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Optimal strategies for the management of antiplatelet and anticoagulation medications prior to cardiac device implantation

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Abstract

Choosing the optimal management strategy for antiplatelet and anticoagulation medications at the time of cardiac device implantation can be challenging. Simply withholding or reversing these medications puts patients at risk of subsequent thromboembolic events. Equally, continuing these medications may unnecessarily increase the risk of bleeding complications. This article summarizes recent findings and provides compelling evidence challenging current recommendations outlined by various professional organizations. (Cardiol J 2011; 18, 1: 103–109)

Key words: pacemaker, implantable cardioverter-defibrillator, complications, anticoagulation

Introduction

The optimal management of antiplatelet and anticoagulation medications prior to cardiac device (pacemaker [PM] or implantable cardioverter-defibrillator [ICD]) implantation has been the subject of several recent publications [1–7]. Some of this attention stems from the pervasive use of new antiplatelet agents, including thienopyridines (e.g. clopidogrel, prasugrel and ticlopidine) and direct thrombin inhibitors (e.g. bivalirudin and argatroban). Until recently, little was known about the risk of bleeding complications in patients taking dual antiplatelet therapy beyond anecdotal experience. Additionally, several recent studies have questioned the practice of heparin bridging, suggesting that it is not cost-effective, lengthens hospitalization, and is perhaps less safe, exposing patients to greater risks of bleeding and thromboembolic complications during transition periods [8–11].

Our article summarizes recent findings and provides compelling evidence that challenges current recommendations outlined by professional organizations [12–14].

Normal hemostasis involves a series of complex, well-regulated interactions between the vascular wall, platelets and coagulation cascade, which are intended to reduce bleeding and promote vascular repair following injury [15]. Antiplatelet and anticoagulation medications, which exert their effects by disrupting these steps, can have profound consequences on periprocedural bleeding complications.

Most patients referred for cardiac PM or ICD implantation are taking some form of antiplatelet or anticoagulation medication. Aspirin and thienopyridines are often prescribed for primary or secondary prevention of cardiovascular events such as myocardial infarction or stroke. Dual antiplatelet therapy, consisting of aspirin and clopidogrel, is

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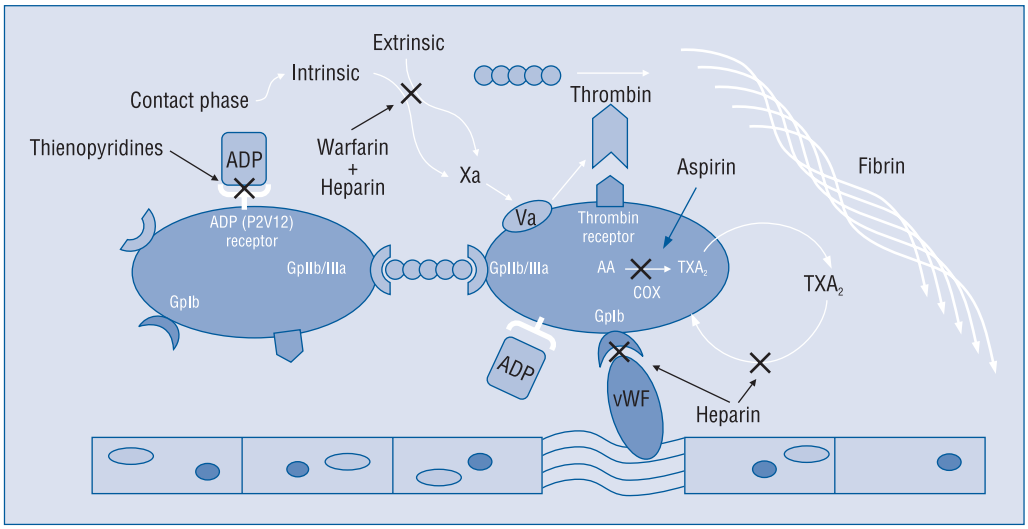

Figure 1. Overview of hemostasis [12].

universally prescribed following percutaneous coronary interventions (PCI) that involve placement of either bare metal or drug-eluting stents to reduce the risk of in-stent thrombosis. With regard to anticoagulants, warfarin is commonly prescribed to reduce the risk of thromboembolic events in patients with atrial fibrillation, mechanical prosthetic valves, previous strokes, reduced left ventricular systolic function, left ventricular apical thrombus, and previous deep venous thrombosis or pulmonary embolism. Heparin is often used to provide short-term anticoagulation while warfarin is being held or titrated to therapeutic goal.

From a clinical perspective, defining the optimal periprocedural management of these medications can be challenging. Simply withholding or reversing these medications places patients at risk of subsequent thromboembolic events, while continuing these medications may unnecessarily increase the risk of bleeding complications.

The most common bleeding complication following cardiac device implantation is the development of a pocket hematoma. In addition to causing significant patient discomfort, pocket hematomas increase the risk of pocket infections, prolong hospitalization (because of the need for continued observation) and expose patients to unprotected periods while antiplatelet and/or anticoagulation medications are being withheld [16–18]. The incidence of pocket hematoma formation varies greatly depending on the periprocedural antiplatelet and anticoagulation medications used, but can exceed 20% [2, 4, 19]. Studies suggest that as many as 1.0% of cardiac device implantations require pocket exploration to address ongoing bleeding, thus exposing patients to a second procedure, increasing hospitalization costs, risk of infection, and patient dissatisfaction [18, 20, 21].

Mechanism of action

Primary hemostasis is mediated by complex interactions between the vascular wall and platelets, which culminate in the formation of a platelet plug (Fig. 1) [15, 22]. This process is initiated by platelet adhesion, which involves the bridging of von Willebrand factor, present on exposed subendothelial collagen, to glycoprotein (Gp) Ib receptor expressed on platelets. Platelet activation ensues, bringing about the expression of GpIIb/IIIa receptors on the platelet surface, and stimulating release factors that trigger the coagulation cascade. Platelet activation is further enhanced by the presence of adenosine diphosphate (ADP), thromboxane, and thrombin with platelet-specific receptors. Platelet aggregation follows, mediated by the cross-linking of fibrinogen to GpIIb/IIIa receptors. A secondary hemostatic plug develops following activation of the coagulation cascade, as the primary platelet plug is reinforced by fibrin cross-linking.

Antiplatelet and anticoagulation medications disrupt hemostasis by targeting specific sites along this cascade (Fig. 1). Aspirin affects platelet activation and aggregation by irreversibly inhibiting cyclooxygenase (COX) enzyme, thereby blocking the formation of thromboxane A2 [23, 24]. Thienopyridines similarly affect platelet activation and aggregation, but they do so by irreversibly in-

hibiting ADP binding to the platelet ADP receptor (P2Y12) [24]. Thus, the mechanism of action of aspirin and clopidogrel affects the expression of GpIIb/IIIa receptors on platelets and inhibits the release of factors that stimulate the coagulation cascade.

The primary target of heparin is disruption of the coagulation cascade [25]. By potentiating the activity of antithrombin III, heparin indirectly inhibits the activity of coagulation factors IIa (thrombin), IXa, Xa, XIa, and XIIa. Of these, factors Xa and IIa are inhibited to the greatest extent by the heparin-antithrombin III complex, thus explaining the anticoagulation properties of heparin. Heparin also influences platelet plug formation as reflected by prolonged bleeding times. Binding of heparin to von Willebrand factor diminishes platelet adhesion, and platelet aggregation is reduced by inhibiting thrombin-mediated activation of platelets. Importantly, the action of heparin is broad, affecting several different steps in the establishment of hemostasis.

Warfarin interferes with the synthesis of vitamin K-dependent coagulation factors, notably Factors II, VII, IX, X, and proteins C and S [26]. The anticoagulation efficacy of warfarin declines when the international normalized ratio (INR) is less than 2.0 and is essentially eradicated when the INR is less than 1.5 [27]. The effect of warfarin is much more specific than heparin and inhibits only the coagulation cascade.

In summary, aspirin, clopidogrel and, to some extent, heparin, affect the development of the primary hemostatic plug by disrupting platelet adhesion and aggregation. Warfarin and heparin block reinforcement of the platelet plug by fibrin cross-linking.

Current antiplatelet/anticoagulant management strategies

Ideally, the strategy chosen to manage antiplatelet and anticoagulation medications should reduce the risk of procedure-related bleeding complications without unnecessarily increasing the risk of thromboembolic events. Perioperative guidelines published by the ACC/AHA support continuing low-dose aspirin monotherapy for non-cardiac surgical procedures, noting only a small increase in procedure-related bleeding (relative risk 1.5), without substantially increasing the severity of bleeding complications or perioperative mortality [12]. A similar recommendation is provided for those receiving monotherapy with clopidogrel or ticlopidine.

Suggestions pertaining to the management of dual antiplatelet therapy are less definitive. This is largely due to uncertainty regarding the appropriate length of treatment following PCI to minimize early and late in-stent thrombosis. In general, the guidelines support delaying elective non-cardiac surgery until the following endpoints are reached [12]:

Dual antiplatelet therapy should be continued for a minimum of:

— 14 days following balloon angioplasty;
— 30–45 days following bare metal stent implantation;
— 12 months or more following uncomplicated on-label use of drug-eluting stent.

Once the recommended duration of dual antiplatelet therapy is complete, the guidelines support holding clopidogrel for at least five days while continuing aspirin in the periprocedural period.

Management strategies for anticoagulation medications are briefly discussed in the atrial fibrillation and valvular heart disease guidelines [13, 14]. The authors of these guidelines suggest that warfarin may be safely held in low-risk patients (Table 1), allowing the INR to drift below 1.5 without initiating heparin. However, in those patients deemed high-risk, the guidelines support holding anticoagulation therapy and administering either unfractionated or low-molecular weight heparin once INR < 2.0. Heparin should then be held for 4–6 hours preoperatively and restarted as soon as possible from a surgical perspective.

In practice, physicians appear to be following these recommendations. deBono et al. [5] carried

Table 1. Assessment of risk of thromboembolic events.

Risk of thromboembolic events	
Low-moderate	**High**
Mechanical aortic valves	Prosthetic mitral and/or tricuspid valves
Atrial fibrillation without prior CVA/TIA	Atrial fibrillation with prior CVA/TIA
	Current treatment for DVT, PE, LAA or LV thrombus
	Documented hypercoagulable conditions*

*Factor V Leiden, prothrombin G2021A mutations, protein C, S or antithrombin III deficiencies, antiphospholipid antibody syndrome; CVA — cerebrovascular accident; TIA — transient ischemic attack; DVT — deep venous thrombosis; PE — pulmonary embolus; LAA — left atrial appendage; LV — left ventricular

out an illuminating questionnaire-based study to determine periprocedural anticoagulation management strategies among physicians implanting cardiac devices in the United Kingdom. Of the respondents, only 11% of implanting physicians would continue anticoagulation in patients with mechanical mitral valves undergoing cardiac device implantation, despite the growing evidence that suggests it is safe to do so. The remaining 89% said that they would hold warfarin for ≤ three days and institute heparin bridging either as unfractionated or low-molecular weight heparin.

Importantly, however, results from our study, and those of others, question these recommendations, suggesting that heparin 'bridging' may actually be more harmful to patients than maintaining warfarin therapy throughout the perioperative period. A recent prospective study by our group [28] demonstrated an increase in thromboembolic and bleeding complications in patients randomized to warfarin interruption prior to cardiac device implantation. Notably, there were no thromboembolic or bleeding complications in those continued on warfarin.

Results from recent investigations

Antiplatelet therapy

We retrospectively assessed the risk of developing bleeding complications in patients undergoing cardiac device implantation. The frequency of bleeding complications in controls who were not receiving any antiplatelet (or anticoagulant) therapy was 1.6% [1]. The likelihood of developing a bleeding complication doubled in patients receiving aspirin therapy alone (1.6% *vs* 3.9%; p = 0.078) and more than quadrupled in those receiving dual antiplatelet therapy (1.6% *vs* 7.2%; p = 0.004).

In a similar retrospective analysis, Thal et al. [4] reported pocket hematomas occurring in 1.2% of patients receiving aspirin only, 2.6% of patients continued on warfarin (mean INR 1.9 ± 0.6), and, remarkably, 20% of patients receiving dual antiplatelet therapy. Kutinsky et al. [2] reported hematoma formation in 18.3% of patients treated with clopidogrel, while no hematomas occurred in patients who had clopidogrel held for four or more days.

Interestingly, when major bleeding complications (defined as the need for blood transfusion, pocket revision, cardiac tamponade requiring emergent pericardiocentesis or prolonged hospitalization) and minor bleeding complications (defined as small hematoma or local ecchymosis not requiring treatment) were combined, Przybylski et al. [6] noted a higher frequency in those receiving dual antiplatelet therapy when compared to aspirin alone (24.5% *vs* 13.9%; p = 0.06). Importantly, however, they found no difference in major bleeding complications between the two groups when assessed separately (3.6% *vs* 3.8%; p = 0.7, respectively), which led them to conclude that dual antiplatelet therapy does not increase the risk of major bleeding complications.

Anticoagulant therapy

Several case series published in the late 1990s challenged the use of heparin 'bridging' for cardiac device implantation [9–11]. Goldstein et al. [9] were among the first to report their experience, implanting devices in 37 patients continued on warfarin at the time of device implantation. They found no difference in wound-related or wound-unrelated complications between patients receiving warfarin (mean INR 2.5) and controls (mean INR 1.1). Al-Khadra [10] reported similar findings in 47 patients with a mean INR 2.3 (range 1.5–3.1) at device implantation. Only one patient in the anticoagulated group developed a small (4 × 3 cm) hematoma that resolved spontaneously.

Giudici et al. [11] published a large retrospective cohort consisting of 1,025 patients referred for device implantation, comparing 470 anticoagulated patients against 555 non-anticoagulated patients. The rates of bleeding complications were similar between the anticoagulated (mean 2.6 ± 1.0) and non-anticoagulated groups (INR < 1.5). Hematomas occurred in 2.6% of the anticoagulated patients (nine in-hospital and three late hematomas), and 2.2% in the non-anticoagulated patients (again, nine in-hospital and three late hematomas). Patients in both groups were treated conservatively with pressure dressings. It should be noted, however, that two patients in the anticoagulation group did require pocket exploration for ongoing bleeding concerns. Alteration in medical therapy (i.e. discontinuation of heparin or warfarin) occurred in rare instances. Importantly, one patient in the non-anticoagulated group suffered a stroke, but it is unclear if this patient was previously on warfarin therapy for thromboembolism prophylaxis.

Shortly thereafter, Wiegand et al. [3] reported their findings on the predictors of intraoperative bleeding or pocket hematoma formation in 3,164 patients who had PM or ICD implantation, generator replacement or lead revision. In this study, aspirin use was associated with a 3.1% incidence of bleeding. The combination of aspirin plus thienopyridine markedly increased the incidence of bleeding,

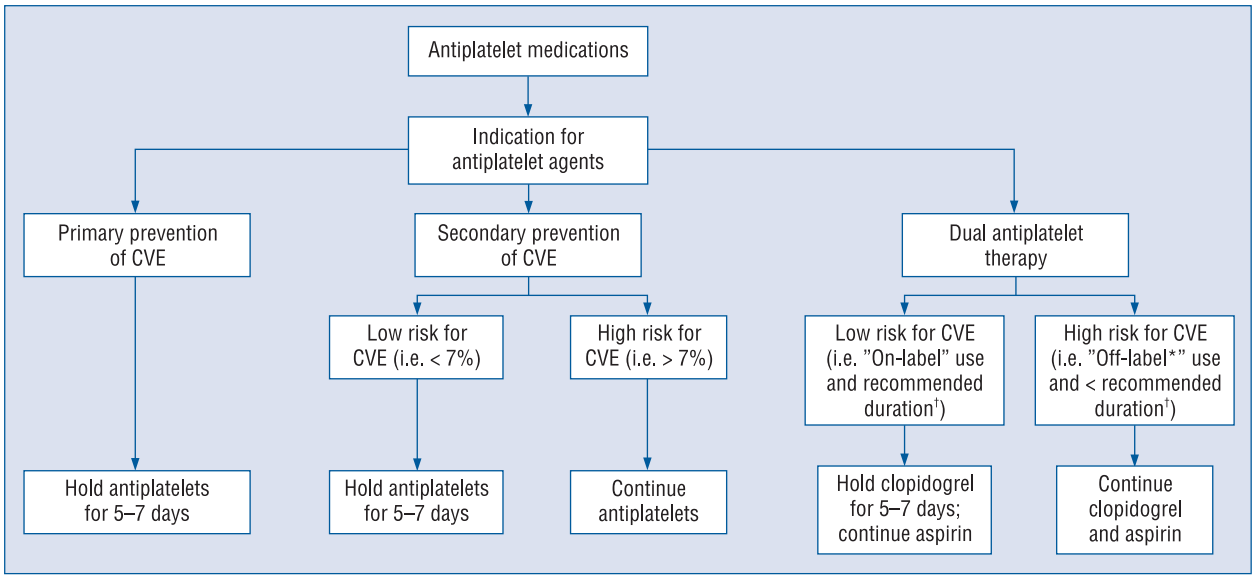

Figure 2. Algorithm for pre-procedure management of antiplatelet medications; CVE — cardiovascular events; *Off-label: bifurcating lesions, ovelapping stents, and/or multiple stents; †see text.

to 21.7%. This study also assessed the use of heparin. Patients receiving anticoagulation with phenprocoumon, a derivative of coumarin, had the medication held until INR drifted below 1.5. Heparin bridging was initiated once the INR < 2.0. Postoperatively, anticoagulation was re-established by heparin infusion, titrated to a partial thromboplastin time of 40–60 s, initiated either with a bolus immediately following the procedure or without a bolus starting within 12 hours of the procedure. As expected, the incidence of hematomas was significantly higher in those receiving heparin with bolus compared to those without a bolus (28.1% *vs* 12.0%; p = 0.05).

The timing of heparin reinitiation following device implantation was assessed by Michaud et al. [19]. They performed a prospective randomized study comparing the incidence of pocket hematomas in 49 patients requiring anticoagulation. Patients were randomized to receive intravenous heparin either six or 24 hours after PM implantation. Pocket hematomas occurred in 20% of patients receiving intravenous heparin, irrespective of the initiation time, compared to 4% of patients continued on warfarin therapy alone and 2% not receiving any anticoagulation therapy. Pocket hematomas were noted in 23% of patients started on heparin six hours following PM implantation, *vs* 17% initiated at 24 hours, which was not statistically significant. Patients treated with heparin were also more likely to remain in the hospital for longer, averaging 3.6 ± 2.9 days *vs* 2.3 ± 1.1 days when on warfarin alone and 2.5 ± 2.5 days when receiving no therapy.

Heparin bridging also contributed to increased hematoma formation and prolonged hospitalization in patients undergoing cardiac resynchronization therapy implantation [7]. In this retrospective study, patients were divided into three groups:

— warfarin group: continued on warfarin such that the INR = 2–3;
— heparin bridging group: pre-implant — warfarin held for four days, unfractionated heparin started when INR ≤ 2; post-implant — unfractionated heparin restarted six hours later;
— control group: warfarin held for four days.

Warfarin was restarted in all patients on the evening of the day cardiac device implantation took place. Once again, the use of heparin bridging significantly increased the rate of hematoma formation (controls: 4.1%; warfarin group: 5.0%; heparin group: 20.7%; p = 0.03) and was associated with longer stays (controls: 1.6 ± 1.6; warfarin group: 2.9 ± 2.7; bridging 3.7 ± 3.2; p < 0.001).

Updated antiplatelet/anticoagulant management strategies

Based on our findings, and those of others, we have altered our management strategies for both antiplatelet and anticoagulation regimens (Figs. 2, 3). In most cases, we recommend holding antiplatelet medications, such as aspirin or thienopyradines (i.e. clopidogrel), for a period of 5–7 days, specifically when prescribed for primary prevention of cardiovascular events. The management of these medica-

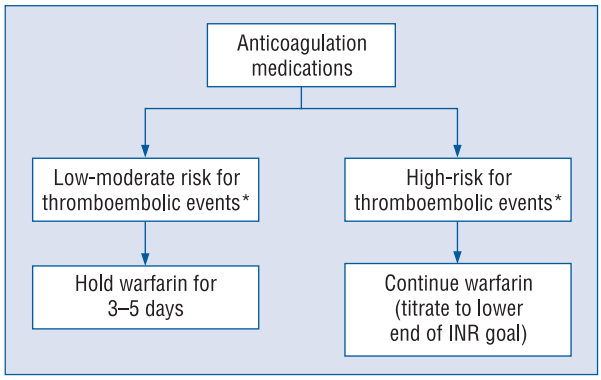

Figure 3. Algorithm for pre-procedure management of anticoagulation medications; *refer to Table 1 for risk assessment; INR — international normalized ratio.

tions becomes less clear when used for secondary prevention. The annual rates of death and myocardial infarction in patients with known coronary artery disease can range from as low as 0.5% in low-risk patients to greater than 25% in high-risk populations [12]. Additionally, the cumulative risk of recurrent stroke or death ranged from 41–46% in patients who had had a previous stroke [29]. Given these uncertain and worrying projections, we feel it is prudent to continue antiplatelet therapy during the perioperative period when prescribed for secondary prevention, particularly in high-risk patients (Fig. 2).

Unquestionably, perioperative dual antiplatelet therapy increases the absolute risk of bleeding complications from 7–22% [1, 3, 4]. The absolute risk of bleeding complications is also increased with aspirin use, but to a lesser extent, ranging from 1––4%. Thus, it seems reasonable to consider holding clopidogrel for a period of five days while continuing aspirin in patients receiving dual antiplatelet therapy who are at low risk of thromboembolic events.

Assuming dual antiplatelet therapy is being used to prevent in-stent thrombosis following PCI, we would define a low-risk population as being those who met the minimum recommended duration of therapy (see above). High-risk patients consist of those who have not completed the recommended duration of therapy and those with 'off-label' indications for stent placement [30] (e.g. bifurcating lesions, overlapping stents, and/or multiple stents). It is our opinion that dual antiplatelet therapy should be continued throughout the perioperative period in these high-risk individuals with an awareness of increased bleeding complications rates.

With regard to anticoagulation therapy, we cannot justify the practice of heparin 'bridging'. Rather, we recommend holding warfarin for a period of 3–5 days to allow the INR to drift below 1.5 in those patients receiving chronic warfarin therapy who are at low-to-moderate risk of thromboembolic events (Table 1). Conversely, patients deemed high-risk should be continued on warfarin throughout the perioperative period. It is reasonable either to hold or reduce one to two doses of warfarin prior to the procedure to allow the INR to trend downwards. However, sub-therapeutic INRs should be avoided to prevent unnecessary non-anticoagulated periods that increase the risk of thromboembolic events. The only notable exceptions here are those patients who undergo simultaneous lead extraction, something which should only be performed when the INR is below 1.5.

Conclusions

The perioperative use of either dual antiplatelet therapy or heparin 'bridging' significantly increases the risk of procedure-related bleeding complications following cardiac device implantation, and unnecessarily exposes patients to non-anticoagulated periods. Recent studies challenge current professional guidelines. To optimize patient care, implanting physicians must pay particular attention to the various management strategies being used, and tailor them as needed on a patient-by-patient basis to minimize periprocedural complications.

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