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EDITORIAL COMMENT

BRUISE CONTROL INFECTION Study

Blood and Bugs*

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Transvenous pacemakers have been used for over 50 years and transvenous defibrillators for over 25 years; efforts to analyze complications affecting patients with cardiac implantable electronic devices (CIEDs) have intensified (1,2). Infection is a devastating complication experienced by patients with CIEDs—impacting morbidity, mortality, quality of life, and heath care costs (3).

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In this issue of the *Journal,* Essebag et al. (4) examine data from the BRUISE CONTROL (BRidge or continUe coumadIn for device SurgEry randomized CONTROLled trial extended follow-up for INFECTION) trial connecting 2 of the more frequent complications of CIED procedures. Study strengths include strict definitions of both clinically significant hematoma (CSH) and significant infections, and the follow-up period of 1 year. The infection rate in this study was 2.4%, greater than described in other recent series (1,5–9). All infections required hospitalization and were treated with parenteral antibiotics and complete system removal. Infection rates differed significantly according to whether patients had a CSH or not; infection rates were 11% in patients with CSH, versus 1.5% in those without. The only factor found in multivariate analysis to be associated with development of an infection was CSH (hazard ratio: 7.7; 95% confidence interval: 2.9 to 20.5; $p < 0.0001$). Nevertheless, 89% of patients with a CSH did not develop infection requiring hospitalization or device removal, and more than one-half of patients who underwent device removal for infection did not have a CSH, underscoring the fact that targeted strategies are needed to address each individual complication.

Important areas of uncertainty persist. First, no patients treated with target specific oral anticoagulants were included in this trial, because inclusion criteria mandated treatment with warfarin. Factor XA and direct thrombin inhibitors are increasingly used in CIED patients, and hematomas have been reported following device implant procedures in patients taking these agents (10). Factor XA inhibitors have been reported to have in vitro anti-inflammatory properties that theoretically could affect the development of infection (11). Whether or not hematoma or infection rates are similar in these patients compared with those taking warfarin is unknown.

Second, this study did not address additional interventions that could affect hematoma formation and/or an infection requiring hospitalization. Use of intrapocket prohemostatic agents, pressure dressings, and sandbags was reported, but not standardized. Furthermore, use was not different between those hospitalized for an infection compared with those who were not. Intriguingly, none of the 16 patients who received an intrapocket prohemostatic agent were hospitalized for a device infection.

Implanting physicians have adopted several strategies hoping to reduce hematomas and infections. One prospective, case-control, nonrandomized series evaluated whether topical thrombin reduced hematomas. The study's primary endpoint was a composite of hematoma requiring evacuation and pocket infection. The study agent, D-stat Hemostat (Vascular Solutions, Minneapolis, Minnesota), is composed of

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thrombin, collagen, and diluents, and is applied subcutaneously in the device pocket. The trial was stopped after enrolling 163 patients when interim analysis demonstrated increased incidence of infection in patients treated with D-Stat (12). Another novel tool to combat device site infection is the antibacterial envelope, a resorbable polypropylene mesh sleeve that surrounds the generator and releases minocycline and rifampin. A recent study demonstrated a reduced infection rate in patients treated with the antibacterial envelope compared with historic controls (6).

Another proposed technique to reduce infection is removal of the existing capsule at the time of generator replacement or interruption of the capsule with cutting electrocautery, hypothesizing that interrupting the fibrous capsule by capsulotomy or capsulectomy allows blood flow to an otherwise sequestered generator pocket. However, a recent single-blind randomized trial demonstrated increased risk of hematoma formation with this approach (13). Essebag et al. (4) do not indicate how they handled the generator capsule in subjects who underwent replacement or revision.

Many physicians use intravenous, oral, or both forms of antibiotics after the implantation procedure to reduce infection; however, this practice has not been prospectively studied. Interestingly, results from the REPLACE registry (Implantable Cardiac Pulse Generator Replacement Registry) demonstrated that patients who developed an infection were actually *more* likely to have had antibiotics continued after their procedure (8).

Retrospective and limited prospective series have investigated clinical and procedural factors associated with CIED infections. Patient factors identified include use of immune modulating therapy, chronic kidney disease, chronic lung disease, elevated blood glucose level on the day of the procedure, number of prior device procedures, use of a temporary pacing wire, presence of a pre-operative fever, and heart failure exacerbations requiring inpatient hospitalization within the past year (3–9). Whether any of these factors may have influenced the infection rates in the current analysis was not investigated. The use of pre-incision antistaphylococcal intravenous antibiotics is a Class I indication for prevention of CIED infection (14). The type of antiseptic skin preparation has been demonstrated to reduce surgical site infection in some series. Presumably, all patients in this study received pre-incisional antibiotics, although it was not specifically reported.

Two clinical trials in progress may be enlightening. One is the PADIT (Prevention of Arrhythmia Device Infection Trial; NCT01613092), a randomized, prospective, international cluster crossover trial investigating the effect of incremental antibiotics versus single-dose cefazolin in patients who are scheduled for higher-risk arrhythmia device surgery. Trial completion is expected in 2017 (15). The role of the antimicrobial envelope in reducing major CIED infections at 1 year in patients with CIEDs for cardiac resynchronization therapy is being evaluated in the WRAP IT (World-Wide Randomized Antibiotic Envelope Infection Prevention Trial), an on-going prospective randomized multicenter multinational trial (NCT02277990).

Results of this subanalysis from the BRUISE CONTROL trial support a strong relationship between clinically significant hematomas and subsequent infection, illustrating how one complication may impact occurrence of a subsequent complication. Quality improvement measures to reduce such complications in the contemporary era where procedures are being performed without interruption of anticoagulation begin with the clinical fundamentals of avoiding dissection into muscle fibers followed by careful inspection and irrigation to identify bleeding vessels prior to closure of the incision. Future clinical trials are required; hematoma and possibly infectious risk outcomes after procedures performed on target-specific oral anticoagulants will be evaluated in the BRUISE CONTROL 2 trial (NCT01675076).

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