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EDITORIAL COMMENT

Continuation Versus Interruption of Direct Oral Anticoagulants for CIED Procedures

New Anticoagulants, Old Dilemma*

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With interest we have read the case report by Hayashi et al. (1) in this issue of *JACC: Case Reports*. This report illustrates an example of significant pocket hematoma secondary to generator change under uninterrupted direct oral anticoagulation and highlights the difficult balance of providing continuous periprocedural stroke protection in patients with atrial fibrillation (AF) while avoiding bleeding events.

SCOPE OF THE PROBLEM

Periprocedural management of oral anticoagulant agents represents a common dilemma in daily surgical practice and requires balancing of thromboembolic risk against bleeding risk. Up to nearly 40% of patients currently referred for cardiac implantable electrophysiological device (CIED) insertion are treated with oral anticoagulant agents; in addition, approximately 57% are receiving antiplatelet agents (2). Management of these patients poses a particular challenge because of their frequently overlapping elevated risks for bleeding *and* ischemic events. AF is the most common reason for long-term anticoagulation, and investigators have demonstrated that even short temporary interruptions of anticoagulant treatment expose the patient to a 3-fold increase in stroke risk (3,4). Similarly, even though standard CIED insertions are traditionally classified as low-bleeding risk interventions, the occurrence of a bleeding event is not benign and may lead to life-threatening complications. These complications include pericardial tamponade, hemothorax, and significant pocket hematoma, which is associated with a 7-fold increased risk of subsequent serious device infection (5) and even up to a 15-fold increased risk if reintervention for hematoma evacuation is required (6).

PARADIGM SHIFTS IN ANTICOAGULATION MANAGEMENT AND HEPARIN BRIDGING

Initial investigations into periprocedural anticoagulation management focused on vitamin K antagonists (VKA) and heparin bridging. The randomized BRUISE CONTROL (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial) (7) demonstrated a reduction of clinically significant pocket hematoma from 16% with heparin bridging to 3.5% with continued VKA treatment. With systematic reviews and meta-analysis overall favoring a strategy of maintenance of VKA therapy for CIED insertion (8,9), uninterrupted VKA use became the standard approach.

However, anticoagulation management has since been revolutionized with the introduction of direct oral anticoagulant (DOAC) agents. After large clinical trials establishing noninferiority with reduced bleeding risk, current European Society of Cardiology/American College of Cardiology guidelines give DOAC agents preference to VKA agents in eligible patients with nonvalvular AF and pulmonary

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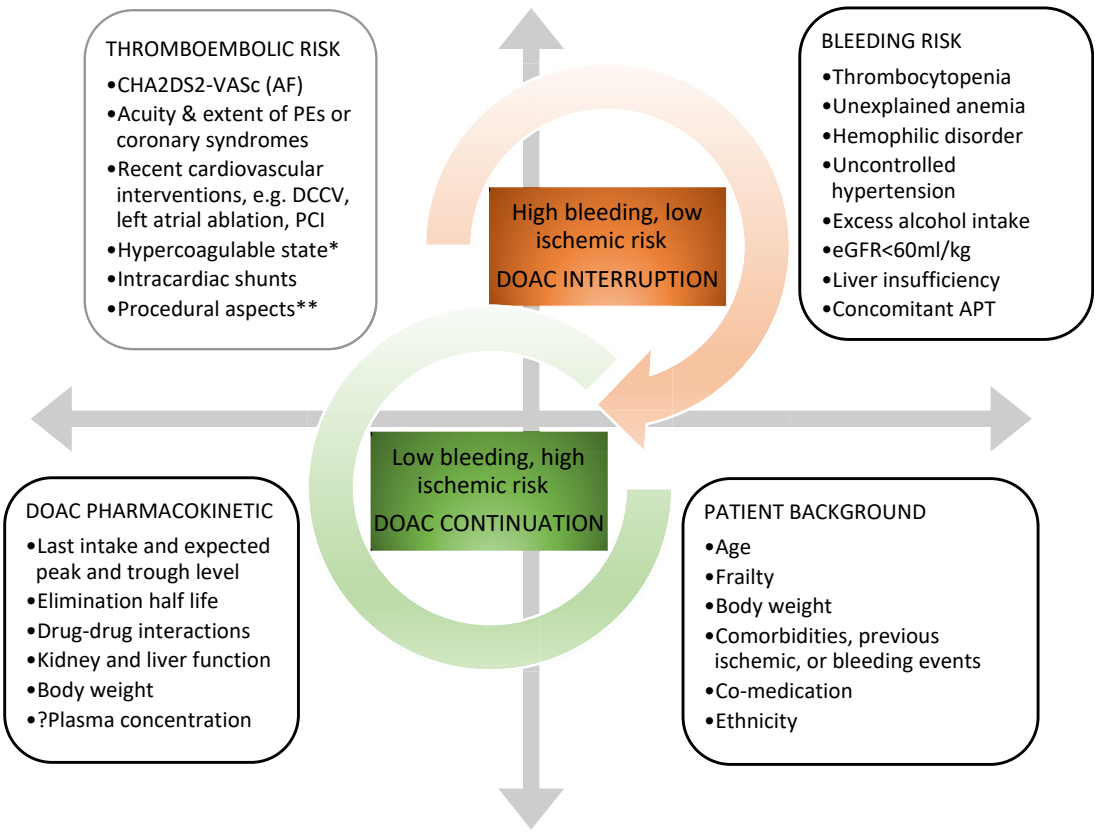
FIGURE 1 Considerations for Periprocedural DOAC Management



*For example inherited or acquired thrombophilia, malignancies, myeloproliferative diseases, nephrotic syndrome, hormonal therapy, and pregnancy/postpartum; **urgency, compressibility of access site, sheath size and number, device configurations, DFT testing requirement. AF = atrial fibrillation; APT = antiplatelet therapy; DCCV = direct current cardioversion; DFT = defibrillation threshold testing; DOAC = direct oral anticoagulant [agent]; eGFR = estimated glomerular filtration rate; PE = pulmonary embolism; PCI = percutaneous coronary intervention.

embolism or deep vein thrombosis. Most recently, clinical benefit of long-term DOAC therapy has also been shown for secondary prevention in coronary artery disease with high ischemic risk (10).

PERIPROCEDURAL DOAC MANAGEMENT FOR CIED IMPLANTATION

The periprocedural strategies for oral anticoagulation management include interruption without bridging, interruption with bridging, and continued uninterrupted anticoagulation.

PERIPROCEDURAL DOAC INTERRUPTION. Given the relatively rapid onset of DOAC agents, predictable peak plasma concentrations and short half-life heparin bridging are rarely necessary in DOAC therapy. This has been confirmed in large, prospective, multicenter trials and registries demonstrating that interruption of DOAC use without heparin bridging was safe, with low rates of major bleeding and systemic thromboembolism (11,12). Moreover, restarting DOAC agents 24 to 36 hours after the procedure was not associated with an increased risk of pocket hematoma, whereas restarting heparin was, thereby reinforcing concerns regarding periprocedural heparin administration.

To reduce periprocedural bleeding further, measurement of plasma concentrations of DOAC agents has been suggested to approximate residual anticoagulant effect. This approach may guide timing of intervention or inform about the need for reversal agents (idaruzicumab, andexanet alfa). However, the clinical benefit, cost-effectiveness, and cutoff values for measuring plasma concentration of DOAC agents before elective procedures are still controversial (13,14). To date, DOAC plasma concentration

measurement is not routinely recommended, but it may be helpful in patients with extreme body weights, severe liver and kidney dysfunction, or a need for urgent surgery.

PERIPROCEDURAL DOAC CONTINUATION. On the basis of the findings for periprocedural VKA continuation, a similar approach has been suggested for DOAC agents at the time of CIED insertion. A small retrospective study demonstrated in 2013 that it was safe to insert CIEDs in patients receiving uninterrupted dabigatran (15). The randomized prospective BRUISE CONTROL-2 study, including patients with nonvalvular AF (mean CHA_2DS_2-VASc of 3.9), reinforced these findings and found no difference in terms of clinically significant pocket hematoma between the interrupted and continued DOAC arms of the trial (equal incidence of 2.1%). On the basis of these findings, continuation of DOAC agents for CIED insertion has been suggested in selected patients (16).

EFFECT OF CONCOMITANT USE OF ANTIPLATELET AGENTS. The risk of pocket hematoma after CIED insertion was found to be 4- to 5-fold increased under dual antiplatelet (aspirin and clopidogrel) therapy and 1.5- to 2-fold increased with aspirin alone compared with no antiplatelet therapy (17). If clinically feasible, CIED insertion should be delayed until dual antiplatelet therapy can be safely temporarily omitted for the insertion. Few data are available on the increase in risk with prasugrel and ticagrelor.

A combined analysis of the BRUISE CONTROL-1 and 2 trials demonstrated a doubling of clinically significant pocket hematoma with anticoagulant (VKA or DOAC) therapy and concomitant antiplatelet use (9.8%). The study was not powered to assess the effect of dual vs single antiplatelet therapy (18).

CONCLUSIONS

The decision to interrupt or continue periprocedural DOAC agents for CIED insertion is not straightforward. Incorporation of all the patient-related, procedural, and pharmacologic factors and good clinical judgment are required to select the appropriate patients for an uninterrupted DOAC strategy (see **Figure 1**). The case report by Hayashi et al (1) is an impressive example of this strategy wrongfully applied to patients with an elevated bleeding risk, thus leading to prolonged hospitalization, patient discomfort, and necessity of prolonged cessation of anticoagulant agents, as well as a significantly elevated risk of infection.

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