacuation or lead revision in 28 patients in the No-AIGISRx group (2.5%) and 12 patients in the Yes-AIGISRx group (3.3%, p=0.433). As noted above, although use of the AIGISRx device required substantial additional pocket dissection, no complications could be attributed specifically to this requirement. One patient in the Yes-AIGISRx group suffered a diffuse erythematous rash beginning approximately 3 days after the procedure, which began in the region of the pocket and persisted for several days. She had no history of collagen vascular disease. She had no known allergies. It was concluded that this was likely to have been an allergic reaction to some element of the AIGISRx device. During the 6-month interval after

the index CIED procedure, 19 patients (1.7%) in the No-AIGISRx group manifested CIED infection, whereas no patient in the Yes-AIGISRx group manifested infection (p=0.012). Among the 19 patients who subsequently developed infection, prophylactic antibiotics had been administered for ≥ 24 hours after the index CIED procedure in 18 (vancomycin [4 patients], cefazolin [9 patients], cephalexin [3 patients], clindamycin [2 patients]). Infections were detected an average of 72 days after the index procedure, and most patients presented with pocket stigmata (Table 2). When defined, microbiology was predominantly staphylococcus (Table 2).

During the 6-month interval after the index CIED procedure, 59 patients (4%) died. The survival rate was significantly higher in the Yes-AIGISRx group (98.1%) than in the No-AIGISRx group (95.3%, p=0.019). On multivariable analysis, the adjusted risk of mortality among patients who did not receive AIGISRx was 2.52 (95% confidence interval [CI] 1.11-5.73; p=0.027). The observed mortality rate among patients with an infection (15.7%) was significantly higher than among patients who did not experience infection (4.5%; HR=5.02; 95% CI 1.43-17.64; p=0.02). Stratifying analyses by infection status revealed a higher adjusted mortality rate among patients in the No-AIGISRx group without infection, when compared to patients in the Yes-AIGISRx group (HR=2.47; 95% CI 1.09-5.62, p=0.031).

Clinical and CIED system data comparing patients in the No-AIGISRx group with and without infection are shown in Table 3. Analysis stratified by preoperative risk score revealed a trend towards significance in the difference between patients with score of less than 3 (N=580, 6 infections, infection rate = 1.0%) and those with a score of greater than or equal to 3 (N=531, 13 infections, infection rate = 2.4%; p=0.069). The infection rate among the 28 patients in the No-AIGISRx group who underwent early reintervention was 7.1% (N=2).

The propensity matching algorithm resulted in a match for 362 of the 365 patients In the Yes-AIGISRx group. Prior to matching, the largest standardized difference between the groups was 0.67 (de novo system implantation) compared to 0.062 (gender) in the matched dataset, indicating that the matching algorithm performed well in identifying patients from the No-AIGISRX group with similar infection risk profiles. Among these patients, 7 (1.93%) experienced CIED infection (compared to 0 in the Yes-AIGISRx group), indicating that use of the AIGISRx device significantly reduced the risk of infection (p=0.023).

One or more hospitalizations were necessary to provide infection care for each of the 19 affected patients. Two patients died during a hospitalization for which infection care was delivered, and in both cases infection was judged to have been a significant contributor. By 6 months after the index procedure, 3 patients with CIED infection had died (15.7%), versus 49 deaths among 1092 No-AIGISRx patients without infection (4.5%, p=0.021). The mean duration of stay for hospitalizations attributable to infection among was 13±11 days (range 1-45 days). The total cost of treating the CIED infections was $1,043,592, mostly attributable to inpatient care. The average cost was $54,926 ± $11,374 per patient. Applying the 1.71% infection rate observed in the overall No-AIGISRx group, we estimated that 6.2 additional patients (1.71% x 365 patients) in the Yes-AIGISRx group would have experienced infection had the device not been used. Among the propensity-matched No-AIGISRx patients, a 1.9% infection rate would translate into 7 infections had the device not been used. The estimated cost to care for those infections was similar to the cost of using AIGISRx in every patient (Table 4). Patient subsets in which greater cost efficiency was observed included those with preoperative risk score ≥3 and those who had undergone early reintervention (Table 4). Extrapolating beyond the data, we estimated the cost implications for the range of infection rates reported previously, from 0.56%[8] to 4.3%,[3] assuming a cost $54,926 per infection and no infections in association with device use (Table 5). At a rate of 1.59%, the cost of infection care would be approximately balanced by the cost of using AIGISRx in every patient (Table 5).

As a further sensitivity analysis, we extended the follow-up period to 1 year following the index CIED implantation. At this interval, 1367 patients (93% of original cohort) had information available. Among the No-AIGISRx group, 1 additional patient manifested a CIED infection at 9 months. Among the Yes-AIGISRx group, no patients manifested a CIED infection. The survival rate at 1 year was 93.3% among No-AIGISRx group patients, versus 95.9% among Yes-AIGISRx group patients; the adjusted 1 year mortality rate was significantly higher in the No-AIGISRx group (HR=.81; 95% CI 1.01-3.22; p=0.046). Among infected patients, the mortality rate was significantly higher than among patients without infection (HR=5.36; 95% CI=1.56-18.49; p=0.008). After excluding patients with infection, there was no significant relationship between AIGISRx use and mortality (HR=1.76; 95% CI=0.98-3.15; p=0.058).

DISCUSSION

In the present study, use of AIGISRx as a standard of care (in all patients) was associated with a lower risk of CIED infection, with attendant morbidity and mortality. To our knowledge, no prior studies have considered health outcomes and economic implications associated using this strategy. In addition to device efficacy, the costs of routine were similar to those of infection care. It is likely that the infection care costs reported here are a significant underestimation, given omission of costs to the health care delivery organization (ambulatory care, home care), patient (physician fees, non-covered service fees, co-pays, lost wages/earning potential, travel, lodging, sustenance), and patient family (lost wages, travel, lodging, sustenance).

These data confirm and extend those reported previously. Bloom et al.[5] and Kolek et al.[3] each reported significantly diminished infection rates in association with AIGISRx use in selected patients, relative to expected rates. Kolek et al. also reported an increased mortality rate associated with infection, as in the present study.[3] This has also been reported elsewhere.[1,2,18] Mittal et al. examined a single-center experience and demonstrated a significantly reduced rate of infection (8 of 1240 patients, 0.8%) during an epoch in which the AIGISRx device was available to them, relative to a preceding epoch in which it was not (25 of 1651 patients, 1.5%).[7] They described a tiered risk scoring system comprised of factors which, as was the trend in the present study, predicted a higher rate of infection as they accumulated. Finally, a preliminary report that combined data from the multicenter CITADEL and CENTURION registries (NCT 01043861 and 01043705, respectively) demonstrated an infection rate of 0.2% among 1000 selected ICD/CRT patients in whom AIGISRx was used.[19]

In the present study, an inverse relationship between AIGISRx use and mortality was observed. As in several previous reports, mortality rates were significantly higher among patients who experienced infection than among those who did not.[3,4,20] Given similar preoperative infection risk scores between Yes-AIGISRx and No-AIGISRx groups coupled with the fact that, after excluding patients who experienced infection, there was no significant intergroup different in mortality rate, we believe that infection was the key driver in the observed increase in mortality among No-AIGISRx patients.

In the present study, early reintervention, defined as pocket reentry within one month of the index CIED procedure, was associated with a high rate of subsequent infection. As this was a factor which could not be predicted preoperatively, we excluded it from our risk scoring system. Although small in number in the present cohort, a relationship between early reintervention and CIED infection has been reported consistently.[5,7]

Multiple previous reports have documented that, beyond the mortality, morbidity, and misery experienced by patients and family members in relation to CIED infection, the care is very costly.[1,4,21,22] In performing the economic analysis, it was assumed that all costs incurred by treating infection would be borne by the health care delivery organization in which the index CIED procedure occurred, and that the cost of the AIGISRx device was not separately reimbursed. Even though our assessment of costs is almost certainly an underestimation, the analysis suggests that routine use of the device is economically reasonable, and that stratifying patients by preoperative risk may further improve cost efficiency.

Several limitations to the current data are notable. First, the data were not derived from a prospective nor randomized format. Although we made an attempt to ensure that patient in the groups were similar *vis a vis* infection risk, including preoperative score and propensity matching, neither of these techniques insures against bias. This was an observational study, and thus the potential for bias should render it hypothesis-generating only. As might be expected in a group of implanters with varied referral patterns, there were significant differences between No-AIGISRx and Yes-AIGISRx groups (Table 1). However, preoperative infection risk score did not differ significantly between groups, nor did the rate of early reintervention. Moreover, the propensity score analysis indicated that when AIGISRx use was compared within a set of patients with similar preoperative infection risk burden, the negative association of AIGISRx use with infection was maintained. Second, our data almost certainly overestimate the efficacy of AIGISRx; the totality of experience makes its clear that early infections will continue to occur despite use.[3,5,7,22] Adjustments for actual infection rates, costs of care, and costs of the AIGISRx devices will be necessary in any future cohort used to assess the value of the device. Third, assessment of CIED infections within 6 months of an index procedure provides only a limited window to the problem of CIED infection in its totality.[2] Given unclarity as to mechanisms underlying "late" (presenting more than 6 months after most recent procedure) CIED infections, the overall impact of technologies that decrease the rate of early infection remains to be determined.[1,2,9,13] Our 12-month sensitivity analysis did not strongly suggest either benefit or harm of the residual AIGISRx device. This issue will be crucial in the cost-benefit analysis of standard of care use. Finally, the device utilized in the present study should be considered obsolete, now replaced by a second-generation device that is fully absorbed several weeks after implantation. Although it is anticipated that the second-generation device will perform similarly, this awaits confirmation.

ACKNOWLEDGEMENTS

The authors thank Kurt Stromberg for his assistance with the statistical analyses.

REFERENCES

1. Baddour LM, Epstein AE, Erickson CC, Knight BP, Levison ME, Lockhart PB, Masoudi FA, Okum EJ, Wilson WR, Beerman LB, Bolger AF, Estes NA III, Gewitz M, Newburger JW, Schron EB, Taubert KA. Update on cardiovascular implantable electronic device infections andtheir management: a scientific statement from the American Heart Association. Circulation. 2010; 121: 458–477.

2. Tarakji KG, Wilkoff BL. Management of cardiac implantable electronic device infections: the challenges of understanding the scope of the problem and its associated mortality. Expert Rev Cardiovasc Ther 2013; 11, 607–16.

3. Kolek MJ, Dresen WF, Well QS, Ellis CR. Use of an antibacterial envelope is associated with reduced cardiac implantable electronic device infections in high-risk patients. Pacing Clin Electrophysiol 2013; 36: 354-61.

4. Sohail MR, Henrikson CA, Braid-Forbes MJ, Forbes KF, Lerner DJ. Mortality and cost associated with cardiovascular electronic device infections. Arch Intern Med 2011; 171: 1821-8.

5. Bloom HL, Constantin L, Dan D, DeLurgio DB, El-Chami M, Ganz LI, Gleed KJ, Hackett FK, Kanuru NK, Lerner DL, Rasekh A, Simons GR, Sogade FO, Sohail MR for the COMMAND investigators. Implantation Success and Infection in Cardiovascular Implantable Electronic Device Procedures Utilizing an Antibacterial Envelope. Pacing Clin Electrophysiol 2011; 34: 133-42.

6. Hansen LK, Brown M, Johnson D, Palme Li DF, Love C, Darouiche R. In vivo model of human pathogen infection and demonstration of efficacy by an antimicrobial pouch for pacing devices. Pacing Clin Electrophysiol 2009; 32: 898-907.

7. Mittal S, Shaw RE, Michel K, Palekar R, Arshad A, Musat D, Preminger M, Sichrovsky T, Steinberg JS. Cardiac implantable electronic device infections: incidence, risk factors, and the effect of the AigisRx antibacterial envelope. Heart Rhythm 2014; 11: 595-601.

8. Klug D, Balde M, Pavin D, Hidden-Lucet F, Clementy J, Sadoul N, Rey JL, Lande G, Lazarus A, Victor J, Barnay C, Grandbastein B, Kacet S, PEOPLE Study Group.. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. Circulation 2007; 116: 1349-55.

9. Prutkin JM, Reynolds MR, Bao H, Curtis JP, Al-Khatib SM, Aggarwal S, Uslan DZ. Rates and factors associated with infection in 200,909 implantable cardioverter-defibrillator implants: results from the NCDR®. Circulation 2014; pii: CIRCULATIONAHA.114.009081.

10. Lekkerkerker JC, van Nieuwkoop C, Trines SA, van der Bom JG, Bernards A, van de

Velde ET, Bootsma M, Zeppenfeld K, Jukema JW, Borleffs JW, Schalij MJ, van Erven L. Risk factors and time delay associated with cardiac device infections: Leiden device registry. Heart 2009; 95: 715-20.

11. Gould PA, Krahn AD; Canadian Heart Rhythm Society Working Group on Device Advisories. Complications associated with implantable cardioverter-defibrillator replacement in response to device advisories. JAMA 2006; 295: 1907-11.

12. Le KY, Sohail MR, Friedman PA, Uslan DZ, Cha SS, Hayes DL, Wilson WR, Steckelberg JM, Baddour LM, Mayo Cardiovascular Infections Study Group. Clinical predictors of cardiovascular implantable electronic device-related infective endocarditis. Pacing Clin Electrophysiol 2011; 34: 450-9.

13. Nagpal A, Baddour LM, Sohail MR. Microbiology and pathogenesis of cardiovascular implantable electronic device infections. Circ Arrhythm Electrophysiol 2012; 5: 433-41.

14. Report to Congress: Medicare and the Health Care Delivery System. Chapter 6; June 2012 (http://www.medpac.gov/chapters/Jun12_Ch06_APPENDIX.pdf).

15. Durable medical equipment, prosthetics, orthotics, and supplies (DMEPOS) revised fee schedule. (http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/DMEPOSFeeSched/index.html).

16. Austin PC. Primer on statistical interpretation or methods report card on propensity-score matching in the cardiology literature from 2004-2006: a systematic review. Circ Cardiovasc Qual Outcomes 2008; 1: 62-7.

17. Stuart EA, Ho D, Imai K, King G. MatchIt: nonparametric preprocessing for parametric causal reference. Journal of Statistical Software 2011; 42(8): 1-28.

18. Greenspon AJ, Prutkin JM, Sohail MR, Vikram HR, Baddour LM, Danik SB, Peacock J, Falces C, Miro JM, Blank E, Naber C, Carillo RG, Tseng CH, Uslan DZ. Timing of the most recent procedure influences the clinical outcome of lead-associated endocarditis, Results of the MEDIC (Multicenter Electrophysiologic Device Infection Cohort). J Am Coll Cardiol 2012; 59: 681-7.

19. Henrikson CA, Sohail MR, Simons GR, Lerner DJ. CITADEL/CENTURION study results: use of an antibacterial envelope is associated with very low 6 month CIED infection rates. Europace 2014; 16 (2S): ii156.

20. Sohail MR, Henrikson CA, Braid-Forbes MJ, Forbes KF, Lerner DJ. Increased long-term mortality in patients with cardiovascular implantable electronic device infections. Pacing Clin Electrophysiol 2015; 38: 231-9.

21. Reynolds MR, Cohen DJ, Kugelmass AD, Brown PP, Becker ER, Ciller SD, Simon AW. The frequency and incremental cost of major complications among Medicare beneficiaries receiving implantable cardioverter-defibrillators. J Am Coll Cardiol 2006; 47: 2493-7.

22. Ferguson TB, Ferguson CL, Crites K, Crimmons-Reda P. The additional hospital costs generated in the management of complications of pacemaker and defibrillator implantations. J Thorac Cardiovasc Surg 1996; 111: 742-52.

Table 1. Clinical and CIED data

Group	No-AIGISRx	Yes-AIGISRx	P
N	1111	365	-
Age (years)	67 ±16	71 ±12	**<0.001**
Male gender, N (%)	735 (66)	221 (61)	0.058
Heart Failure, N (%)	699 (63)	236 (65)	0.616
Diabetes Mellitus, N (%)	351 (32)	102 (28)	0.214
Hypertension, N (%)	787 (71)	293 (80)	**<0.001**
Prior cardiac surgery, N (%)	364 (33)	122 (33)	0.847
Renal Insufficiency, N (%)	229 (21)	69 (19)	0.500
Renal Failure, N (%)	27 (2)	9 (3)	1.000
Corticosteroid use, N (%)	56 (5)	19 (5)	0.891
Oral anticoagulation, N (%)	394 (36)	177 (49)	**<0.001**
Prior CIED Infection, N (%)	55 (6)	7 (2)	**0.010**
Procedure Type, N (%) New system implantation Pulse generator replacement System upgrade	 744 (67) 217 (20) 150 (13)	 128 (35) 179 (49) 58 (16)	**<0.001**
System Type, N (%) PM ICD CRT	 378 (34) 377 (34) 356 (32)	 107 (29) 105 (29) 153 (42)	**0.003**
More than 2 leads, N (%)	378 (34)	165 (45)	**<0.001**
Epicardial leads, N (%)	12 (1)	5 (1)	0.584
Temporary pacemaker, N (%)	75 (7)	8 (2)	<0.001
Procedure duration (min)	164±65	151±66	0.124
Hematoma, N (%)	8 (1)	4 (1)	0.505
Early reintervention, N (%)	28 (3)	12 (3)	0.458
Preoperative risk score	2.4±1.4	2.5±1.4	0.234

Legend: PM = pacemaker (single or dual chamber); ICD = implantable cardioverter-defibrillator (single or dual chamber); CRT = cardiac resynchronization system (tachy or brady)

Table 2. Details of CIED Infections

Patient	System Type	Time to Detection	Microbiology	Presentation	Status at 6 months
1	CRT	175	NG	Pocket	no reimp/alive
2	ICD	29	MSSA	Pocket	reimp/alive
3	ICD	62	NG	Pocket	reimp/alive
4	ICD	18	Pseudomonas	Pocket	no reimp/alive
5	CRT	99	NG	Pocket	reimp/alive
6	ICD	39	MSSA	Pocket	reimp/alive
7	CRT	28	NG	Pocket	reimp/alive
8	CRT	63	NG	Pocket	reimp/alive
9	CRT	29	NG	Pocket	reimp/dead
10	PM	44	CoNS	Pocket	reimp/alive
11	CRT	26	MSSA	Pocket	reimp/alive
12	CRT	163	Enterobacter	Bacteremia	no reimp/alive
13	PM	148	NG	Pocket	reimp/alive
14	ICD	42	MSSA	Bacteremia	reimp/alive
15	PM	28	MSSA	Pocket	reimp/alive
16	CRT	29	MRSA	Pocket	no reimp/dead
17	CRT	179	NG	Pocket	reimp/alive
18	CRT	149	CoNS	Pocket	reimp/alive
19	PM	16	MRSA	Bacteremia	no reimp/dead

Legend: PM = pacemaker (single or dual chamber); ICD = implantable cardioverter-defibrillator (single or dual chamber); CRT = cardiac resynchronization system (tachy or brady). MRSA = methicillin-resistant staphylococcus aureus. MSSA = methicillin-sensitive staphylococcus aureus. CoNS = coagulase negative staphylococcus. Pocket = infection stigmata were localized to the subcutaneous or submuscular pocket housing the CIED pulse generator. Reimp = CIED system reimplanted after infection treated. NG = no bacterial growth.

Table 3. Patients with and without infection in the No-AIGISRx group

	No Infection	Infection	Odds Ratio (95% CI)	P
N	1092	19		
Age (years)	67 ±16	61 ±12	0.97 (0.92-1.03)	0.280
Male gender, N (%)	723 (66)	12 (63)	1.14 (0.45-2.93)	0.781
Heart Failure, N (%)	685 (63)	14 (74)	1.65 (0.59-4.60)	0.337
Diabetes Mellitus, N (%)	344 (32)	7 (37)	1.27 (0.49-3.25)	0.620
Hypertension, N (%)	772 (71)	15 (79)	1.53 (0.51-4.72)	0.433
Prior cardiac surgery, N (%)	359 (33)	5 (26)	0.73 (0.26-2.04)	0.546
Renal Insufficiency, N (%)	224 (21)	5 (26)	1.38 (0.49-3.88)	0.535
Renal Failure, N (%)	25 (2)	2 (11)	5.02 (1.10-22.91)	**0.021**
Corticosteroid use, N (%)	55 (5)	1 (5)	1.05 (0.14-7.99)	0.964
Oral anticoagulation, N (%)	390 (36)	4 (21)	0.48 (0.16-1.45)	0.185
Prior CIED Infection, N (%)	55 (5)	0 (0)	-	0.316
Procedure Type, N (%)				0.444
New system implantation	731 (67)	13 (68)	1.15 (0.44-3.02)	0.771
Pulse generator replacement	215 (20)	2 (11)	0.45 (0.10-1.97)	0.278
System upgrade	146 (13)	4 (21)	1.62 (0.53-4.91)	0.391
System Type, N (%)				0.146
PM	374 (34)	4 (21)	0.51 (0.16-1.55)	0.229
ICD	372 (34)	5 (26)	0.69 (0.24-1.93)	0.479
CRT	346 (32)	10 (53)	2.39 (0.96-5.95)	0.052
More than 2 leads, N (%)	368 (34)	10 (53)	2.18 (0.88-5.43)	0.084
Epicardial leads, N (%)	11 (1)	1 (5)	5.46 (0.67-44.56)	0.075
Temporary pacemaker, N (%)	73 (7)	2 (11)	1.64 (0.37-7.24)	0.508
Procedure duration (min)	165±65	148±49	0.99 (0.98-1.01)	0.542
Hematoma, N (%)	7 (1)	1 (5)	8.61 (1.01-73.66)	**0.018**
Early reintervention, N (%)	26 (2)	2 (11)	4.82 (1.06-21.96)	**0.025**
Preoperative risk score	2.4±1.4	2.8±1.3	1.19 (0.87-1.65)	0.273

Legend: CI = confidence interval; PM = pacemaker (single or dual chamber); ICD = implantable cardioverter-defibrillator (single or dual chamber); CRT = cardiac resynchronization system (tachy or brady)

Table 4. Financial Implications of Use of AIGISRx as a Standard of Care

	N	Infection Rate (N)	Infection care cost	Differential cost*
All Patients	365	1.71% (6.20)	$342,854	$23,863
Preoperative risk score <3	179	1.03% (1.85)	$101,708	- $54,729
Preoperative risk score ≥3	186	2.45% (4.55)	$250,115	$87,560
Early Reintervention	12	6.67% (0.80)	$43,941	$33,453

Hypothetical projection which assumes Yes-AIGISRx patients experienced the same infection rate as actually observed among No-AIGISRx patients. *Differential cost = cost of infection care minus cost of AIGISRx as a standard of care.

Table 5. Financial Implications of Infection Rate

Infection Rate	Infections	Infection care cost	Differential cost*
0.56%	2.03	$111,346	- $205,023
1.59%	5.76	$316,371	$2
1.93%	7.00	$384,481	$68,112
4.3%	15.57	$854,976	$538,607

Hypothetical projection, using propensity-matched Yes-AIGISRx patients only (N=362), surveying different infection rates. Included are the low (0.56%) and high (4.3%) values from prior reports, the rate actually observed in the present study (1.93%), and the rate at which the cost of infection care was approximately balanced by the cost of AIGISRx as a standard of care. *Differential cost = cost of infection care minus cost of AIGISRx use in all patients.

