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Review

Management of antithrombotic therapy during cardiac implantable device surgery

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ABSTRACT

Anticoagulants are commonly used drugs that are frequently encountered during device placement. Deciding when to halt or continue the use of anticoagulants is a balance between the risks of thromboembolism versus bleeding. Patients taking warfarin with a high risk of thromboembolism should continue to take their warfarin without interruption during device placement while ensuring their international normalized ratio remains below 3. For patients who are taking warfarin and have low risk of thromboembolism, either interrupted or continued warfarin may be used, with no evidence to clearly support either strategy. There is little evidence to support continuing direct acting oral anticoagulants (DOACs) for device implantation. The timing of halting these medications depends largely on renal function. If bleeding occurs, warfarin's anticoagulation effect is reversible with vitamin K and activated prothrombin complex concentrate. There are no DOAC reversal agents currently available, but some are under development. Regarding antiplatelet agents, aspirin alone can be safely continued while clopidogrel alone may also be continued, but with a slightly higher bleeding risk. Dual antiplatelet therapy for bare-metal stent/drug-eluting stent implanted within 4 weeks/6 months, respectively, should be continued due to high risk of stent thrombosis; however, if they are implanted after this period, then clopidogrel can be halted 5 days before the procedure and resumed soon after, while aspirin is continued. If the patient is taking both aspirin and warfarin, aspirin should be halted 5 days prior to the procedure, while warfarin is continued.

Contents

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1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia managed in clinical practice and the most common arrhythmia requiring hospitalization [1,2]. Thromboembolism occurs with similar incidence, regardless of the form of AF [3,4]. AF management includes anticoagulation to prevent thromboembolic stroke, its most debilitating complication [2,5]. Anticoagulation with warfarin, at a target international normalized ratio (INR), or with a direct acting oral anticoagulant (DOAC), has consistently been shown to reduce the risk of stroke and is therefore a major goal of therapy for AF [6,7]. AF is the most common reason for anticoagulation [8]. Anticoagulants are also frequently used for other indications, ranging from venous thromboembolism to mechanical prosthetic heart valves [9]. Indeed, their widespread use in clinical practice leads to a high likelihood of their being encountered in patients undergoing invasive procedures. Cardiac implantable electrophysiological device (CIED) surgeries, which include pacemaker (PM) and implantable cardioverter defibrillator (ICD) placements, are now commonplace worldwide with approximately 1.5 million procedures performed per year. Of patients who undergo such procedures, up to 35% require long-term anticoagulation [10].

When determining who should receive anticoagulation, a risk-stratification model is used. The rationale behind risk stratification is that although anticoagulation has clearly been shown to be more effective than antiplatelet agents or placebos in the prevention of thromboembolic stroke, their use should be restricted to patients whose risk for a thromboembolic event exceeds their risk of hemorrhage [11–13]. Risk factors for thromboembolic events in nonvalvular AF include a history of stroke, diabetes mellitus, hypertension, heart failure, and age. These were incorporated into the initial score called $CHADS_2$ [6,14]. The annual risk of stroke increased incrementally from 2%, with a score of 0, to as high as 22%, with a score of 6, in the absence of anticoagulant therapy [11,15,16]. A second score known as CHA_2DS_2-VASc was developed to further delineate the risk in the perceived low-risk groups using additional risk factors [6,17,18].

The risk of bleeding also increases substantially with the use of anticoagulants, and this presents a challenge to their clinical use [6,19]. A problem that arises is how to manage patients on anticoagulation treatment who require an invasive procedure that inherently increases their risk of bleeding. In this review, we will discuss the management of antithrombotic therapy in patients undergoing CIED surgery, including anticoagulants, such as warfarin and the DOACs, and antiplatelet drugs, such as aspirin and clopidogrel.

2. Oral anticoagulants

Warfarin has been the main oral anticoagulant used in clinical practice for nearly fifty years, especially in patients with AF. It inactivates vitamin K in the hepatic microsomes by inhibiting epoxide reductase, which hinders the formation of clotting factors that are dependent on vitamin K, such as factors II (prothrombin), VII, IX, and X [20]. The onset of the therapeutic action of warfarin is delayed by two to seven days while the preformed factors are depleted. Warfarin dosing is targeted to a therapeutic INR, which is usually 2–3 in AF but may be higher for mechanical mitral valves [20,21]. It has few side effects other than its major and most significant side effect, which is bleeding [22]. In addition, the INR requires monitoring in order to maintain it in a therapeutic range. Numerous medications interact with warfarin and affect its metabolism [20]. Over-anticoagulation leads to a significant risk of bleeding when the INR is greater than 3 [23,24]. While there is a trend away from warfarin treatment towards use of the newer anticoagulants, most clinicians maintain warfarin treatment in patients who are already taking the drug and have a stable INR [13].

DOACs are drugs that directly inhibit either thrombin or activated factor X and were designed in response to the need for an oral anticoagulant that did not require frequent monitoring and was less likely to have dietary and medication interactions. Three drugs gained approval in rapid succession: dabigatran etexilate, rivaroxaban, and apixaban [12]. A fourth followed soon after: edoxaban [25,26] (awaiting approval in Canada). All four are oral medications that do not require anticoagulation monitoring via blood tests. All four DOACs have rapid time to peak plasma concentrations of 2 (rivaroxaban/edoxaban) to 6 h (dabigatran); therefore, immediately after the first dose, patients are well anticoagulated [27]. The first of these drugs, dabigatran, is a potent direct competitive inhibitor of thrombin. The RE-LY trial demonstrated that dabigatran was comparable to warfarin in terms of stroke prevention with lesser rates of major hemorrhage in the 110 mg group, and superior to warfarin with equal rates of hemorrhage in the 150 mg group [28]. Rivaroxaban is an oral, direct factor Xa inhibitor and was shown in the ROCKET-AF trial to be similar to warfarin for the prevention of stroke in nonvalvular AF with no significant difference in the risk of major bleeding [29]. Rivaroxaban is used at a dose of 20 mg once daily or 15 mg daily if the creatinine clearance (CrCl) is between 30 and 49 mL/min. Apixaban, also an oral direct factor Xa inhibitor, was demonstrated to be superior to warfarin in preventing stroke or systemic embolism in nonvalvular AF in the ARISTOTLE trial [30]. The dose of apixaban is 5 mg twice daily with a dose reduction to 2.5 mg twice daily if two of the following three conditions are present: age 80 years or older, body weight of 60 kg or less, and a serum creatinine level of 133 μmol/L or greater [27,30]. Edoxaban is another oral direct factor Xa inhibitor that was shown to be noninferior to warfarin with respect to the prevention of stroke or systemic embolism in nonvalvular AF and was associated with significantly lower rates of bleeding in the ENGAGE AF-TIMI 48 trial [31]. The recommended dose of edoxaban is 60 mg once daily with a reduced dose of 30 mg once daily if CrCl is between 15 and 50 mL/min [32]. DOACs may be useful for use in elderly patients on a multitude of medications that may interact with warfarin; indeed, DOACs have been shown to be safe in the elderly [33].

3. Management of warfarin during pacemaker/implantable cardioverter defibrillator insertion

Until recently, warfarin use was halted before PM/ICD insertion and the patient was bridged with intravenous (IV) unfractionated heparin or subcutaneous low-molecular-weight heparin (LMWH) if the thromboembolic risk was considered high (usually $CHADS_2 \geq 3$) [34–36]. This was usually performed by discontinuing warfarin use five days before the procedure and initiating IV heparin or LMWH 3 days before the procedure, once the INR decreased below 2; the procedure was usually performed when the INR was less than 1.5 and after halting IV heparin 4 h prior to the procedure or after halting the last dose of LMWH 24 h prior [36]. This process is marred by several difficulties and logistical issues. To start IV heparin, the patient must be a hospital inpatient for several days before the procedure. In addition, heparin requires frequent checking of the PTT with dose adjustments to ensure a therapeutic time; LMWH is less problematic in terms of monitoring, but still requires daily injections and CrCl above 30 mL/min [34]. Sometimes, the INR does not decrease below 1.5 on the day of the procedure, leading to the administration of vitamin K to decrease the INR, which results in restoring the INR to the therapeutic range after post-procedural reinitiation of warfarin and a further increase in