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Complication Rates Associated With Pacemaker or Implantable Cardioverter-Defibrillator Generator Replacements and Upgrade Procedures

Results From the REPLACE Registry

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Background—Prospective studies defining the risk associated with pacemaker or implantable cardioverter-defibrillator replacement surgeries do not exist. These procedures are generally considered low risk despite results from recent retrospective series reporting higher rates.

Methods and Results—We prospectively assessed predefined procedure-related complication rates associated with elective pacemaker or implantable cardioverter-defibrillator generator replacements over 6 months of follow-up. Two groups were studied: those without (cohort 1) and those with (cohort 2) a planned transvenous lead addition for replacement or upgrade to a device capable of additional therapies. Complications were adjudicated by an independent events committee. Seventy-two US academic and private practice centers participated. Major complications occurred in 4.0% (95% confidence interval, 2.9 to 5.4) of 1031 cohort 1 patients and 15.3% (95% confidence interval, 12.7 to 18.1) of 713 cohort 2 patients. In both cohorts, major complications were higher with implantable cardioverter-defibrillator compared with pacemaker generator replacements. Complications were highest in patients who had an upgrade to or a revised cardiac resynchronization therapy device (18.7%; 95% confidence interval, 15.1 to 22.6). No periprocedural deaths occurred in either cohort, although 8 later procedure-related deaths occurred in cohort 2. The 6-month infection rates were 1.4% (95% confidence interval, 0.7 to 2.3) and 1.1% (95% confidence interval, 0.5 to 2.2) for cohorts 1 and 2, respectively.

Conclusions—Pacemaker and implantable cardioverter-defibrillator generator replacements are associated with a notable complication risk, particularly those with lead additions. These data support careful decision making before device replacement, when managing device advisories, and when considering upgrades to more complex systems.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00395447.

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Key Words: complications ■ electrophysiology ■ implantable cardioverter defibrillators ■ pacemakers

The number of patients in North America and Europe who receive a new pacemaker or implantable cardioverter-defibrillator (ICD) yearly is rising.[1,2] The need for a pacemaker increases as patients age, and ICD implantation has expanded as a result of the publication of recent clinical trials.[3–9] In the years after initial implantation, device replacement may become necessary for battery depletion or for upgrades to more complex multilead pacemakers or ICDs. The increase in generator or lead advisories and recalls contributes further to those patients considered for replacement.[10–12]

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The determination of procedural adverse events is complex, related to the specific type of procedure and patient comorbidities such as congestive heart failure.[13] Longer-term patient outcomes may also be affected by the procedure; thus,

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reporting of complications should include both short- and long-term results.[14]

Although retrospective series have examined complications with generator replacements, prospective data are unavailable.[15–19] Furthermore, risks related to generator replacements with lead additions are not well understood, particularly upgrades to cardiac resynchronization therapy (CRT).[20–23] To answer these questions, we prospectively collected 6-month complication rates in patients undergoing pacemaker or ICD generator replacement, including CRT-pacemakers and CRT-ICDs.

Methods

Study Design and Participants

The REPLACE Registry was a prospective, multicenter study designed to collect complication data on patients for 6 months after replacement of a pacemaker or ICD generator. This study was approved by the ethics committee of each participating institution, and all patients provided written informed consent.

Two cohorts of patients undergoing generator replacement were prespecified: those without (cohort 1) and those with (cohort 2) the intent to add 1 or more leads. Cohort assignment was made at the time of enrollment in the study. Investigators were encouraged to enroll all patients who met inclusion criteria: age ≥18 years, ability to provide informed consent, life expectancy >6 months, geographic stability, and availability for the 6 months of follow-up. Exclusion criteria were expected heart transplant within 6 months or a planned lead extraction for any cause, including infection. Investigators were instructed to perform the generator replacement within 30 days of enrollment and baseline data collection.

Any commercially available generator or lead could be included. The decision to perform the generator replacement or to upgrade an existing device was made according to the investigators' clinical assessment of their patient. The study did not mandate specific surgical or implantation techniques such as venous access, use of temporary pacemakers, or surgical site choices.

Follow-up included a wound examination performed per the investigators' routine practice, a 3-month clinic or telephone query evaluation, and a final 6-month clinic visit. Clinical data, complications, and patient medical complaints related to the replacement procedure were prospectively captured with a secure electronic data management system.

Definitions of major and minor complications were predefined and purposely comprehensive (Table 1). Major complications were those that placed the patient at significant risk, requiring an intervention, procedure, or hospitalization for management. Minor complications were associated with significant symptoms or a decline in status.

All reported complications were adjudicated by the Clinical Events Committee, which included electrophysiology and infectious disease physicians. Medical records were reviewed to ensure that active medical conditions present at the time of the procedure were not adjudicated as complications. If a patient experienced multiple events, the clinical time course was reviewed to ensure that complications counted were distinct separate occurrences related to the replacement procedure. If the investigators reported events that were not prespecified, the Clinical Events Committee considered each for its relationship to the generator replacement procedure. Procedural infections conformed to the Center for Disease Control definitions, which include deep and superficial surgical site infections exclusive of stitch abscesses.[24]

The reporting of deaths related to pacemaker or ICD procedures is often limited to the immediate periprocedural time.[5,7,8] Commonly, however, the surgical literature reports all-cause 30-day mortality rates, which consider both immediate procedural survival and deaths from subsequent complications.[14] Adopting a similar approach, the Clinical Events Committee examined all deaths that occurred within 30 days of the enrollment replacement procedure. Death was considered procedure related if caused by a mechanical complication

Table 1. Definitions of Major and Minor Complications

Major complications
Death within 30 d related to the procedure
Cardiac arrest within 24 h of the procedure
Respiratory arrest/failure within 24 h of the procedure requiring ventilator support or intubation
Acute coronary syndrome directly related to the procedure
Cardiac perforation with or without pericardial tamponade, requiring pericardiocentesis or other surgical intervention
Pneumothorax requiring observation or chest tube placement
Hemothorax
Stroke within 30 d of the replacement procedure
Hemodynamic instability during the procedure requiring unplanned intervention and/or aborting the procedure
Infection requiring intravenous antibiotics and or system removal/extraction
Generator or lead malfunction requiring reoperation
Pocket revision requiring reoperation
Prolonged hospitalization attributable to the device replacement procedure*
Hematoma requiring evacuation, drainage, blood transfusion, hospitalization, or extension of hospital stay to treat hematoma
Hospital readmission directly related to the generator replacement procedure
Coronary venous dissection with hemodynamic instability
Pulmonary embolus
Peripheral arterial embolus
Deep vein thrombosis
Drug reaction resulting in an aborted procedure
Cardiac valve injury
New AV conduction block developing as a result of the procedure
AV fistula related to the replacement procedure
Minor complications
Hematoma lasting >7 d with tenseness, drainage, or minor dehiscence managed as an outpatient
Hematomas without tenseness but requiring additional outpatient evaluation
Implant related pain lasting >7 d requiring prolonged use of narcotic pain medications†
Cellulitis treated as an outpatient with oral antibiotics
Stitch abscess
Minor surgical wound findings‡
Unanticipated device reprogramming resulting from inadequate lead performance with significant patient symptoms or status change, excluding asymptomatic threshold changes
Reversal of sedation for respiratory compromise requiring benzodiazepine or opioid receptor antagonist
Peripheral nerve injury
Superficial phlebitis

AV indicates atrioventricular.

*Unexpected prolonged hospitalization (excludes patients with preprocedure exacerbation of medical illness or those requiring routine intravenous anticoagulation after the procedure).

†Excluding patients taking long-term narcotic medications.

‡Includes complaints such as noninfectious rashes, superficial incisional dehiscence, and painful blistering from tape.

Table 2. Baseline Clinical Characteristics and Medications

Clinical Characteristic	Cohort 1 (n=1031)	Cohort 2 (n=713)	P*
Age, mean (±SD), y	70.6 (±14.1)	69.5 (±12.9)	0.10
Female sex, n (%)	389 (37.7)	172 (24.1)	<0.001
Race, n (%)			0.83
White	903 (87.6)	630 (88.4)	
Black	108 (10.5)	74 (10.4)	
Other	20 (1.9)	9 (1.3)	
Hispanic ethnicity,† n (%)	41 (4.0)	26 (3.6)	0.80
NYHA heart failure class,‡ n (%)			<0.001
Class I	160 (15.5)	52 (7.3)	
Class II	281 (27.3)	137 (19.2)	
Class III	138 (13.4)	378 (53.0)	
Class IV	5 (0.5)	19 (2.7)	
No heart failure symptoms	423 (41.0)	112 (15.7)	
Heart failure hospitalization within 12 mo, n (%)	72 (7.0)	176 (24.7)	<0.001
Ejection fraction,§ mean (±SD), %	44.3 (±16.7)	29.7 (±13.1)	<0.001
Other medical history, n (%)			
Pacemaker dependent,‖ n (%)	298 (28.9)	208 (29.2)	0.96
CABG or valve surgery	353 (34.2)	285 (40.0)	0.02
Peripheral vascular disease	123 (11.9)	89 (12.5)	0.77
Cerebrovascular disease	169 (16.4)	105 (14.7)	0.38
Recent MI (≤4 wk)	4 (0.4)	3 (0.4)	1.00
Remote MI (>4 wk)	321 (31.1)	283 (39.7)	<0.001
Chronic pulmonary disease	165 (16.0)	122 (17.1)	0.56
Renal disease (creatinine ≥1.3 mg/dL)	149 (14.5)	138 (19.4)	0.007
Diabetes mellitus¶	295 (28.6)	217 (30.4)	0.39
Currently smokes cigarettes, n (%)	78 (7.6)	59 (8.3)	0.59
Medications, n (%)			
ACE inhibitor	437 (42.4)	396 (55.5)	<0.001
Aspirin	495 (48.0)	359 (50.4)	0.36
Angiotensin receptor blocker	185 (17.9)	115 (16.1)	0.33
β-blocker	679 (65.9)	566 (79.4)	<0.001
Calcium channel blocker	169 (16.4)	65 (9.1)	<0.001
Digoxin	272 (26.4)	237 (33.2)	0.002
Diuretic	575 (55.8)	494 (69.3)	<0.001
Statin	564 (54.7)	433 (60.7)	0.014
Steroids	34 (3.3)	17 (2.4)	0.31
Antiarrhythmic drugs#			
Amiodarone	102 (9.9)	121 (17.0)	<0.001
Sotalol	62 (6.0)	30 (4.2)	0.10
Other	40 (3.9)	22 (3.1)	0.43
Anticoagulant/Antiplatelet Drugs			
Warfarin	386 (37.4)	328 (46.0)	<0.001
Dipyridamole	8 (0.8)	2 (0.3)	0.21
Heparin-low molecular weight	9 (0.9)	21 (2.9)	0.001
Clopidogrel/ticlopidine	117 (11.3)	112 (15.7)	0.009
No medications	39 (3.8)	16 (2.2)	0.09

NYHA indicates New York Heart Association; CABG, coronary artery bypass graft; MI, myocardial infarction; and ACE, angiotensin-converting enzyme.

*P values compare cohort 1 to cohort 2.

†Ethnicity unknown for 1 cohort 1 patient.

‡NYHA class unknown for 24 cohort 1 patients and 15 cohort 2 patients.

§Ejection fraction data, requested if obtained within 6 months before enrollment, was available for 443 cohort 1 patients and 530 cohort 2 patients.

‖Pacemaker dependency was determined by the investigator.

¶Diabetes mellitus status was unknown for 2 cohort 2 patients.

#Patients could be taking >1 antiarrhythmic drug.

or acute medical deterioration during or after the procedure; was a result of related interventions; or was unexplained and unanticipated.

Management of periprocedural anticoagulation was at the discretion of each investigator; routine reinitiation of anticoagulation with intravenous heparin after the procedure was not considered a complication. In cohort 2, an unsuccessful attempt to implant a new transvenous lead resulting from patient anatomy was not reported as a complication. In both cohorts, the unanticipated finding of a lead malfunction at the time of the replacement procedure requiring an unplanned lead extraction was not considered a complication. A lead extraction might be considered necessary, for instance, if venous access was limited by vessel crowding from indwelling leads so that removal of a lead was needed to complete the procedure.

Statistical Analysis

The REPLACE registry was designed as a fixed-sample-size trial, with a total of 1750 patients considered adequate to achieve predetermined levels of precision in the estimation of complication rates in the 2 study cohorts. Previously published data suggested that complications associated with generator replacement could occur in 1% to 10% of patients.[15–19] A minimum of 700 patients would permit estimating a 95% confidence interval (CI) width of ±1% around an observed event rate of 1%, whereas an event rate of 10% would have an associated interval width of ±2.5%. Because complication rates were expected to be lower in cohort 1, a minimum of 1000 patients was planned for this cohort to enable detection of infrequent events, with the remainder, or up to 750 patients, in cohort 2. Prespecified variables were collected in both cohorts. Patients were evaluated on an intention-to-treat basis according to original cohort classification assignment by the investigator. Standard descriptive statistics were used to summarize the registry data. Continuous variables were reported with means and SDs.

Complications are reported both as the number of patients experiencing each type of complication and as patient-level event rates with associated exact 95% CIs. In cases when group differences in registry variables were statistically tested, nominal unadjusted *P* values were reported for associated tests of continuous (Student *t* test) and categorical measures (χ^2, Fisher exact, and Cochran-Mantel-Haenszel tests).

Study Oversight and Authorship

The REPLACE Registry Steering Committee (Appendix A in the online-only Data Supplement) was responsible for overall study guidance, including the study protocol, data analysis, and interpretation of the results. Reported events were adjudicated by the Clinical Events Committee (Appendix B in the online-only Data Supplement), blinded to institution and investigator (Appendix C in the online-only Data Supplement). Novella Clinical independently managed the database and participating sites and provided on-site

Table 3. Device Characteristics at Enrollment

Characteristic	Cohort 1 (n=1031)	Cohort 2 (n=713)	P*
Existing device type, n (%)			<0.001
Pacemaker, single	90 (8.7)	71 (10.0)	
Pacemaker, dual	425 (41.2)	258 (36.2)	
ICD, single	101 (9.8)	137 (19.2)	
ICD, dual	226 (21.9)	183 (25.7)	
CRT-pacemaker	14 (1.4)	15 (2.1)	
CRT-ICD	175 (17.0)	49 (6.9)	
Existing device location, n (%)			0.75
Prepectoral	918 (89.0)	642 (90.0)	
Subpectoral	94 (9.1)	64 (9.0)	
Abdomen, prerectus	11 (1.1)	4 (0.6)	
Abdomen, subrectus	4 (0.4)	2 (0.3)	
Unknown	4 (0.4)	1 (0.1)	
Prior generator replacement, n (%)	234 (22.7)	183 (25.7)	0.17
Duration of implantation,† mean (±SD), y	6.2 (±2.7)	4.4 (±3.3)	<0.001

*P values compare cohort 1 to cohort 2.

†Duration of implant data is unavailable for 3 cohort 1 patients and 5 cohort 2 patients.

monitoring services throughout the study (Appendix D in the online-only Data Supplement).

All authors take full responsibility for the integrity of the data and the writing of this report. Dr Poole had full access to all the data in the study and had final responsibility for the decision to submit this article for publication.

Results

Study Population

A total of 1750 patients were enrolled. Six patients were later censored because they met exclusion criteria after review of source documents; therefore, data on 1031 cohort 1 patients and 713 cohort 2 patients were analyzed. Enrollment began July 23, 2007, and ended November 7, 2008, with final follow-up ending June 15, 2009. Seventy-two institutions enrolled patients into one or both cohorts. Thirty-four private practice and 34 academic sites enrolled in cohort 1; 32 private practice and 37 academic sites enrolled in cohort 2. All scheduled follow-up appointments were completed by 98.0% of surviving cohort 1 and 98.5% of surviving cohort 2 patients. The wound evaluation appointment occurred at 15.1±12.4 days after the procedure.

Baseline clinical characteristics are shown in Table 2. Patients in cohort 2 compared with cohort 1 patients were less likely to be female; had a lower ejection fraction, a higher New York Heart Association class, more prior cardiac surgery, and more myocardial infarction; and were more likely to be taking cardiac medications.

The surgical site location and type of device the patients had at enrollment are shown in Table 3. Patients in cohort 1 were more likely to have an existing dual-chamber pacemaker and CRT-ICD.

The indications for the generator replacement in cohort 1 patients included normal battery depletion in 997 patients (96.7%), generator under advisory in 12 patients (1.2%), malfunction in 6 patients (0.6%), and elective replacement prior to battery depletion in 16 patients (1.6%). The planned procedure in cohort 2 included an upgrade to a CRT in 407 patients (57.1%), an upgrade from a single-chamber to a dual-chamber pacemaker or ICD in 114 patients (16.0%), an upgrade of a CRT-pacemaker to a CRT-ICD in 13 patients (1.8%), and replacement or evaluation of suspected malfunctioning lead(s) in 179 patients (25.1%). Only 5 (0.7%) cohort 2 patients had a generator under advisory.

Complications

The numbers of patients experiencing distinct types of major complications are shown in Figure 1A and 1B and the numbers of patients experiencing minor complications are shown in Figure 2A and 2B for cohorts 1 and 2, respectively. Complications are grouped as periprocedural (usually identified within 24 hours of the procedure) or subsequent out to 6 months of follow-up including those identified after 24 hours.

Major Complications, Cohort 1

No patient experienced death during the procedure. Only 2 patients (0.2%) experienced a periprocedural complication (hemodynamic instability requiring intervention with vasoactive medications in both). All other complications were identified subsequently. The most common complication was the need for reoperation resulting from lead dislodgement or lead malfunction in 10 patients (1.0%).

Seven patients (0.7%) developed hematomas requiring evacuation. Six of these patients were treated long-term with antiplatelet or anticoagulation medications. These included ticlopidine or clopidogrel alone in 2 patients, warfarin alone in 3 patients, and both warfarin and clopidogrel in 1 patient.

Major Complications, Cohort 2

Periprocedural complications included cardiac perforation in 5 patients (0.7%), a pneumothorax or hemothorax in 6 patients (0.8%), and cardiac arrest in 2 patients (0.3%). The most common subsequent complication was the need to reoperate in 56 patients (7.9%) because of a lead dislodgment or lead malfunction. Prolonged hospitalization as a result of procedure-related exacerbation of heart failure or acute renal failure occurred in 18 patients (2.5%), all of whom had an upgrade to CRT. Hematomas requiring evacuation developed in 11 patients (1.5%). Long-term anticoagulant or antiplatelet medication prescribed in these patients included warfarin in 7 and clopidogrel or ticlopidine in 3; 1 patient took none of these drugs.

No deaths occurred in the periprocedural time, but 8 procedure-related patient deaths occurred (1.1%) within 30 days. In 4 patients, an unsuccessful attempt to place a transvenous left ventricular (LV) lead for a CRT upgrade prompted a surgical approach to place an epicardial LV lead. In all 4 patients, this procedure resulted in subsequent complications and death. In the remaining 4 patients, unexplained death occurred without an alternative explanation such as progressive heart failure or other terminal medical disease. The lead addition in these 4 patients was a new right ventricular ICD lead in 1 patient, new right ventricular pacing

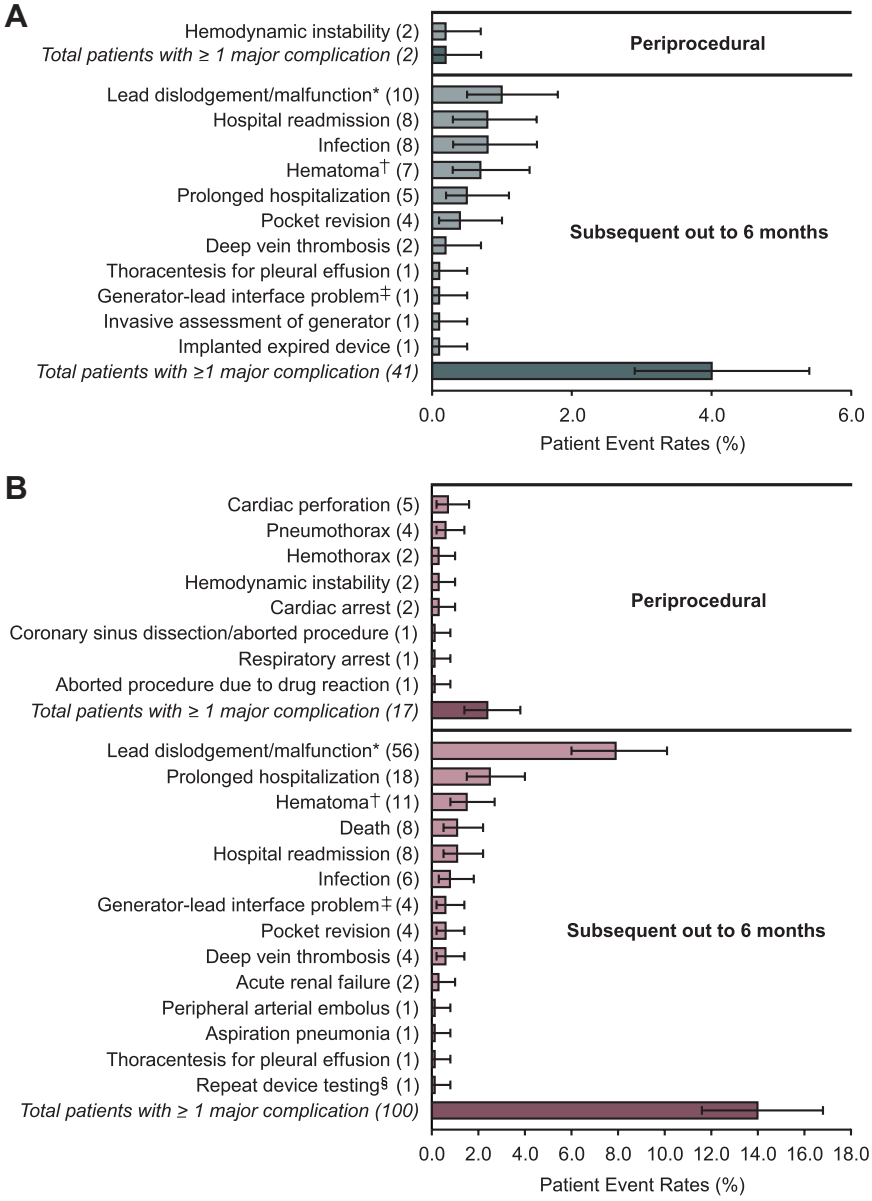

Figure 1. Major complications: A, cohort 1; B, cohort 2. Complications are reported as the number of patients experiencing each type of complication (n). The bars represent the % of patients experiencing each complication type. A patient could have >1 complication. Complications are shown as periprocedural or subsequent out to 6 months of follow-up. CIs for the accuracy of estimation are displayed within the error bars. *Requiring reoperation. †Hematoma requiring evacuation, hospitalization, or transfusion. ‡Such as, loose connection. §To assess defibrillation lead integrity.

lead in 1 patient, and a transvenous LV lead for CRT upgrade in the remaining 2 patients.

Minor Complications, Cohorts 1 and 2

The most frequent minor complications were hematomas persisting >7 days but managed on an outpatient basis. They occurred in 36 cohort 1 patients (3.5%) and in 31 cohort 2 patients (4.3%).

Infectious Complications

Eight patients (0.8%) in cohort 1 experienced a major infection; 5 required extraction of their generator and leads. A minor infection (surgical site cellulitis) occurred in 6 patients (0.6%), who were treated with outpatient oral antibiotics. The cohort 1 combined major and minor infection rate was 1.4% (95% CI, 0.7 to 2.3). Six patients (0.8%) in cohort 2 experienced a major infection; 5 required extraction of the generator and leads. Two additional patients (0.3%) developed cellulitis treated with outpatient oral antibiotics. The cohort 2 combined major and minor infection rate was 1.1% (95% CI, 0.5 to 2.2). All patients in both cohorts received preprocedural intravenous antibiotics and antiseptic skin preparation.

Summary of Complications: Patient Event Rates

Cohort 1

Forty-one patients had 1 or more major complication and 76 patients had 1 or more minor complication. The major complication rate was 4.0% (95% CI, 2.9 to 5.4) with a periprocedural event rate of 0.2% (95% CI, 0.0 to 0.7) and a subsequent event rate out to 6 months of 4.0% (95% CI, 2.9 to 5.4). The minor complication rate was 7.4% (95% CI, 5.9 to 9.1).

Cohort 2

One hundred nine patients had 1 or more major complication, and 54 patients had 1 or more minor complication. The major

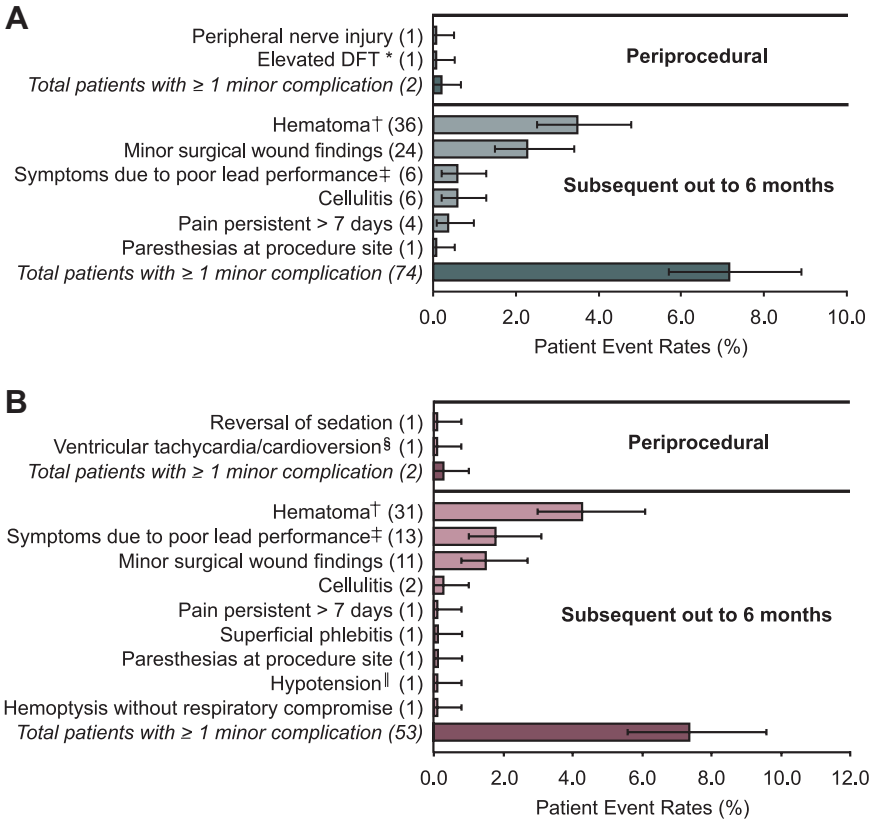

Figure 2. Minor complications: A, cohort 1; B, cohort 2. Complications are reported as the number of patients experiencing each type of complication (n). The bars represent the % of patients experiencing each complication type. A patient could have >1 complication. Complications are shown as periprocedural or subsequent out to 6 months of follow-up. CIs for the accuracy of estimation are displayed within the error bars. *Multiple VF inductions with prolonged anesthesia and patient recovery. †Hematoma persistent >7 days managed as an outpatient. ‡Significant symptoms, such as syncope, resulting in device reprogramming to manage. §VT unanticipated and thought due to electrocautery over generator/leads. ‖Symptomatic hypotension reversed with intravenous fluids. DFT indicates defibrillation threshold.

complication rate was 15.3% (95% CI, 12.7 to 18.1) with a periprocedural event rate of 2.4% (95% CI, 1.4 to 3.8) and a subsequent event rate of 14.0% (95% CI, 11.6 to 16.8). The minor complication rate was 7.6% (95% CI, 5.7 to 9.8).

Major Complication Rates by Generator Implanted

The Cochran-Mantel-Haenszel test was used to evaluate the odds ratios (ORs) for device comparisons across cohorts and device types (Figure 3). We found that the risk of complications across generator type was consistently higher in cohort 2 than in cohort 1 (OR, 2.84; 95% CI, 1.86 to 4.35; $P<0.001$) and that the risk of complications across both cohorts was higher for ICD compared with pacemaker (OR, 2.38; 95% CI, 1.30 to 4.38; $P=0.004$) and for CRT compared with pacemaker (OR, 3.68; 95% CI, 1.98 to 6.84; $P<0.001$). No significant difference in risk was noted between CRT and ICD (OR, 1.50; 95% CI, 0.97 to 2.32; $P=0.07$).

Cohort 2 Major Complication Rates by Lead Procedure

Patient event rates by the type of lead addition or upgrade procedure performed were compared in 3 groups: (1) Patients who underwent an upgrade to or revision of a CRT had a major complication rate of 18.7% (95% CI, 15.1 to 22.6); (2) patients who underwent an upgrade to or revision of a single-chamber pacemaker or ICD to a dual-chamber pacemaker or ICD had a rate of 11.1% (95% CI, 7.4 to 15.9); and (3) patients who ultimately did not receive a new lead addition had a rate of 4.4% (95% CI, 0.5 to 15.2). The difference across risk groups was significant ($P=0.004$; Figure 4).

Discussion

We performed the first prospective, multicenter study of complications related to pacemaker, ICD, and CRT generator changes. Our goal was to collect specific events within the periprocedural time and long-term complications. In this manner, we could provide data to physicians for complications related to the technical aspects of performing the procedure and highlight complications that may arise as a cascade effect of having had the procedure performed.

We found a major complication rate of 4.0% in patients who had a generator replacement without a plan to add a transvenous lead. An earlier retrospective report from 17 Canadian centers described a major complication rate of 5.8% in 533 patients at 3 months and a 5.9% rate in 451 patients at 12 months for patients undergoing an ICD generator replacement because of an advisory indication.[15,16] A subsequent single-center study of 407 patients undergoing ICD replacements reported a major complication rate of 2.1% at 6 months. Two further single-center studies included pacemakers and ICDs and reported major complication rates of 1.2% in 732 patients at 2 months and 4.1% in 222 patients at 3 months, respectively.[17,18]

We report novel data on complication rates in patients who had a generator replacement combined with a plan to add 1 or more transvenous leads. The clinical profile of these patients suggests more advanced cardiovascular disease compared with the patients who had a generator replacement alone.

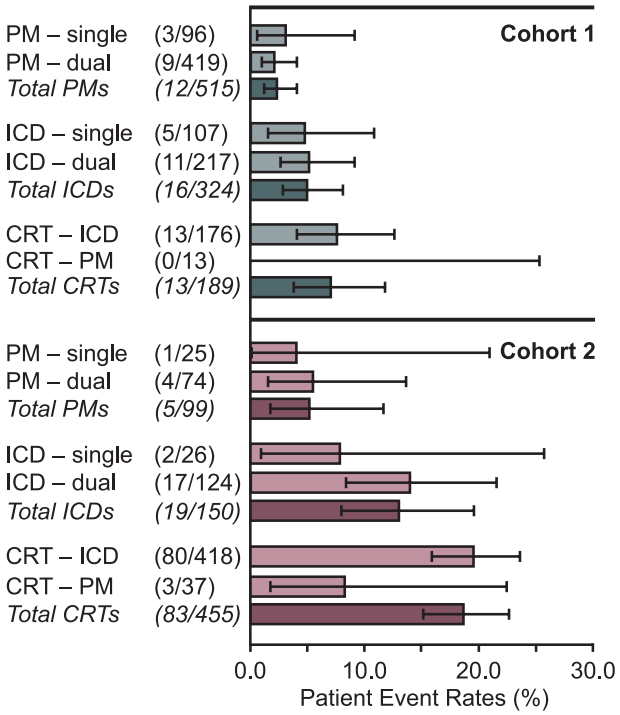

Figure 3. Cohort 1 and 2 major complications by device generator type implanted. The bars represent patient complication event rates and 95% CIs. The numbers in parentheses (n/nn) indicate the number of patients with a complication/the number of patients with each device type. No generator was implanted into 3 cohort 1 patients (no complications occurred) because of physician decision to abandon the procedure. No generator was implanted into 9 cohort 2 patients (2 complications occurred) because of adequate battery voltage but inability to add a lead or decision not to add a lead. PM indicates pacemaker; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy.

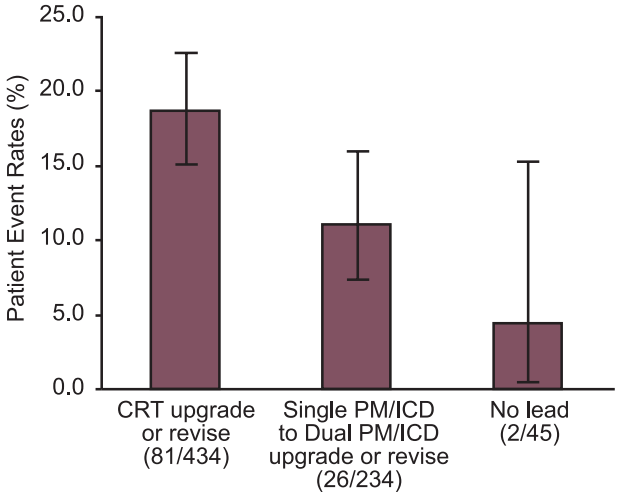

Figure 4. Cohort 2 major complications by lead addition or revision. The bars represent patient complication event rates and 95% confidence intervals. The numbers in parentheses below each bar (n/nn) indicate the number of patients with a complication/the number of patients with each procedure type. CIs for the accuracy of estimation are displayed within the error bars. The lead categories refer to (1) add/revise a transvenous LV lead for the purpose of CRT upgrade or revision, (2) add/revise a transvenous RA or RV lead for upgrade of single chamber PM or ICD to dual chamber PM or ICD, or revision of existing system, and (3) no lead added or revised. The procedure category is regardless of procedural success. In 47 of 434 patients (10.8%), the transvenous LV lead attempts were unsuccessful; in 9 of 234 patients (3.9%), the transvenous right atrial/right ventricular lead attempts were unsuccessful. In 45 patients, a new lead was ultimately not attempted; in 15 of these 45, the plan to replace a malfunctioning right atrial lead was abandoned because of atrial fibrillation; in 6, a chronic capped lead was used; and in the remainder, the lead was repaired or considered adequate after testing. $P=0.004$ for the difference across the 3 procedure types. LV indicates left ventricular; RA, right atrial; RV, right ventricular.

Although the periprocedural major complication rate for this group of patients was low, 2.4%, the overall 6-month major complication rate was substantial, 15.3%. The highest risk of a major complication occurred in patients whose procedure was to add an LV lead for CRT. The reason for this high complication rate may relate to the challenges of venous structures with indwelling leads or the advanced cardiovascular and medical diseases in these individuals. Data on adding leads to existing systems are limited. Several small retrospective studies have reported complication rates between 8.3% and 45.5% in a total of 179 patients.[20–23]

Our observed rate of infectious complications was low. Recent publications have suggested that infection rates associated with generator implantations are increasing and are higher with replacements compared with initial implantation.[25,26] Although we may have missed late-onset lead-associated endocarditis, the methodical reporting and review of all complications allow an accurate assessment of the incidence of pacemaker or ICD infections out to 6 months after replacement.

In both cohorts, a higher complication rate was seen with more complex devices, similar to published series of initial device implantations in which adverse event rates increase from pacemaker to ICD to CRT.[27–30] These observations may reflect differences in severity of underlying cardiac disease.

Minor complications were common, occurring in 7.4% of cohort 1 patients and 7.6% of cohort 2 patients. Although these events could be interpreted as inconsequential, they frequently prompt additional phone calls and clinic visits and may increase the use of healthcare resources to allay concerns.

Limitations

This study reflects results for only those centers and patient populations enrolled and may not be generalizable to all patients undergoing replacement procedures. By design, we did not identify complications beyond 6 months. Infrequent events may not have been captured or, if observed, may have had low precision associated with their estimation. This observational study was not designed to evaluate the relationship of individual patient risk factors and subsequent complications.

Conclusions and Implications

This is the first prospective multicenter report of comprehensive 6-month complication rates associated with pacemaker and ICD generator replacements. Our findings highlight the overall risk and variety of complications that can occur with these procedures and provide systematically captured data

that better approximate the true procedural risks. Recommendations for lifelong device therapy should include consideration of the risks associated with generator replacements and lead additions, especially in situations in which the benefit may be less certain. These data emphasize the need for future efforts directed at extending battery longevity and minimizing lead-related complications.

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Disclosures

Dr Poole reports receiving research grant support from BIOTRONIK and the National Heart, Lung, and Blood Institute; speaking honoraria from Medtronic and Boston Scientific; travel reimbursement from BIOTRONIK, Medtronic, and Boston Scientific; and honoraria from Cardiac Science. Dr Poole has been an expert witness. Dr Poole also reports fellowship training grants to her institution from Medtronic, Boston Scientific, and St. Jude Medical. Dr Gleva has received research support from BIOTRONIK, honoraria from Medtronic and BIOTRONIK, and travel reimbursement from BIOTRONIK; Dr Gleva's spouse has ownership stock in Medtronic. Dr Mela reports speaking honoraria, advisory board, and travel reimbursement from BIOTRONIK. Dr Chung reports research grants from Medtronic, Boston Scientific, St. Jude Medical, and BIOTRONIK, as well as travel reimbursement from BIOTRONIK, St. Jude Medical, Medtronic, and Boston Scientific. Dr Uslan has received research grants from the American Heart Association, honoraria from BIOTRONIK, consulting fees from Tyrx, travel reimbursement from BIOTRONIK, and fees for participation in study review activities from BIOTRONIK. Dr Borge reports speakers' bureau honoraria from BIOTRONIK, Boston Scientific, St. Jude Medical, and Sanofi-Aventis, as well as a consultancy with Medtronic and travel reimbursement from BIOTRONIK. Dr Gottipaty has received honoraria from BIOTRONIK, St. Jude Medical, Boston Scientific, Medtronic, and Sanofi-Aventis and travel reimbursement from BIOTRONIK. Dr Shinn has received research grants from Boston Scientific, Medtonic, Sonofi-Aventis, and BIOTRONIK; travel reimbursement from BIOTRONIK; speaker's fees from BIOTRONIK; and honoraria from Medtronic. Dr Shinn has a consultancy with Medtronic and BIOTRONIK and has been an expert witness; his brother-in-law is a Medtronic employee. Dr Dan has received speaker fees from Boston Scientific, Medtronic, and Sorin; honoraria from Boston Scientific, Medtronic, St. Jude Medical, Sorin, and Sanofi-Aventis; and travel reimbursement from BIOTRONIK. Dr Dan also has a consultancy with BIOTRONIK, Boston Scientific, and Sorin. Dr Feldman reports that his institution has received research support from Medtronic, Boston Scientific, St. Jude Medical, and BIOTRONIK. Dr Feldman receives speakers' bureau fees from Medtronic and Boston Scientific and receives travel reimbursement from and has a consultancy with Boston Scientific and BIOTRONIK. Dr Winston reports research grants from Medtronic, Boston Scientific, St. Jude Medical, and BIOTRONIK to his institution and receives honoraria from St. Jude Medical, Boston Scientific, and BIOTRONIK. Dr Langberg reports that his institution receives research support from BIOTRONIK. K. Mitchell is a paid employee of BIOTRONIK and receives a fixed salary with no bonus payments tied to research results. Dr Holcomb has received consulting fees from BIOTRONIK to perform the statistical analysis for the study. In addition to the individual disclosures noted above, the institutions of several authors (Drs Poole, Gleva, Mela, Chung, Borge, Gottipaty, Shinn, Winston, Dan, Feldman, Seide, Gallagher, and Langberg) participated as an enrolling site in REPLACE and received research support from BIOTRONIK for the conduct of the trial. Drs Seide and Gallagher report no conflicts.

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CLINICAL PERSPECTIVE

Cardiac implantable electronic device use is increasing worldwide. Improvements in medical therapy will result in many patients requiring subsequent procedures for generator replacement or "upgrades" to multilead systems. Although data from retrospective series have been available, REPLACE is the first prospective multicenter trial to examine complications related to generator replacement. The 2 patient populations studied included patients who needed only a generator replacement and those who required a lead addition or revision for advanced therapy. This study examined a broad range of major and minor complications. Major complications with planned generator replacements alone were modest; however, when a transvenous lead addition or revision was combined with a generator replacement, the risk was markedly higher, especially for left ventricular leads. Our results support the use and development of devices with long battery life to minimize the lifetime surgical risk for a patient. The choice of device for each patient must be carefully considered. Mitigation of lead-related risks is also important. Using the fewest leads necessary for the clinical need of the patient is critical. The risk associated with upgrade procedures is concerning and favors performing indicated complex procedures before the development of advanced end-stage medical and cardiac disease, situations in which the risk may be prohibitive. Finally, our results provide insight into procedural outcomes for the next phase of life for patients who receive cardiac implantable electronic devices and a more robust analysis that can be used to establish a benchmark for comparative performance in this time of healthcare reform.

SUPPLEMENTAL MATERIAL

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