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Clinically Significant Pocket Hematoma Increases Long-Term Risk of Device Infection

BRUISE CONTROL INFECTION Study

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ABSTRACT

BACKGROUND The BRUISE CONTROL trial (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial) demonstrated that a strategy of continued warfarin during cardiac implantable electronic device surgery was safe and reduced the incidence of clinically significant pocket hematoma (CSH). CSH was defined as a post-procedure hematoma requiring further surgery and/or resulting in prolongation of hospitalization of at least 24 h, and/or requiring interruption of anticoagulation. Previous studies have inconsistently associated hematoma with the subsequent development of device infection; reasons include the retrospective nature of many studies, lack of endpoint adjudication, and differing subjective definitions of hematoma.

OBJECTIVES The BRUISE CONTROL INFECTION (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial Extended Follow-Up for Infection) prospectively examined the association between CSH and subsequent device infection.

METHODS The study included 659 patients with a primary outcome of device-related infection requiring hospitalization, defined as 1 or more of the following: pocket infection; endocarditis; and bloodstream infection. Outcomes were verified by a blinded adjudication committee. Multivariable analysis was performed to identify predictors of infection.

RESULTS The overall 1-year device-related infection rate was 2.4% (16 of 659). Infection occurred in 11% of patients (7 of 66) with previous CSH and in 1.5% (9 of 593) without CSH. CSH was the only independent predictor and was associated with a >7-fold increased risk of infection (hazard ratio: 7.7; 95% confidence interval: 2.9 to 20.5; $p < 0.0001$). Empiric antibiotics upon development of hematoma did not reduce long-term infection risk.

CONCLUSIONS CSH is associated with a significantly increased risk of infection requiring hospitalization within 1 year following cardiac implantable electronic device surgery. Strategies aimed at reducing hematomas may decrease the long-term risk of infection. (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial [BRUISE CONTROL]; NCT00800137) (J Am Coll Cardiol 2016;67:1300–8) © 2016 by the American College of Cardiology Foundation.

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Device pocket hematomas are a common complication of cardiac implantable electronic device (CIED) surgery, particularly in patients receiving perioperative anticoagulation. The risk of device pocket hematoma with heparin bridging has been reported to range from 17% to 31% (1–3). The BRUISE CONTROL (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial) demonstrated that a strategy of continued warfarin at the time of device surgery is safe and reduced the incidence of clinically significant pocket hematoma (CSH) from 16% to 3.5% (4–7).

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Reported rates of device system infections have varied between 0.68% and 2.2% of implants (8–13). Device infections occur within days to years following surgery; require complete system removal for cure; and are associated with significant morbidity, mortality, and cost to the health care system (14). There is therefore much effort to reduce infection.

Previous studies have inconsistently correlated hematoma with the subsequent development of device infection. These inconsistent results may in part relate to the largely retrospective nature of studies, lack of endpoint adjudication, and differing subjective definitions of hematoma (8,11,12,15–17). In this study, we prospectively examined the association between objectively defined CSH and subsequent device infection.

METHODS

STUDY DESIGN. The BRUISE CONTROL trial was a multicenter single-blind randomized controlled trial designed to determine whether a strategy of continued warfarin (compared with bridging with heparin) at the time of pacemaker or defibrillator surgery reduced the incidence of CSH in patients with moderate to high risk of thromboembolic events (4,18). CSH was objectively defined as a post-procedure hematoma requiring further surgery and/or resulting in prolongation of hospitalization for least 24 h, and/or requiring interruption of anticoagulation. All potential CSH were adjudicated by a blinded team of evaluators.

The current BRUISE CONTROL INFECTION (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial Extended Follow-Up for Infection) extends the follow-up to 1 year with a primary outcome of infection requiring hospitalization.

The trial was supported by a peer-reviewed grant from the Canadian Institutes of Health Research. The protocol was approved by the research ethics board at each of the participating centers. The University of Ottawa Heart Institute Cardiovascular Research Methods Center coordinated the study, collected the data, maintained the database, and performed all data analyses. The steering committee decided to publish the data. All coauthors critically reviewed the manuscript and approved the final version.

PATIENTS. Patients were enrolled at 17 centers in Canada and 1 in Brazil. Procedures and results of the BRUISE CONTROL trial have been previously published (4). The study included patients with a >5% annual predicted risk of thromboembolism taking warfarin, and undergoing nonemergency CIED surgery. All patients provided written informed consent. Subjects that completed BRUISE CONTROL follow-up were included in the BRUISE CONTROL INFECTION study.

STUDY PROCEDURES. Patients enrolled in BRUISE CONTROL were randomized in a 1:1 ratio to continued warfarin or heparin bridging as previously described (4). A blinded team was responsible for diagnosing, following, and making all decisions about management of CSH. Patients developing CSH were followed until resolution of their hematoma for the primary analysis of BRUISE CONTROL (4).

In BRUISE CONTROL INFECTION, data collection included vital status, empiric use of antibiotics for CSH, other procedures on the device pocket, hospitalization information for device infection, evidence for the infection, culture and microorganism details, management of the infection, and complications from the infection or its management. All patients were followed up at 1 year by chart review and/or telephone contact.

OUTCOME MEASURES. The primary outcome of the present BRUISE CONTROL INFECTION study was device-related infection requiring hospitalization occurring within 12 months after CIED surgery. Infection was defined as follows: 1) pocket infection; 2) endocarditis (either valve or lead); or 3) bloodstream infection (19,20). Pocket infections were defined according to the 2008 National Healthcare Safety Network and U.S. Center for Disease Control definitions for surgical site infections (21). Endocarditis was defined according to the Modified Dukes' criteria (22), adapted as suggested to help diagnose endocarditis in patients with implantable cardiac devices (23). Secondary outcomes included repeat procedures on the pocket, whether the repeat procedure was due to hematoma, complications of infection or procedures required to manage infection, and death.

A blinded adjudication committee evaluated all potential primary endpoints (CIED-related infections requiring hospitalization). The committee consisted of an adjudication coordinator, 2 experts in cardiac

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CIED = cardiac implantable electronic device

CSH = clinically significant pocket hematoma

HR = hazard ratio

IQR = interquartile range

electrophysiology, with consultation of an expert in infectious disease as required. Each outcome was classified as to whether it met the protocol study definition for CIED-related infection. This adjudicated result was then used in the final analyses.

STATISTICAL ANALYSIS. Descriptive statistics were reported for baseline patient characteristics and details related to CIED surgery. Continuous variables were presented as mean ± SD for normally distributed variables and medians and interquartile ranges (IQR) for non-normally distributed variables. Categorical variables were presented as frequencies with percentages. To compare the patients with and without hospitalization for device infection, Student *t* test or Wilcoxon rank sum test were used to compare continuous variables, and Fisher exact test was used for categorical variables. Because death competes with hospitalization for device infection, a competing risks analysis was performed for hospitalization for device infection with death as the competing risk. Only variables with $p < 0.05$ in the univariable analysis were included in the subsequent multivariable model. For multivariable analysis, the subdistribution hazard model proposed by Fine and Gray (24) was used to assess the predictors of hospitalization for device infection. Only variables remaining significant ($p < 0.05$) were included in the final prediction model. Hazard ratio (HR) and associated 95% confidence interval (CI) were reported. The validity of the proportional hazard assumption was tested by evaluating Schoenfeld residuals and the interaction between predictors and time. The proportional hazard assumption was met and model overfitting was considered. Cumulative incidence function was used in estimating the probability of hospitalization for infection and in creating the cumulative incidence curves to compare patients with and without CSH. Analysis was performed using SAS (version 9.3, SAS Institute Inc., Cary, North Carolina), and statistical significance was defined as $p < 0.05$.

RESULTS

All 659 patients that completed the BRUISE CONTROL study follow-up were included in the BRUISE CONTROL INFECTION study. Long-term follow-up (until infection, death, or 1-year follow-up encounter) was available for 651 patients. Details of trial enrollment and follow-up are shown in Figure 1.

DEVICE-RELATED INFECTION RATE. The overall rate of device-related infection requiring hospitalization at 1 year was 2.4% (16 of 659) (Table 1).

INFECTION MANAGEMENT AND OUTCOMES. Sixteen patients developed a device-related infection. Of these 16 patients, 7 (44%) had a previous CSH and 9 (56%) patients did not. Infections were classified as limited to the pocket in 8 patients; associated with bloodstream infection in 2 patients and endocarditis in 3 patients; or both bloodstream infection and endocarditis in 3 patients (Table 2). Hospitalization for infection occurred at a median of 56 days (IQR: 26 to 192) following initial surgery. The time to infection hospitalization in the 7 patients with previous CSH was not significantly shorter than in patients without previous CSH (median: 30 days [IQR: 21 to 53] vs. 114 days [IQR: 58 to 207]; $p = 0.13$).

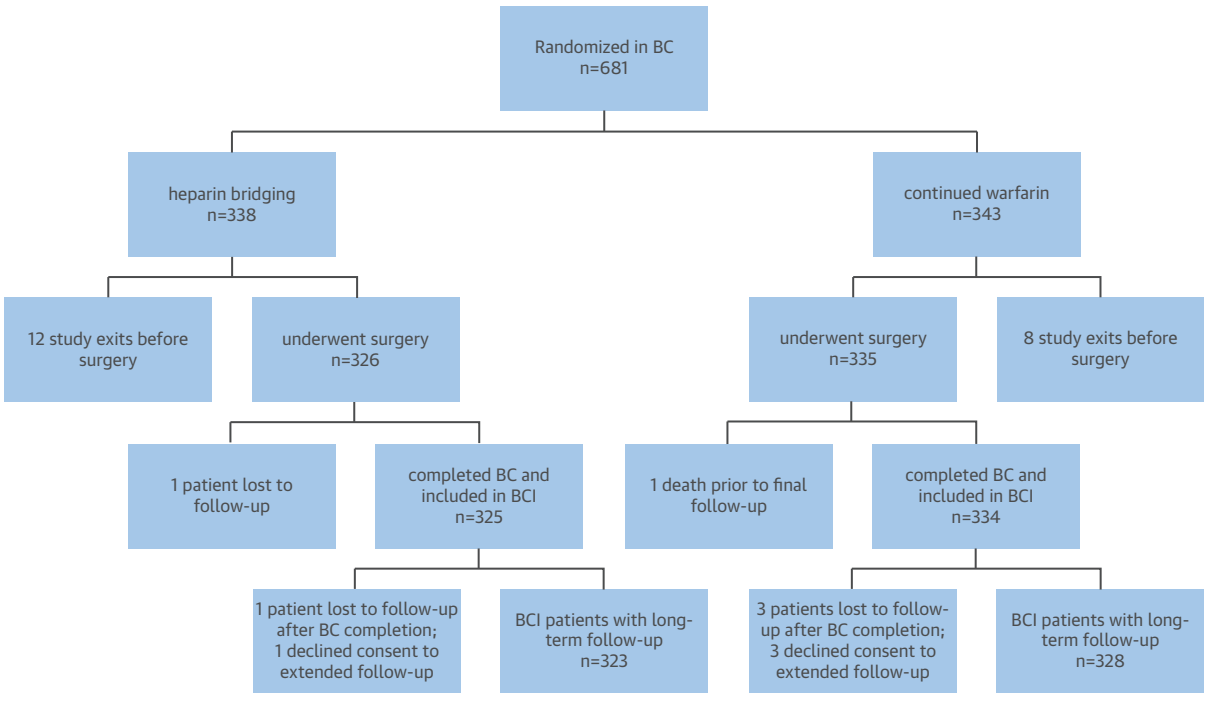
The median hospitalization was 20 days (IQR: 16 to 41) including 3 days (IQR: 0 to 8) in intensive care. All patients received antibiotic therapy including intravenous antibiotics for a total duration of 30.8 ± 14.1 days.

An organism was isolated in 69% of cases (11 of 16). Of these, 10 were a *Staphylococcus* species and 1 was *Moraxella*. All 16 patients were treated surgically, with generator removal in 2 patients (13%), generator plus mechanical lead extraction in 11 patients (69%), and generator plus laser lead extraction in 3 patients (19%). Other major complications included septic shock in 2 patients, acute antibiotic-induced hepatitis in 1 patient, and renal failure requiring dialysis in 1 patient (Table 2).

There was an additional patient diagnosed with infective endocarditis of a mechanical aortic valve that was adjudicated to be unrelated to the CIED procedure and not included as an outcome in the final analysis. Although a vegetation was documented by transesophageal echocardiogram on the prosthetic aortic valve, there was no evidence of right-sided CIED lead involvement or pocket infection. The patient was successfully treated with 6 weeks of intravenous antibiotics (without device removal), with resolution of infection and disappearance of the valvular vegetation on repeat transesophageal echocardiogram.

PATIENT CHARACTERISTICS ASSOCIATED WITH DEVELOPMENT OF INFECTION. The baseline characteristics comparing patients with hospitalization for infection to patients without infection are presented in Table 1. Infection rates were not significantly different in the heparin-bridging arm versus the warfarin arm (3.1% vs. 1.8%, $p = 0.32$). There was no difference in baseline demographics, sex, medication use, or medical history other than a higher rate of mechanical valve replacement in the infection group ($p = 0.03$). The median CHADS2 (congestive heart failure history, hypertension history, age ≥75 years, diabetes mellitus history, stroke or transient ischemic attack symptoms previously) score in patients with nonrheumatic atrial fibrillation was 3 (IQR: 3 to 4) and did not differ according to infection.

FIGURE 1 Trial Enrollment and Follow-Up



A total of 681 patients were enrolled in the BRUISE CONTROL (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial) trial. The 659 patients that completed BC follow-up were included in the BRUISE CONTROL INFECTION (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial Extended Follow-Up for Infection) study. Of these, 651 patients completed long-term follow-up (until infection, death, or 1-year follow-up encounter). BC = BRUISE CONTROL; BCI = BRUISE CONTROL INFECTION.

PROCEDURAL DETAILS ASSOCIATED WITH DEVELOPMENT OF INFECTION. There were no differences in initial BRUISE CONTROL procedural details between patients who later did or did not develop an infection, including device type, de novo versus non-de novo implant, procedure duration, operating physician, vascular access, and hemostatic techniques (Table 3).

RISK OF INFECTION FOLLOWING CSH. Sixty-six of the 659 patients (10%) developed a CSH following initial CIED surgery. The presence of CSH significantly correlated with a greater risk of subsequent infection. The infection rate was 11% (7 of 66) in the group of patients with previous CSH compared with an infection rate of only 1.5% (9 of 593) in the group of patients without previous CSH ($p < 0.0001$). The cumulative incidence of infection according to presence or absence of CSH is demonstrated in the Central Illustration.

EFFECT OF EMPIRIC ANTIBIOTICS ON RISK OF INFECTION. Data regarding empiric antibiotic therapy at time of CSH diagnosis was available for 55 patients. Sixteen patients with CSH received empiric antibiotics upon development of CSH; however, there was no association between empiric antibiotic use and subsequent device infection ($p = 0.18$). There was also no association between empiric antibiotic use and time to subsequent infection ($p = 0.50$).

RISK OF INFECTION FOLLOWING REPEAT POCKET PROCEDURE. There were a total of 24 patients with repeat procedures on the pocket after the index surgery. Of these, 14 cases were for device or lead reasons such as device upgrade ($n = 3$), device extraction prior to radiation therapy ($n = 1$), lead revision ($n = 9$), or cosmetic pocket revision ($n = 1$). There were no documented cases of subsequent device-related infection in this group. The other 10 cases of repeat pocket procedure were for surgical management of CSH (requiring hematoma evacuation or wound revision due to hematoma). Among the 66 patients with CSH, the infection rate in the group that underwent surgical management of CSH was 20% (2 of 10) as compared to an infection rate of 8.9% (5 of 56) in the group of patients whose CSH was not managed surgically ($p = 0.29$).

PREDICTORS OF INFECTION. In multivariable analysis, the presence of a CSH was the only variable

TABLE 1 Baseline Characteristics by Presence or Absence of Hospitalization for Device Infection

	Hospitalization for Device Infection (n = 16)	No Hospitalization for Device Infection (n = 643)	p Value
Demographics			
Age, yrs	70.8 ± 9.4	71.7 ± 10.4	0.74
Male	13 (81)	466 (72)	0.58
BMI, kg/m^2	27.6 ± 5.0	28.3 ± 5.9	0.64
Medical history			
Mechanical heart valve replacement	9 (56)	189 (29)	0.03
Previous myocardial infarction	9 (56)	250 (39)	0.20
Previous coronary revascularization	8 (50)	249 (39)	0.44
Atrial fibrillation and/or atrial flutter	13 (81)	569 (88)	0.42
Previous embolic TIA	5 (31)	117 (18)	0.19
Previous embolic stroke	0	116 (18)	0.09
Previous peripheral embolus	0	21 (3.3)	1.00
Hypertension	12 (75)	456 (71)	1.00
Diabetes mellitus	3 (19)	252 (39)	0.12
Nonischemic cardiomyopathy	4 (25)	149 (23)	0.77
Ischemic cardiomyopathy	10 (63)	255 (40)	0.07
Deep vein thrombosis	2 (13)	22 (3.4)	0.11
Pulmonary embolus	0	13 (2.0)	1.00
Rheumatic valvular heart disease	3 (19)	54 (8.4)	0.15
Medications			
Statin	11 (69)	465 (72)	0.78
ACEI	8 (50)	371 (58)	0.61
ARB	3 (19)	147 (23)	1.00
Amiodarone	4 (25)	92 (14)	0.27
Beta-blocker	12 (75)	489 (76)	1.00
ASA	8 (50)	250 (39)	0.44
Clopidogrel	2 (13)	38 (5.9)	0.25
ASA and Clopidogrel	8 (50)	267 (42)	0.61
Loop diuretic	8 (50)	434 (68)	0.18

Values are mean ± SD or n (%). Clopidogrel is marketed by Bristol-Myers Squibb (New York, New York) and Sanofi (Gentilly, France).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ASA = aspirin; BMI = body mass index; TIA = transient ischemic attack.

significantly associated with an increased risk of future development of infection (HR: 7.7; 95% CI: 2.9 to 20.5; p < 0.0001).

DEATHS. There was 1 death following infection. The patient was a 93-year-old man with a history of mechanical aortic and mitral valves, coronary bypass surgery, heart failure, and atrial fibrillation. After undergoing a generator change, he required a repeat procedure for CSH (hematoma evacuation). Fourteen days later, he developed a pocket and bloodstream infection. Therapy included removal of pacemaker generator only plus intravenous antibiotics until the patient was discharged. Three months later, he died of worsening heart failure and pneumonia. It was determined that the previous device infection was not causally related to the patient's death.

DISCUSSION

The purpose of this study was to prospectively evaluate the association between objectively defined device pocket hematoma, a short-term postoperative complication of CIED surgery, with long-term risk of subsequent device infection. BRUISE CONTROL showed that a strategy of uninterrupted warfarin reduces the rate of CSH in the 2 weeks following surgery (3.5% vs. 16% for heparin bridging) (4), while significantly decreasing periprocedural costs (25). The trial also found that CSH was associated with worsening of some quality of life and pain scores evaluated perioperatively, as reported in the supplemental appendix of Birnie et al. (4). Now, with the results of BRUISE CONTROL INFECTION, the clinical importance of trying to avoid CSH is even clearer. We show for the first time in a prospective study, with adjudicated objective endpoints, that there is a clear and significant association between significant pocket hematomas and subsequent infection. Patients with CSH had a >7-fold increased risk of subsequent serious device infection compared with patients without CSH (**Central Illustration**).

Previous studies have inconsistently correlated pocket hematoma with CIED infection. De Oliveira et al. (15) followed 649 patients after device implantation, randomizing patients to perioperative antibiotics or placebo. Thirteen patients (2%) developed an infection. Multivariable analysis identified nonuse of antibiotic (p = 0.037) and postoperative hematoma (p = 0.023) as independent predictors of infection. Hematoma was defined as swelling of the pocket site. In a second study, the REPLACE (Implantable Cardiac Pulse Generator Replacement Registry), infection developed in 22 patients (1.3%) (11,12). Patients with infections were more likely to have had postoperative hematomas (5 of 22 [22.7%] vs. 17 of 1,722 [0.98%], p = 0.002). However, this was only a univariate analysis; multivariate analysis was not reported. In a third study, Raad et al. (16) found an association between infection and hematoma using retrospective case control methodology, but hematoma was only defined as swelling beyond the generator and again only univariate analysis was presented. In contrast, a fourth study by Klug et al. (8) determined that hematoma (not defined) was not a predictor of infection in a large prospective trial with 6,319 patients following device implantation, whereas early reintervention for hematoma or lead dislodgement was strongly correlated with infection risk (adjusted odds

TABLE 2 Infection Details

Randomized Group (Warfarin vs. Bridging)	Presence of CSH (Y/N)	Repeat Procedure on Pocket	Time to Infection (Days Post Device Surgery)	Infection Classification	Microorganism Identified	Microorganism Source	Surgical Treatment of Infection	Other Complications of infection	Length of Admission
Bridge	Y	Hematoma evacuation	19	Pocket and endocarditis	Moraxella	ICD lead culture	Generator and lead extraction (mechanical)	None	39
Bridge	Y	Hematoma evacuation	21	Pocket	Coagulase negative *Staphylococcus*	Wound	Generator explanted	None	16
Bridge	Y		53	Pocket	Coagulase negative *Staphylococcus*	Tissue	Generator and lead extraction (mechanical)	None	9
Bridge	Y		35	Pocket and bloodstream	*Staphylococcus* aureus	Blood	Generator and lead extraction (laser)	Site bleeding and hematoma post extraction	22
Bridge	Y		21	Pocket	*Staphylococcus* other	Wound	Generator and lead extraction (mechanical)	None	3
Bridge	N		99	Pocket and bloodstream	*Staphylococcus* aureus	Blood and device swab	Generator and lead extraction (mechanical)	Acute renal failure requiring dialysis, upper gastrointestinal bleed, deep venous thrombosis	66
Bridge	N		217	Pocket	None	N/A	Generator and lead extraction (mechanical)	None	18
Bridge	N		49	Endocarditis and bloodstream	Coagulase negative *Staphylococcus*	Blood	Generator and lead extraction (laser)	Mechanical mitral valve endocarditis-treated intravenous antibiotics	16
Bridge	N		114	Pocket, endocarditis and bloodstream	*Staphylococcus* aureus	Wound, blood, and lead	Generator and lead extraction (mechanical)	Septic shock, hepatitis, intracranial hemorrhage	42
Bridge	N		58	Pocket and endocarditis	Coagulase negative *Staphylococcus*	Wound and lead	Generator and lead extraction (mechanical)	None	52
Warfarin	Y		335	Pocket	None	N/A	Generator and lead extraction (mechanical)	Site bleeding and hematoma post extraction	22
Warfarin	Y		30	Pocket	*Staphylococcus* aureus	Wound	Generator and lead extraction (mechanical)	None	13
Warfarin	N		287	Pocket	None	N/A	Generator and lead extraction (laser)	None	16
Warfarin	N		177	Pocket	None	N/A	Generator explanted	None	16
Warfarin	N		13	Endocarditis	None	N/A	Generator and lead extraction (mechanical)	Required redo aortic valve replacement as well as mitral valve repair and repair of ascending aorta	43
Warfarin	N		207	Endocarditis and bloodstream	*Staphylococcus* aureus	Blood	Generator and lead extraction (mechanical)	Septic shock	40

ICD = implantable cardioverter-defibrillator; N/A = not available.

TABLE 3 Procedure Details by Presence or Absence of Hospitalization for Device Infection

	Hospitalization for Device Infection (n = 16)	No Hospitalization for Device Infection (n = 643)	p Value
Procedure duration, min	58 (33–78)	51 (30–85)	0.81
Physician who performed the procedure			0.66
Electrophysiology staff physician	15 (94)	601 (93)	
Staff surgeon	1 (6.3)	31 (4.8)	
Cardiologist	0	11 (1.7)	
Fellow participated in the procedure	10 (63)	308 (48)	0.31
Access used for new leads			
Cephalic	1 (6.3)	111 (17)	0.50
Subclavian	5 (31)	176 (27)	0.78
Axillary	4 (25)	154 (24)	1.00
Intrapocket prohemostatic agent given	0	16 (2.5)	1.00
Pressure dressing applied postoperatively	8 (50)	367 (57)	0.62
Sandbag applied postoperatively	3 (19)	44 (6.8)	0.10
De novo implant	8 (50)	299 (47)	0.81
Preoperative international normalized ratio	1.4 (1.1–2.1)	1.7 (1.2–2.3)	0.52

Values are median (interquartile range) or n (%).

ratio: 15.0; $p < 0.001$) in multivariable analysis. These 4 studies highlight the broad differences found in the literature regarding methodology, endpoints, and subjective definitions of hematoma used, limiting the comparisons across studies and conclusions that can be drawn. The strength of our study is that it is an extension of a randomized prospective trial that included an objective definition of pocket hematoma, based on outcomes that were considered clinically significant (i.e., CSH defined as hematoma that required reoperation, prolongation of hospitalization, or interruption of anticoagulation). Also, all potential CSH and device infections were independently adjudicated by blinded investigators.

The observation that CSH was a powerful independent predictor of serious long-term CIED infection in our study further validates that our definition of CSH is indeed highly clinically relevant. This supports a recent opinion article that suggested a 3-level grading system of pocket hematomas, with a grade 3 hematoma characterized according to our definition of CSH (26).

A number of possible mechanisms by which hematomas predispose to CIED infection have been suggested. These include tension from a hematoma leading to a breach in the wound allowing for postoperative contamination. Pressure from the hematoma may lead to low-grade tissue necrosis. Finally, it has been shown that up to 48% of intraoperative pocket cultures will grow bacteria, most commonly *Staph* species found in skin flora (27). An accompanying hematoma then provides a fertile environment for sustained microorganism colonization.

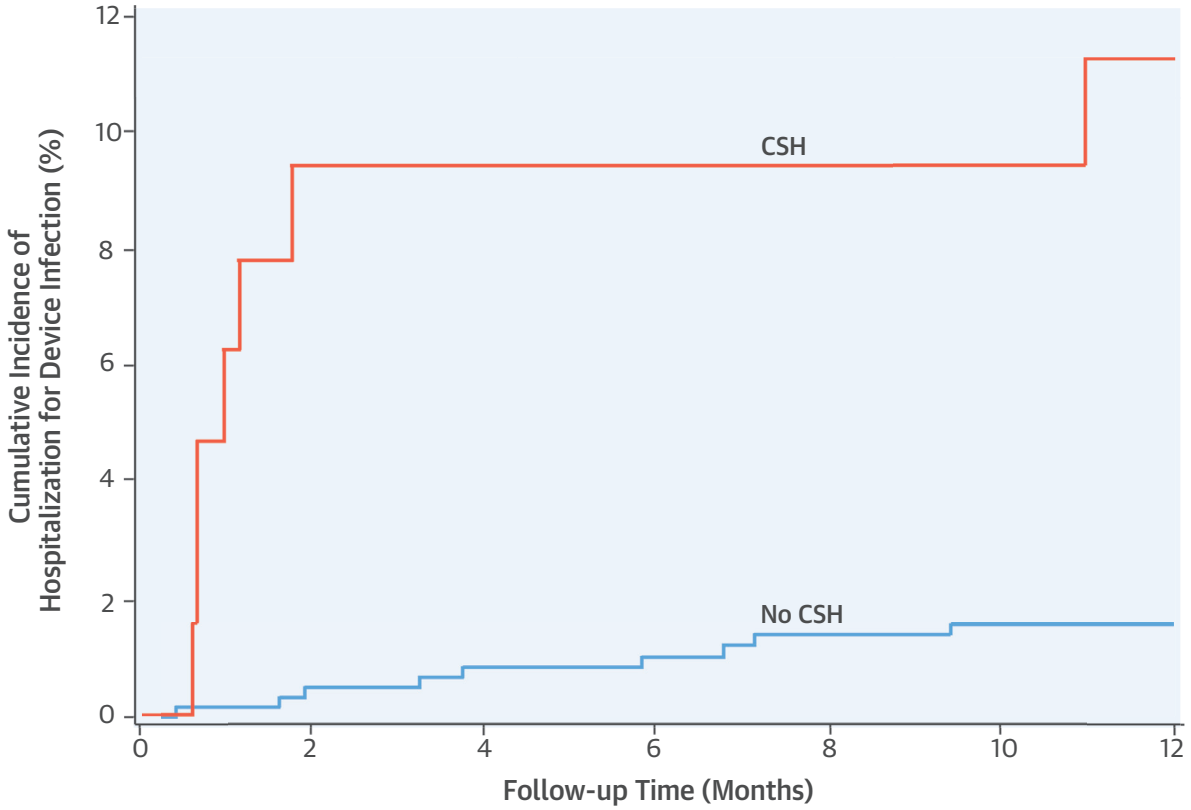
The presence of a CSH increased the risk of infection by more than 7-fold at 1 year in our multivariable analysis. No other risk factor was a significant independent predictor of infection.

Our study also found no increased risk of subsequent infection following elective non-de novo implants in the absence of CSH. This is consistent with data from 2 registries, REPLACE (6-month follow-up) and PEOPLE (Prospective Evaluation of Pacemaker Lead Endocarditis) (1-year follow-up), which found relatively low infection rates of 1.3% and 0.99%, respectively, following elective non-de novo implants (8,11).

Importantly, the use of empiric antibiotics at the time of CSH diagnosis did not reduce the risk of infection later on. A possible explanation is poor antibiotic penetration into the extravascular space of the pocket. In our study, device infection led to surgical intervention in all cases, as well as disseminated infection or end-organ damage in a few cases. Although there were no deaths attributable to CIED infection in our study, device infection has been reported to be associated with a mortality rate of 0% to 18% in other studies (14,15,28,29). Our study did not include a cost analysis related to infection but a previous report by Sohail et al. (14) estimated the adjusted total cost of treating a device infection to range from $28,676 to $53,349 depending on such variables as type of device infected, hospital length of stay, and, most importantly, intensive care length of stay, which contributed nearly one-half the additional cost. The device type itself contributed a minor portion. In that study, the mean admission length of stay ranged from 15.5 days for pacemaker infections to 24.3 days for biventricular pacemaker infections, similar to our reported median length of stay of 20 days. As such, just as preventing CIED infections is crucial, early recognition of device infections and prompt initiation of therapy, including minimizing time to device removal, may help to reduce intensive care admission duration and the overall costs involved.

STUDY LIMITATIONS. In our study, infections were included if they involved the CIED system. However, although the original source of infection is generally attributed to the pocket, it is difficult to exclude the possibility of late CIED infection occurring as a result of secondary seeding from a distant entry site. An adjudication committee was employed to address this issue and individually evaluate all cases of CIED infection. In addition, we defined the primary outcome as CIED infection requiring hospitalization in order to have an objective clinically meaningful endpoint.

CENTRAL ILLUSTRATION **Pocket Hematoma Predicts Long-Term Infection: Cumulative Incidence Curves by Presence or Absence of Clinically Significant Hematoma**



CSH	66	54	54	53	51	49	39
No CSH	593	571	556	547	532	502	374

Essebag, V. et al. J Am Coll Cardiol. 2016; 67(11):1300–8.

Cumulative incidence of hospitalization for device infection by presence or absence of clinically significant hematoma (CSH).

Decisions regarding surgical intervention to evacuate CSH were not randomized. As such, it is not possible to conclude whether surgical CSH evacuation increases risk of infection associated with CSH. Also, that there were no infections in the group of patients who underwent repeat procedure unrelated to CSH may reflect an inadequate sample size or follow-up time to detect infections in this group.

CONCLUSIONS

We show for the first time in a prospective study with adjudicated objective endpoints that there is a clear and strong association between significant pocket hematomas and subsequent infection. Patients with CSH had more than a 7-fold subsequent risk of serious device infection. Strategies aimed at reducing hematomas may decrease the long-term risk of infection.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients undergoing implantation of electronic cardiac devices, strategies to reduce pocket hematomas, such as continuing oral anticoagulation rather than bridging with heparin, may reduce the long-term risk of infection.

TRANSLATIONAL OUTLOOK: Further investigation is needed to define optimum strategies for prevention of thromboembolism and bleeding when patients who are anticoagulated with target-specific oral agents undergo implantation of electronic cardiac devices.

REFERENCES

1. Marquie C, De Geeter G, Klug D, et al. Post-operative use of heparin increases morbidity of pacemaker implantation. Europace 2006;8:283–7.

2. Feng L, Li Y, Li J, Yu B. Oral anticoagulation continuation compared with heparin bridging therapy among high risk patients undergoing implantation of cardiac rhythm devices: a meta-analysis. Thromb Haemost 2012;108:1124–31.

3. Ghanbari H, Phard WS, Al-Ameri H, et al. Meta-analysis of safety and efficacy of uninterrupted warfarin compared to heparin-based bridging therapy during implantation of cardiac rhythm devices. Am J Cardiol 2012;110:1482–8.

4. Birnie DH, Healey JS, Wells GA, et al., for the BRUISE CONTROL Investigators. Pacemaker or defibrillator surgery without interruption of anticoagulation. N Engl J Med 2013;368:2084–93.

5. Birnie DH, Healey JS, Essebag V. Device surgery without interruption of anticoagulation. N Engl J Med 2013;369:1571–2.

6. Birnie DH, Healey JS, Essebag V. Management of anticoagulation around pacemaker and defibrillator surgery. Circulation 2014;129:2062–5.

7. Sant'anna RT, Leiria TL, Nascimento T, et al. Meta-analysis of continuous oral anticoagulants versus heparin bridging in patients undergoing CIED surgery: reappraisal after the BRUISE study. Pacing Clin Electrophysiol 2015;38:417–23.

8. Klug D, Balde M, Pavin D, et al., for the 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. Lekkerkerker JC, van Nieuwkoop C, Trines SA, et al. Risk factors and time delay associated with cardiac device infections: Leiden device registry. Heart 2009;95:715–20.

10. Nery PB, Fernandes R, Nair GM, et al. Device-related infection among patients with pacemakers and implantable defibrillators: incidence, risk factors, and consequences. J Cardiovasc Electrophysiol 2010;21:786–90.

11. Uslan DZ, Gleva MJ, Warren DK, et al. Cardiovascular implantable electronic device replacement infections and prevention: results from the REPLACE registry. Pacing Clin Electrophysiol 2012;35:81–7.

12. Poole JE, Gleva MJ, Mela T, et al., for the REPLACE Registry Investigators. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures: results from the REPLACE registry. Circulation 2010;122:1553–61.

13. Polyzos KA, Konstantelias AA, Falagas ME. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. Europace 2015;17:767–77.

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

15. de Oliveira JC, Martinelli M, Nishioka SA, et al. Efficacy of antibiotic prophylaxis before the implantation of pacemakers and cardioverter-defibrillators: results of a large, prospective, randomized, double-blinded, placebo-controlled trial. Circ Arrhythm Electrophysiol 2009;2:29–34.

16. Raad D, Irani J, Akl EG, et al. Implantable electrophysiologic cardiac device infections: a risk factor analysis. Eur J Clin Microbiol Infect Dis 2012;31:3015–21.

17. Sridhar AR, Yarlagadda V, Yeruva MR, et al. Impact of haematoma after pacemaker and CRT device implantation on hospitalization costs, length of stay, and mortality: a population-based study. Europace 2015;17:1548–54.

18. Birnie D, Healey JS, Krahn A, et al. Bridge or continue Coumadin for device surgery: a randomized controlled trial rationale and design. Curr Opin Cardiol 2009;24:82–7.

19. Baddour LM, Epstein AE, Erickson CC, et al. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. Circulation 2010;121:458–77.

20. Connolly SJ, Philippon F, Longtin Y, et al. Randomized cluster crossover trials for reliable, efficient, comparative effectiveness testing: design of the Prevention of Arrhythmia Device Infection Trial (PADIT). Can J Cardiol 2013;29:652–8.

21. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008;36:309–32.

22. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633–8.

23. Klug D, Lacroix D, Savoye C, et al. Systemic infection related to endocarditis on pacemaker leads: clinical presentation and management. Circulation 1997;95:2098–107.

24. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.

25. Coyle D, Coyle K, Essebag V, et al. Cost effectiveness of continued-warfarin versus heparin-bridging therapy during pacemaker and defibrillator surgery. J Am Coll Cardiol 2015;65:957–9.

26. De Sensi F, Miracapillo G, Cresti A, Severi S, Airaksinen KE. Pocket hematoma: a call for definition. Pacing Clin Electrophysiol 2015;38:909–13.

27. Da Costa A, Lelievre H, Kirkorian G, et al. Role of the preaxillary flora in pacemaker infections: a prospective study. Circulation 1998;97:1791–5.

28. Baman TS, Gupta SK, Valle JA, Yamada E. Risk factors for mortality in patients with cardiac device-related infection. Circ Arrhythm Electrophysiol 2009;2:129–34.

29. Tarakji KG, Chan EJ, Cantillon DJ, et al. Cardiac implantable electronic device infections: presentation, management, and patient outcomes. Heart Rhythm 2010;7:1043–7.

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APPENDIX For a complete list of acknowledgments including institutions and investigators, please see the online version of this article.